U.S. FOOD & DRUG ADMINISTRATION

April 22, 2019

Siri & Glimstad LLP
Aaron Siri, Esq.
200 Park Avenue
Suite 1700
New York, NY 10166

In reply refer to file: **2018-8865**

Dear Mr. Siri,

This is in reply to your Freedom of Information Act (FOIA) request dated October 25, 2018, in which you requested "a copy of the package insert for each DTP vaccine manufactured by Connaught Laboratories, Inc. or Connaught Laboratories, Limited and licensed by the FDA." Your request was received in the Center for Biologics Evaluation and Research (CBER) on November 1, 2018.

A search of the application file located the enclosed records.

If you are not satisfied with any aspect of the processing and handling of this request, please contact:

Food and Drug Administration (FDA)
Sarah Kotler, Director
Division of Freedom of Information, OES
U.S. Food & Drug Administration
5630 Fishers Lane
Room-1035
Rockville, Maryland 20857
301-796-3900 (main)
301-827-9267 (fax)

You also have the right to contact:

FDA FOIA Public Liaison
Office of the Executive Secretariat
5630 Fishers Lane
Room-1050
Rockville, MD 20857
Email: FDAFOIA@fda.hhs.gov

If you have any questions or if I can be of further assistance, please let me know by referencing the above file number. I can be reached by phone at 240-402-8079 or by e-mail at John.Hyder@fda.hhs.gov.

Sincerely,

John M. Hyder -S

Digitally signed by John M. Hyder -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=John M. Hyder -S, 0.9.2342.19200300.100.1.1=2000432462
Date: 2019.04.22 13:27:38 -04'00'

John Matthew Hyder, Science Disclosure Analyst
Center for Biologics Evaluation and Research
Food and Drug Administration

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®SQUIBB/CONNAUGHT®

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP

FOR PEDIATRIC USE

SPECIAL NOTICE: *EXPOSURE OF THIS VACCINE TO TEMPERATURES BELOW 2°C (35°F) OR ABOVE 25°C (77°F) FOR AS LITTLE AS 24 HOURS RESULTS IN CONDITIONS WHICH MAKE RESUSPENSION OF THE VACCINE DIFFICULT.*
CARE SHOULD BE TAKEN NOT TO STORE THIS PRODUCT NEAR FREEZING SURFACES. ALWAYS RETURN UNUSED PORTION TO REFRIGERATION, 2°C TO 8°C (35°F to 46°F), IMMEDIATELY AFTER USE.
DO NOT USE IF RESUSPENSION CANNOT BE ACHIEVED BY VIGOROUS SHAKING.

DESCRIPTION

This product combines diphtheria and tetanus toxoids, adsorbed with pertussis vaccine in a sterile isotonic sodium chloride solution containing sodium phosphate to control pH; each 0.5 ml injection contains not more than 0.25 mg of aluminum added in the form of aluminum potassium sulfate. Thimerosal (mercury derivative) 1:10,000 is added as a preservative. The mixture provides an immunizing dose of each component in the total dosage prescribed below. Each single dose contains 4 protective units of Pertussis Vaccine based on the U.S. Standard Pertussis Vaccine.

INDICATIONS

For active immunization of infants and young children against diphtheria, tetanus and pertussis simultaneously. Injections should be started at 2 to 3 months of age and be completed no later than the age of 6 years. Immunization should always be started at once if whooping cough or diphtheria is present in the community.

CONTRAINDICATIONS

Persons 7 years of age and older should not be immunized with Pertussis Vaccine. Immunization should be deferred during the course of any acute illness, however, a minor illness not associated with fever such as a mild upper respiratory infection need not preclude vaccination. The benefit/risk ratio of routine immunization with this product should be carefully considered by the responsible physician if the child has a personal or family history of central nervous system disease or convulsions.[2] The occurrence of a severe reaction following administration of this product, consisting of high fever (39°C or above), somnolence, screaming, shock, convulsions, encephalopathy or thrombocytopenia, is a contraindication to further use of this vaccine. Anaphylactoid and/or allergic reactions, immunosuppressive therapy, recent gammaglobulin, plasma, or blood transfusions, immunodeficiency disorders, leukemia, lymphoma, or generalized malignancy are also contraindications.[2] Simultaneous administration of DTP with another vaccine should be avoided unless they have been shown to be effective when used together. The clinical judgment of the responsible physician should prevail at all times.
The occurrence of any type of neurological symptoms or signs following administration of this product is an absolute contraindication to further use.
Elective immunization of patients over the age of six months should be deferred during an outbreak of poliomyelitis.

WARNING

This product is not recommended for immunizing persons 7 years of age and older.

The benefit/risk ratio of routine immunization with this product should be carefully considered by the responsible physician if the child has a personal or family history of central nervous system disorders or convulsions.[2] Should any symptomatology related to neurological disorders develop following administration, do not attempt further administration of pertussis antigen. The development of "excessive screaming syndrome" is an absolute contraindication for any further use of pertussis vaccine.
If the vaccine is used in persons receiving immunosuppressive therapy, a recent injection of immune globulin or having an immunodeficiency disorder, the expected antibody response may not be obtained.[2]
Special care should be taken so the injection is not made into a blood vessel.

ADVERSE REACTIONS

Adverse reactions may be local and include pain, erythema, tenderness, heat, edema and induration at the site of injection. Significant reactions attributed to the pertussis vaccine component have been high fever (greater than 39°C), a transient shock-like episode, excessive screaming, somnolence, convulsions, encephalopathy, thrombocytopenia, and hemolytic anemia.[3,4] Such reactions almost always appear within 24 to 48 hours after injection but have been thought to occur after an interval as long as seven days. A small nodule may develop at the site of injection and remain for a few weeks before being completely absorbed. Sterile abscesses have been reported. Systemic reactions include mild to moderate transient fever, chills, malaise, and irritability.
Neurological disorders such as encephalopathy, possibly due to the pertussis component, have been reported to occur rarely following the injection of this product and they may be fatal or result in permanent damage to the central nervous system.
There have been rare reports of Sudden Infant Death Syndrome (crib death) after the administration of DTP Vaccine. However, available data indicate no association between DTP vaccination, in general, and sudden infant death, in particular.[5]

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Neurological complications have been reported. These include cochlear lesion,[6] brachial plexus neuropathies,[7,8] paralysis of the radial nerve,[9] paralysis of the recurrent nerve,[10] accommodation paresis, EEG disturbances, and one reported case of swallowing difficulty.[11] In the differential diagnosis of polyradiculoneuropathies following administration of tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[12]
Should symptomatology referable to the central nervous system develop following administration, no further immunization with this product should be attempted.
The benefit/risk ratio of routine immunization with this product should be carefully considered by the responsible physician for patients with acute infections or a personal or family history of neurological disturbances.[2]
Epinephrine Injection (1:1000) must always be immediately available to combat unexpected anaphylactoid and other allergic reactions.

DOSAGE

SHAKE VIAL WELL *before withdrawing each dose. Product contains a bacterial suspension. Vigorous agitation may be required to resuspend the contents of the vial.*

Primary Immunization[13,14]

For children 2 months through 6 years (ideally beginning at age 2-3 months or at time of a 6-week "check-up").
Give 0.5 ml intramuscularly on three occasions at 4-6 week intervals with a reinforcing dose given approximately one year after the third injection.

Booster Immunization[13,14]

For children between 4 and 6 years of age (preferably at time of school entrance, kindergarten or elementary school), 0.5 ml intramuscularly.
Thereafter, and for all other individuals, booster immunization should be with Tetanus and Diphtheria Toxoids Adsorbed (FOR ADULT USE), at intervals of 10 years. Persons 7 years of age and older should not be immunized with Pertussis Vaccine.

CAUTION

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ADMINISTRATION

Inject deeply into muscle tissue; superficial or subcutaneous injections are more painful. The vastus lateralis (mid-thigh laterally) is the preferred injection site for infants. During the course of primary immunization, inoculations should not be made more than once at the same site.

HOW SUPPLIED

Vial, 7.5 ml

STORAGE

Store between 2°-8°C (35°-46°F). DO NOT FREEZE.

REFERENCES

1. Data available from Connaught Laboratories, Inc.
2. Active Immunization Procedures. Report of the Committee on Infectious Diseases. American Academy of Pediatrics, Evanston, Illinois, p. 9, 13, 1977
3. Pertussis. Report of the Committee on Infectious Diseases. American Academy of Pediatrics, Evanston, Illinois, p. 205, 1977
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12. Schlenska, G.K.: Unusual neurological complications following tetanus toxoid administration, J. Neurol. 215: 209-302, 1977
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14. Advisory Committee on Immunization Practices. Diphtheria and Tetanus Toxoids and Pertussis Vaccine. MMWR 26: 401-402, 1977

For information contact: SQUIBB/CONNAUGHT, Inc.
P.O. Box 3028 330 Alexander St. Princeton, NJ 08540

Mfd. by: **CONNAUGHT** LABORATORIES, INC.
Swiftwater, Pennsylvania 18370

Product information as of July, 1980

Distributed by: E.R. SQUIBB & SONS, Inc.
Princeton, New Jersey 08540

Printed in U.S.A.
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CONNAUGHT

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INDICATIONS

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CONTRAINDICATIONS

Persons 7 years of age and older should not be immunized with Pertussis Vaccine. Immunization should be deferred during the course of any acute illness, however, a minor illness not associated with fever such as a mild upper respiratory infection need not preclude vaccination. The benefit/risk ratio of routine immunization with this product should be carefully considered by the responsible physician if the child has a personal or family history of central nervous system disease or convulsions.[2] The occurrence of a severe reaction following administration of this product, consisting of high fever (39°C or above), somnolence, screaming, shock, convulsions, encephalopathy or thrombocytopenia, is a contraindication to further use of this vaccine. Anaphylactoid and/or allergic reactions, immunosuppressive therapy, recent gammaglobulin, plasma, or blood transfusions, immunodeficiency disorders, leukemia, lymphoma, or generalized malignancy are also contraindications.[2] Simultaneous administration of DTP with another vaccine should be avoided unless they have been shown to be effective when used together. The clinical judgment of the responsible physician should prevail at all times.
The occurrence of any type of neurological symptoms or signs following administration of this product is an absolute contraindication to further use.
Elective immunization of patients over the age of six months should be deferred during an outbreak of poliomyelitis.

WARNING

This product is not recommended for immunizing persons 7 years of age and older.

The benefit/risk ratio of routine immunization with this product should be carefully considered by the responsible physician if the child has a personal or family history of central nervous system disorders or convulsions.[2] Should any symptomatology related to neurological disorders develop following administration, do not attempt further administration of pertussis antigen. The development of "excessive screaming syndrome" is an absolute contraindication for any further use of pertussis vaccine.
If the vaccine is used in persons receiving immunosuppressive therapy, a recent injection of immune globulin or having an immunodeficiency disorder, the expected antibody response may not be obtained.[2]
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ADVERSE REACTIONS

Adverse reactions may be local and include pain, erythema, tenderness, heat, edema and induration at the site of injection. Significant reactions attributed to the pertussis vaccine component have been high fever (greater than 39°C), a transient shocklike episode, excessive screaming, somnolence, convulsions, encephalopathy, thrombocytopenia, and hemolytic anemia.[3,4] Such reactions almost always appear within 24 to 48 hours after injection but have been thought to occur after an interval as long as seven days. A small nodule may develop at the site of injection and remain for a few weeks before being completely absorbed. Sterile abscesses have been reported. Systemic reactions include mild to moderate transient fever, chills, malaise, and irritability.
Neurological disorders such as encephalopathy, possibly due to the pertussis component, have been reported to occur rarely following the injection of this product and they may be fatal or result in permanent damage to the central nervous system.
There have been rare reports of Sudden Infant Death Syndrome (crib death) after the administration of DTP Vaccine. However, available data indicate no association between DTP vaccination, in general, and sudden infant death, in particular.[5]
Neurological complications have been reported. These include cochlear lesion,[6] brachial plexus neuropathies,[7,8] paralysis of the radial nerve,[9] paralysis of the recurrent nerve,[10] accommodation paresis, EEG disturbances, and one reported case of swallowing difficulty.[11] In the differential diagnosis of polyradiculoneuropathies following administration of tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[12]

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SHAKE VIAL WELL *before withdrawing each dose. Product contains a bacterial suspension. Vigorous agitation may be required to resuspend the contents of the vial.*

Primary Immunization[13, 14]
For children 2 months through 6 years (ideally beginning at age 2-3 months or at time of a 6-week "check-up").
Give 0.5 ml intramuscularly on three occasions at 4-6 week intervals with a reinforcing dose given approximately one year after the third injection.

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CAUTION

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ADMINISTRATION

Inject deeply into muscle tissue; superficial or subcutaneous injections are more painful. The vastus lateralis (mid-thigh laterally) is the preferred injection site for infants. During the course of primary immunization, inoculations should not be made more than once at the same site.

HOW SUPPLIED

Vial, 7.5 ml

STORAGE

Store between 2°-8°C (35°-46°F). DO NOT FREEZE.

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Product information as of July, 1980

Manufactured by:
CONNAUGHT LABORATORIES, INC.
Swiftwater, Pennsylvania 18370, U.S.A.

Printed in U.S.A.
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DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP FOR PEDIATRIC USE

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WARNING

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DOSAGE

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Primary Immunization[13,14]

For children 2 months through 6 years (ideally beginning at age 2-3 months or at time of a 6-week "check-up").

Give 0.5 ml intramuscularly on three occasions at 4-6 week intervals with a reinforcing dose given approximately one year after the third injection.

Booster Immunization[13,14]

For children between 4 and 6 years of age (preferably at time of school entrance, kindergarten or elementary school), 0.5 ml intramuscularly.

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CAUTION

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ADMINISTRATION

Inject deeply into muscle tissue; superficial or subcutaneous injections are more painful. The vastus lateralis (mid-thigh laterally) is the preferred injection site for infants. During the course of primary immunization, inoculations should not be made more than once at the same site.

HOW SUPPLIED

Vial, 7.5 ml - Product Number 1946-33

STORAGE

Store between 2°-8°C (35°-46°F). DO NOT FREEZE.

REFERENCES

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Lederle

Mfd. by:
CONNAUGHT LABORATORIES, INC.
Swiftwater, PA 18370
Dist. by:
LEDERLE LABORATORIES DIVISION
American Cyanamid Company, Pearl River, N.Y. 10965

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CONNAUGHT

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This product combines diphtheria and tetanus toxoids, adsorbed with pertussis vaccine in a sterile isotonic sodium chloride solution containing sodium phosphate to control pH; each 0.5 ml injection contains not more than 0.25 mg of aluminum added in the form of aluminum potassium sulfate. Thimerosal (mercury derivative) 1:10,000 is added as a preservative. The mixture provides an immunizing dose of each component in the total dosage prescribed below. Each single dose contains 4 protective units of Pertussis Vaccine based on the U.S. Standard Pertussis Vaccine.

INDICATIONS

For active immunization of infants and young children against diphtheria, tetanus and pertussis simultaneously. Injections should be started at 2 to 3 months of age and be completed no later than the age of 6 years. Immunization should always be started at once if whooping cough or diphtheria is present in the community.

CONTRAINDICATIONS

Persons 7 years of age and older should not be immunized with Pertussis Vaccine. Immunization should be deferred during the course of any acute illness, however, a minor illness not associated with fever such as a mild upper respiratory infection need not preclude vaccination. The benefit/risk ratio of routine immunization with this product should be carefully considered by the responsible physician if the child has a personal or family history of central nervous system disease or convulsions.[2] The occurrence of a severe reaction following administration of this product, consisting of high fever (39°C or above), somnolence, screaming, shock, convulsions, encephalopathy or thrombocytopenia, is a contraindication to further use of this vaccine. Anaphylactoid and/or allergic reactions, immunosuppressive therapy, recent gammaglobulin, plasma, or blood transfusions, immunodeficiency disorders, leukemia, lymphoma, or generalized malignancy are also contraindications.[2] Simultaneous administration of DTP with another vaccine should be avoided unless they have been shown to be effective when used together. The clinical judgment of the responsible physician should prevail at all times.
The occurrence of any type of neurological symptoms or signs following administration of this product is an absolute contraindication to further use.
Elective immunization of patients over the age of six months should be deferred during an outbreak of poliomyelitis.

WARNING

This product is not recommended for immunizing persons 7 years of age and older.

The benefit/risk ratio of routine immunization with this product should be carefully considered by the responsible physician if the child has a personal or family history of central nervous system disorders or convulsions.[2] Should any symptomatology related to neurological disorders develop following administration, do not attempt further administration of pertussis antigen. The development of "excessive screaming syndrome" is an absolute contraindication for any further use of pertussis vaccine.
If the vaccine is used in persons receiving immunosuppressive therapy, a recent injection of immune globulin or having an immunodeficiency disorder, the expected antibody response may not be obtained.[2]
Special care should be taken so the injection is not made into a blood vessel.

ADVERSE REACTIONS

Adverse reactions may be local and include pain, erythema, tenderness, heat, edema and induration at the site of injection. Significant reactions attributed to the pertussis vaccine component have been high fever (greater than 39°C), a transient shocklike episode, excessive screaming, somnolence, convulsions, encephalopathy, thrombocytopenia, and hemolytic anemia.[3,4] Such reactions almost always appear within 24 to 48 hours after injection but have been thought to occur after an interval as long as seven days. A small nodule may develop at the site of injection and remain for a few weeks before being completely absorbed. Sterile abcesses have been reported. Systemic reactions include mild to moderate transient fever, chills, malaise, and irritability.
Neurological disorders such as encephalopathy, possibly due to the pertussis component, have been reported to occur rarely following the injection of this product and they may be fatal or result in permanent damage to the central nervous system.
There have been rare reports of Sudden Infant Death Syndrome (crib death) after the administration of DTP Vaccine. However, available data indicate no association between DTP vaccination, in general, and sudden infant death, in particular.[5]
Neurological complications have been reported. These include cochlear lesion,[6] brachial plexus neuropathies,[7,8] paralysis of the radial nerve,[9] paralysis of the recurrent nerve,[10] accommodation paresis, EEG disturbances, and one reported case of swallowing difficulty.[11] In the differential diagnosis of polyradiculoneuropathies following administration of tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[12]

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Should symptomatology referable to the central nervous system develop following administration, no further immunization with this product should be attempted.
The benefit/risk ratio of routine immunization with this product should be carefully considered by the responsible physician for patients with acute infections or a personal or family history of neurological disturbances.[2]
Epinephrine Injection (1:1000) must always be immediately available to combat unexpected anaphylactoid and other allergic reactions.

DOSAGE

SHAKE VIAL WELL *before withdrawing each dose. Product contains a bacterial suspension. Vigorous agitation may be required to resuspend the contents of the vial.*

Primary Immunization[13,14]
For children 2 months through 6 years (ideally beginning at age 2-3 months or at time of a 6-week "check-up").
Give 0.5 ml intramuscularly on three occasions at 4-6 week intervals with a reinforcing dose given approximately one year after the third injection.

Booster Immunization[13,14]
For children between 4 and 6 years of age (preferably at time of school entrance, kindergarten or elementary school), 0.5 ml intramuscularly.
Thereafter, and for all other individuals, booster immunization should be with Tetanus and Diphtheria Toxoids Adsorbed (FOR ADULT USE), at intervals of 10 years. Persons 7 years of age and older should not be immunized with Pertussis Vaccine.

CAUTION

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ADMINISTRATION

Inject deeply into muscle tissue; superficial or subcutaneous injections are more painful. The vastus lateralis (mid-thigh laterally) is the preferred injection site for infants. During the course of primary immunization, inoculations should not be made more than once at the same site.

HOW SUPPLIED

Vial, 7.5 ml

STORAGE

Store between 2°-8°C (35°-46°F). DO NOT FREEZE.

REFERENCES

1. Data available from Connaught Laboratories, Inc.
2. Active Immunization Procedures. Report of the Committee on Infectious Diseases. American Academy of Pediatrics, Evanston, Illinois, p. 9, 13, 1977
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5. Follow-up on DTP vaccination and sudden infant deaths-Tennessee. MMWR 28: 134-135, 1979
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9. Blumstein, G.I., Kreithen, H.: Peripheral neuropathy following tetanus toxoid administration. J.A.M.A. 198: 1030-1031, 1966
10. Eicher, W., Neundorfer, B.: Recurrenslähmung nach Tetanustoxoid—Auffrischimpfung. Munch. med. Wschr. 34: 1692-1695, 1969
11. Harrer, G., Melnizky, U., Wendt, H.: Akkomadationsparese und Schlucklähmung nach Tetanus-Toxoid-Auffrischimpfung. Wien. med. Wschr. 15: 296-297, 1971
12. Schlenska, G.K.: Unusual neurological complications following tetanus toxoid administration, J. Neurol. 215: 209-302, 1977
13. Active Immunization Procedures. Report of the Committee on Infectious Diseases. American Academy of Pediatrics, Evanston, Illinois, p. 3, 1977
14. Advisory Committee on Immunization Practices. Diphtheria and Tetanus Toxoids and Pertussis Vaccine. MMWR 26: 401-402, 1977

Product information as of July, 1980

Manufactured by:
CONNAUGHT LABORATORIES, INC.
Swiftwater, PA 18370, U.S.A.
Dist. in the Continental U.S.A. by:
Elkins-Sinn, Inc.
A subsidiary of A.H. Robins Company
2 Esterbrook Lane
Cherry Hill, NJ 08034, U.S.A.

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CONNAUGHT

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP

FOR PEDIATRIC USE

COMPOSITION/DESCRIPTION

This product combines diphtheria and tetanus toxoids, adsorbed with pertussis vaccine in a sterile isotonic sodium chloride solution containing sodium phosphate to control pH; each 0.5 ml. injection contains not more than 0.25 mg. of aluminum added in the form of aluminum potassium sulfate. 1:10,000 thimerosal (mercury derivative) is added as a preservative. Each total immunizing course supplies one immunizing dose of each agent. Each single dose contains 4 protective units of Pertussis Vaccine based on the U.S. Standard Pertussis Vaccine.

INDICATIONS

For active immunization of infants and young children against diphtheria, tetanus and pertussis simultaneously. Injections should be started at 2 to 3 months of age and be completed no later than the age of 6 years. Immunization should always be started at once if whooping cough or diphtheria is present in the community.

ADMINISTRATION

Inject deeply into muscle tissue; superficial or subcutaneous injections are more painful. The vastus lateralis (mid-thigh laterally) is the preferred injection site for infants. During the course of primary immunization, inoculations should not be made more than once at the same site.

DOSAGE

SHAKE WELL before withdrawing each dose. Product contains a bacterial suspension. Vigorous agitation may be required to resuspend the contents of the vial.

Primary Immunization[1,2]

For children 2 months through 6 years (ideally beginning at age 2-3 months or at time of a 6-week "check-up").

Give 0.5 ml. intramuscularly on three occasions at 4-6 week intervals with a reinforcing dose given approximately one year after the third injection.

Booster Immunization[1,2]

For children between 4 and 6 years of age (preferably at time of school entrance, kindergarten or elementary school), 0.5 ml. intramuscularly.

Thereafter, and for all other individuals, booster immunization should be with Tetanus and Diphtheria Toxoids Adsorbed (FOR ADULT USE), at intervals of 10 years. Children beyond the age of 6 years should not be immunized with Pertussis Vaccine.

CONTRAINDICATIONS

Immunization injections should be deferred during the course of any acute illness. Routine immunization with this product should not be attempted if the child has a personal or family history of central nervous system disease or convulsions.[3] The development of "excessive screaming syndrome" following any inoculation with this product or vaccine containing the pertussis component is an absolute contraindication for further pertussis vaccine. If shock, convulsions, encephalopathy and thrombocytopenia develop after pertussis inoculation and the physician believes they are due to the pertussis antigen, then this represents absolute contraindication to further use of pertussis vaccine. The clinical judgment of the responsible physician should prevail at all times.

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The occurrence of any type of neurological symptoms or signs following administration of this product is an absolute contraindication to further use.

Elective immunization of patients over the age of six months should be deferred during an outbreak of poliomyelitis.

WARNING

This product is not recommended for immunizing persons over six years of age.

Do not attempt routine immunization if the child has a personal or family history of central nervous system disorders or convulsions. Should any symptomatology related to neurological disorders develop following administration do not attempt further administration of pertussis antigen. The development of "excessive screaming syndrome" is an absolute contraindication for any further use of pertussis vaccine.

If the vaccine is used in persons receiving immunosuppressive therapy, the expected antigenic response may not be obtained.

Special care should be taken so the injection is not made into a blood vessel.

CAUTION

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of homologous serum hepatitis or other infectious agents from one person to another.

ADVERSE REACTIONS

Adverse reactions may be local and include pain, erythema, tenderness and induration at the site of injection. Significant reactions attributed to the pertussis vaccine component have been high fever (greater than 39.5°C.), a transient shock-like episode, excessive screaming, somnolence, convulsions, encephalopathy and thrombocytopenia. Such reactions almost always appear within 24 to 48 hours after injection but have been thought to occur after an interval as long as seven days. A small nodule may develop at the site of injection and remain for a few weeks before being completely absorbed. Systemic reactions include mild to moderate transient fever, chills, malaise, and irritability.

Neurological disorders such as encephalopathy, possibly due to the pertussis component, have been reported to occur rarely following the injection of this product and they may be fatal or result in permanent damage to the central nervous system.

Should symptomatology referable to the central nervous system develop following administration no further immunization with pertussis antigen should be attempted.

Routine immunization should be postponed or avoided in patients with acute infections or a personal or family history of neurological disturbances.

Epinephrine injection 1:1000 must always be immediately available to combat unexpected anaphylactoid and other allergic reactions.

SUPPLIED

Vial, 7.5 ml.

STORAGE

Store between 2°-8° C. (35°-46° F.). DO NOT FREEZE.

Product Informatiion as of November, 1977

REFERENCES

1. Active Immunization Procedures. In: Report of the Committee on Infectious Diseases. American Academy of Pediatrics, Evanston, Illinois, 1974, p. 3.
2. Morbidity and Mortality Weekly Reports 21: 1972, (Suppl.).
3. WHO Chron. 29: 365-367, 1975.

Manufactured by:
CONNAUGHT LABORATORIES, INC.
Swiftwater, Pennsylvania 18370, U.S.A.
Distributed by:
Elkins-Sinn, Inc.
2 Esterbrook Lane
Cherry Hill, New Jersey 08034, U.S.A.

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CONNAUGHT

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP

FOR PEDIATRIC USE

SPECIAL NOTICE:[1] *EXPOSURE OF THIS VACCINE TO TEMPERATURES BELOW 2°C (35°F) OR ABOVE 25°C (77°F) FOR AS LITTLE AS 24 HOURS RESULTS IN CONDITIONS WHICH MAKE RESUSPENSION OF THE VACCINE DIFFICULT.*

CARE SHOULD BE TAKEN NOT TO STORE THIS PRODUCT NEAR FREEZING SURFACES. ALWAYS RETURN UNUSED PORTION TO REFRIGERATION, 2°C TO 8°C (35°F to 46°F), IMMEDIATELY AFTER USE.

DO NOT USE IF RESUSPENSION CANNOT BE ACHIEVED BY VIGOROUS SHAKING.

COMPOSITION/DESCRIPTION

This product combines diphtheria and tetanus toxoids, adsorbed with pertussis vaccine in a sterile isotonic sodium chloride solution containing sodium phosphate to control pH; each 0.5 ml injection contains not more than 0.25 mg of aluminum added in the form of aluminum potassium sulfate. 1:10,000 thimerosal (mercury derivative) is added as a preservative. The mixture provides an immunizing dose of each component in the total dosage prescribed below. Each single dose contains 4 protective units of Pertussis Vaccine based on the U.S. Standard Pertussis Vaccine.

INDICATIONS

For active immunization of infants and young children against diphtheria, tetanus and pertussis simultaneously. Injections should be started at 2 to 3 months of age and be completed no later than the age of 6 years. Immunization should always be started at once if whooping cough or diphtheria is present in the community.

ADMINISTRATION

Inject deeply into muscle tissue; superficial or subcutaneous injections are more painful. The vastus lateralis (mid-thigh laterally) is the preferred injection site for infants. During the course of primary immunization, inoculations should not be made more than once at the same site.

DOSAGE

SHAKE WELL before withdrawing each dose. Product contains a bacterial suspension. Vigorous agitation may be required to resuspend the contents of the vial.

Primary Immunization[2, 3]

For children 2 months through 6 years (ideally beginning at age 2-3 months or at time of a 6-week "check-up").

Give 0.5 ml intramuscularly on three occasions at 4-6 week intervals with a reinforcing dose given approximately one year after the third injection.

Booster Immunization[2, 3]

For children between 4 and 6 years of age (preferably at time of school entrance, kindergarten or elementary school), 0.5 ml intramuscularly.

Thereafter, and for all other individuals, booster immunization should be with Tetanus and Diphtheria Toxoids Adsorbed (FOR ADULT USE), at intervals of 10 years. Children beyond the age of 6 years should not be immunized with Pertussis Vaccine.

CONTRAINDICATIONS

Immunization injections should be deferred during the course of any acute illness. Routine immunization with this product should not be attempted if the child has a personal or family history of central nervous system disease or convulsions.[4] The occurrence of a severe reaction following administration of this product, consisting of high fever (39°C or above), somnolence, screaming, shock, convulsions, encephalopathy or thrombocytopenia, is a contraindication to further use of this vaccine. The clinical judgment of the responsible physician should prevail at all times.

The occurrence of any type of neurological symptoms or signs following administration of this product is an absolute contraindication to further use.

Elective immunization of patients over the age of six months should be deferred during an outbreak of poliomyelitis.

WARNING

This product is not recommended for immunizing persons over six years of age.

Do not attempt routine immunization if the child has a personal or family history of central nervous system disorders or convulsions. Should any symptomatology related to neurological disorders develop following administration, do not attempt further administration of pertussis antigen. The development of "excessive screaming syndrome" is an absolute contraindication for any further use of pertussis vaccine.

If the vaccine is used in persons receiving immunosuppressive therapy, the expected antigenic response may not be obtained.

Special care should be taken so the injection is not made into a blood vessel.

CAUTION

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ADVERSE REACTIONS

Adverse reactions may be local and include pain, erythema, tenderness and induration at the site of injection. Significant reactions attributed to the pertussis vaccine component have been high fever (greater than 39°C), a transient shock-like episode, excessive screaming, somnolence, convulsions, encephalopathy and thrombocytopenia. Such reactions almost always appear within 24 to 48 hours after injection but have been thought to occur after an interval as long as seven days. A small nodule may develop at the site of injection and remain for a few weeks before being completely absorbed. Sterile abcesses have been reported. Systemic reactions include mild to moderate transient fever, chills, malaise, and irritability.

Neurological disorders such as encephalopathy, possibly due to the pertussis component, have been reported to occur rarely following the injection of this product and they may be fatal or result in permanent damage to the central nervous system.

Neurological complications following tetanus toxoid administration such as paralysis of the radial nerve,[5] recurrent nerve,[6] cochlear lesion,[7] brachial plexus neuropathies[8, 9] and a case with difficulty in swallowing, accomodation paresis, and EEG disturbances[10] have been reported. In the differential diagnosis of polyradiculoneuropathies following administration of tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[11]

Should symptomatology referable to the central nervous system develop following administration, no further immunization with this product should be attempted.

Routine immunization should be postponed or avoided in patients with acute infections or a personal or family history of neurological disturbances.

Epinephrine Injection (1:1000) must always be immediately available to combat unexpected anaphylactoid and other allergic reactions.

SUPPLIED

Vial, 7.5 ml

STORAGE

Store between 2°-8°C (35°-46°F). DO NOT FREEZE.

REFERENCES

1. Data available from Connaught Laboratories, Inc.
2. Active Immunization Procedures. Report of the Committee on Infectious Diseases. American Academy of Pediatrics, Evanston, Illinois, p. 3, 1977
3. Morbidity and Mortality Weekly Report 26: 401-402, 1977
4. WHO Chron. 29: 365-367, 1975
5. Blumstein, G. I., Kreithen, H.: Peripheral neuropathy following tetanus toxoid administration. J.A.M.A. 198: 1030-1031, 1966
6. Eicher, W., Neundörfer, B.: Recurrenslähmung nach Tetanustoxoid—Auffrischimpfung. Munch. med. Wschr. 34:1692-1695, 1969
7. Wirth, G.: Reversible Kochlearisschädigung nach Tetanol-Injektion. Münch. med. Wschr. 107: 379-381, 1965
8. Gersbach, P., Waridel, D.: Paralysis après prévention antitétanique. Schweiz. med. Wschr. 106: 150-153, 1976
9. Tsairis, P., Duck, P.J., Mulder, D. W.: Natural history of brachial plexus neuropathy. Arch. Neurol. 27: 109-117, 1972
10. Harrer, G., Melnizky, U., Wendt, H.: Akkomadationsparese und Schlucklähmung nach Tetanus-Toxoid-Auffrischimpfung. Wien. med. Wschr. 15: 296-297, 1971
11. Schlenska, G. K.: Unusual neurological complications following tetanus toxoid administration, J. Neurol. 215: 209-302, 1977

Product Information as of November, 1978

Manufactured by:
CONNAUGHT LABORATORIES, INC.
Swiftwater, PA 18370, U.S.A.
Dist. in the Continental U.S.A. by:
Elkins-Sinn, Inc.
2 Esterbrook Lane
Cherry Hill, NJ 08034, U.S.A.

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This vaccine is recommended for children 6 weeks through 6 years of age (up to the seventh birthday) ideally beginning when the infant is 6 weeks to 2 months of age in accordance with the following schedules indicated in Table 2.[2]

TABLE 2.[2] Routine diphtheria, tetanus, and pertussis immunizati... ...dule summary for children under 7 years old - United States, 1985*

Dose	Age/Interval†	Product
Primary 1	6 weeks old or older	DTP† ¶
Primary 2	4-8 weeks after first dose§	DTP ¶
Primary 3	4-8 weeks after second dose§	DTP ¶
Primary 4	6-12 months after third dose§	DTP ¶
Booster	4-6 years old, before entering kindergarten or elementary school (not necessary if fourth primary immunizing dose administered on or after fourth birthday)	DTP ¶
Additional boosters	Every 10 years after last dose	Td

* Important details are in the text.
† Customarily begun at 8 weeks of age, with second and third doses given at 8-week intervals.
§ Prolonging the interval dose does not require restarting series.
¶ DT, if pertussis vaccine is contraindicated. If the child is 1 year of age or older at the time the primary dose is given, a third dose 6-12 months after the second completes primary immunization with DT.

Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.

HOW SUPPLIED

Vial, 7.5 ml - Product No. 49281-280-84

STORAGE

Store between 2° - 8°C (35° - 46°F). DO NOT FREEZE. Temperature extremes may adversely affect resuspendability of this vaccine.

REFERENCES

1. Code of Federal Regulations, 21CFR620.4 (g), 1985
2. Recommendation of the Immunization Practices Advisory Committee. Diphtheria, Tetanus, and Pertussis: Guidelines for vaccine prophylaxis and other preventive measures. MMWR 34: 405-426, 1985
3. Manclark, C.R., et al: Pertussis. In R. Germanier (ed), Bacterial Vaccines Academic Press Inc., NY 69-106, 1984
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18. Fenichel, G.M., Neurological complications of immunization. Ann Neurol 12: 119-128, 1982
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20. Tsairis, P., et al: Natural history of brachial plexus neuropathy. Arch Neurol 27: 109-117, 1972
21. Blumstein, G.I., et al: Peripheral neuropathy following Tetanus toxoid administration. JAMA 198: 1030-1031, 1966
22. Schlenska, G.K.: Unusual neurological complications following tetanus toxoid administration. J Neurol 215: 299-302, 1977

Manufactured by:
CONNAUGHT LABORATORIES, INC.
Swiftwater, PA 18370, U.S.A.

Product information as of July, 1986

Printed in U.S.A.
0906

CONNAUGHT

A.H.F.S. Category 80:08

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE)

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

DESCRIPTION

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP, for intramuscular use, combines diphtheria and tetanus toxoids, adsorbed with pertussis vaccine in a sterile isotonic sodium chloride solution containing sodium phosphate to control pH; each 0.5 ml injection contains not more than 0.25 mg of aluminum added in the form of aluminum potassium sulfate. Thimerosal (mercury derivative) 1:10,000 is added as a preservative. The vaccine, in suspension, is a turbid liquid, whitish in color. Each single dose of 0.5 ml is formulated to contain 6.7 Lf units of diphtheria toxoid and 5 Lf units of tetanus toxoid. The total human immunizing dose (the first three 0.5 ml doses given) contains an estimate of 12 units of pertussis vaccine.[1] Each component of the vaccine - diphtheria, tetanus and pertussis - meets the required potency standards.

CLINICAL PHARMACOLOGY

Simultaneous immunization against diphtheria, tetanus, and pertussis during infancy and childhood has been a routine practice in the United States since the late 1940s. This practice has played a major role in markedly reducing the incidence rates of cases and deaths from each of these diseases.[2]

DIPHTHERIA

Cornyebacterium diphtheriae may cause both a localized and a generalized disease. The systemic intoxication is caused by diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C. diphtheriae*.

At one time, diphtheria was common in the United States. More than 200,000 cases, primarily among children, were reported in 1921. Approximately 5%-10% of cases were fatal; the highest case-fatality ratios were in the very young and the elderly. Reported cases of diphtheria of all types declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state. After 1979, cutaneous diphtheria was no longer reportable. From 1980 to 1983, only 15 cases of respiratory diphtheria were reported; 11 occurred among persons 20 years of age or older.[2]

The current rarity of diphtheria in the United States is due primarily to the high level of appropriate immunization among children (96% of children entering school have received three or more doses of Diphtheria and Tetanus Toxoids and Pertussis Vaccine [DTP]) and to an apparent reduction of the circulation of toxigenic strains of *C. diphtheriae*. Most cases occur among unimmunized or inadequately immunized persons. The age distribution of recent cases and the results of serosurveys indicate that many adults in the United States are not protected against diphtheria. Thus, it appears that in addition to continuing to immunize children more emphasis should be placed on adult immunization programs.[2]

Both toxigenic and non-toxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce toxin cause myocarditis and neuritis. Furthermore, toxigenic strains are more often associated with severe or fatal illness in noncutaneous (respiratory or other mucosal surface) infections and are more commonly recovered from respiratory than from cutaneous infections.[2]

C. diphtheriae can contaminate the skin of certain individuals, usually at the site of a wound. Although a sharply demarcated lesion with a pseudomembraneous base often results, the appearance may not be distinctive and the infection can be confirmed only by culture. Usually other bacterial species can also be isolated. Cutaneous diphtheria has most commonly affected indigent adults and certain groups of Native Americans.[2]

Complete immunization significantly reduces the risk of developing diphtheria, and immunized persons who develop disease have milder illnesses. Protection is thought to last at least 10 years. Immunization does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nose or on the skin.[2]

TETANUS

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*.

The occurrence of tetanus in the United States has decreased markedly because of the routine use of tetanus toxoid immunization. Nevertheless, the number of reported cases has remained relatively constant in the last decade at an annual average of 90 cases. In 1983, 91 tetanus cases were reported from 29 states. In recent years, approximately two-thirds of patients have been 50 years of age or older. The age distribution of recent cases and the results of serosurveys indicate that many United States adults are not protected against tetanus. The disease has occurred almost exclusively among persons who are unimmunized or inadequately immunized or whose immunization histories are unknown or uncertain.[2]

In 6% of tetanus cases reported during 1982 and 1983, no wound or other condition could be implicated. Nonacute skin lesions, such as ulcers, or medical conditions, such as abscesses, were reported in 17% of cases.[2]

Spores of *C. tetani* are ubiquitous. Serological tests indicate that naturally acquired immunity to tetanus toxin does not occur in the United States. Thus, universal primary immunization, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect all age groups. Tetanus toxoid is a highly effective antigen, and a completed primary series generally induces protective levels of serum antitoxin that persist for 10 or more years.[2]

PERTUSSIS

Pertussis is a disease of the respiratory tract caused by *Bordetella pertussis*. This gram-negative coccobacillus produces a variety of biologically active components which have been associated with a number of effects such as lymphocystosis, leukocytosis, sensitivity to histamine, changes in glucose and/or insulin levels, neurological effects, and adjuvant activity.[3] The role of each of the different components in either the pathogenesis of or the immunity to pertussis is not well understood.

General use of standardized pertussis vaccine has resulted in a substantial reduction in cases and deaths from pertussis disease. However, the annual number of reported cases has changed relatively little during the last 10 years, when annual averages of 1,835 cases and 10 fatalities have occurred. In 1983, 2,463 cases were reported; in 1981, the latest year for which final national mortality statistics are available from the National Center for Health Statistics, six deaths were recorded. More precise data do not exist, since many cases go unrecognized or unreported, and diagnostic tests for *B. pertussis* - culture and direct-immunofluorescence assay (DFA) - may be unavailable, difficult to perform, or incorrectly interpreted.[2]

For 1982 and 1983, 53% of reported illnesses from *B. pertussis* occurred among children under 1 year of age and 78% in children less than 5 years of age; 13 of 15 deaths reported to the Centers for Disease Control (CDC) occurred in children less than 1 year old. Before widespread use of DTP, about 20% of cases and 50% of pertussis-related deaths occurred among children less than 1 year old.[2]

Pertussis is highly communicable (attack rates of over 90% have been reported for unimmunized household contacts) and can cause severe disease, particularly in very young children. Of patients under 1 year of age reported to CDC during 1982 and 1983, 75% were hospitalized; approximately 22% had pneumonia; 2% had one or more seizures; and 0.7% died. Because of the substantial risks of complications of the disease, completion of a primary series of DTP early in life is recommended.[2]

In older children and adults, including in some instances those previously immunized, infection may result in nonspecific symptoms of bronchitis or an upper respiratory tract infection, and pertussis may not be diagnosed because classic signs, especially the inspiratory whoop, may be absent. Older preschool-aged children and school-aged siblings who are not fully immunized and develop pertussis can be important sources of infection for young infants, the group at highest risk of disease and disease severity. The importance of the infected adult in overall transmission remains to be defined.[2]

Controversy regarding use of pertussis vaccine led to a formal reevaluation of the benefits and risks of this vaccine. The analysis indicated that the benefits of the vaccine continue to outweigh its risks.[3,4]

Because the incidence and severity of pertussis decrease with age and because the vaccine may cause side effects and adverse reactions, pertussis immunization is not recommended for children after their seventh birthday.[1]

Evidence of the efficacy of pertussis vaccine can be provided by the recent British experience, where a reduction in the number of immunized individuals from 79% in 1973, to 31% in 1978 was associated with an epidemic of 102,500 pertussis cases and 36 deaths between late 1977 and 1980, and 1,440 cases per week reported during the winter of 1981-1982.[3] A similar situation occurred in Japan.[5,6]

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The appropriate age for immunization of prematurely born infants is uncertain. Available data indicate that immunization with DTP is recommended to begin at a chronological age of 2 m[illegible],[3,4]

As with any vaccine, vaccination with DTP may not protect 100% of susce[illegible]individuals.

INDICATIONS AND USAGE

For active immunization of infants and children to age 7 years against diphtheria, tetanus and pertussis (whooping cough) simultaneously. DTP is recommended for primary immunization of infants and children up to 7 years of age. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.

CONTRAINDICATIONS

Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.

Absolute contraindications:[1]

1. Allergic hypersensitivity to any component of the vaccine.
2. Fever of 40.5°C (105°F) or greater within 48 hours.
3. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
4. Persisting, inconsolable crying lasting 3 hours or more or an unusual, high-pitched cry occurring within 48 hours.
5. Convulsion(s) with or without fever occurring within 7 days.
6. Encephalopathy occurring within 7 days; this includes severe alterations in consciousness with generalized or focal neurologic signs.

The presence of a neurologic condition characterized by changing developmental or neurologic findings, regardless of whether a definitive diagnosis has been made, is also considered *an absolute contraindication* to receipt of pertussis vaccine, because administration of DTP may coincide with or possibly even aggravate manifestations of the disease. Such disorders include uncontrolled epilepsy, infantile spasms, and progressive encephalopathy.[2]

Use of this product is also contraindicated if the child has a personal or family history of a seizure disorder. However, the ACIP does not accept family histories of convulsions or other central nervous system disorders as contraindications to pertussis vaccination.[2]

IT IS ALSO A CONTRAINDICATION TO ADMINISTER DTP TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL. IN ANY CASE, EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.[4]

WARNINGS

This vaccine must NOT be used for immunizing persons 7 years of age and older.

IMMUNIZATION SHOULD BE DEFERRED DURING THE COURSE OF ANY ACUTE ILLNESS. THE OCCURRENCE OF ANY TYPE OF NEUROLOGICAL SYMPTOMS OR SIGNS, INCLUDING ONE OR MORE CONVULSIONS (SEIZURES) FOLLOWING ADMINISTRATION OF THIS PRODUCT IS *AN ABSOLUTE CONTRAINDICATION* TO FURTHER USE. USE OF THIS PRODUCT IS ALSO CONTRAINDICATED IF THE CHILD HAS A PERSONAL OR FAMILY HISTORY OF A SEIZURE DISORDER.

THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A CONTRAINDICATION TO ADMINISTRATION OF DTP REGARDLESS OF WHETHER THE SUSPECTED NEUROLOGICAL DISORDER IS ASSOCIATED WITH OCCURRENCE OF SEIZURE ACTIVITY OF ANY TYPE.

The administration of DTP to children with proven or suspected underlying neurologic disorders, must be decided on an individual basis.

The ACIP recommends the following:

1. **Infants as yet unimmunized who are suspected of having underlying neurologic disease.** Possible latent central nervous system disorders that are suspected because of perinatal complications or other phenomena may become evident as they evolve over time. Because DTP administration may coincide with onset of overt manifestations of such disorders and result in confusion about causation, it is prudent to delay initiation of immunization with DTP or DT (but not OPV) until further observation and study have clarified the child's neurologic status. In addition, the effect of treatment, if any, can be assessed. The decision whether to commence immunization with DTP or DT should be made no later than the child's first birthday. In making this decision, it should be recognized that children with severe neurologic disorders may be at enhanced risk of exposure to pertussis from institutionalization or from attendance at clinics and special schools in which many of the children may be unimmunized. In addition, because of neurologic handicaps, these children may be in greater jeopardy from complications of the disease.[2]
2. **Infants and children with neurologic events temporally associated with DTP.** Infants and children who experience a seizure within 3 days of receipt of DTP or an encephalopathy within 7 days should not receive further pertussis vaccine, even though cause and effect may not be established (see CONTRAINDICATIONS).[1]
3. **Incompletely immunized children with neurologic events occurring between doses.** Infants and children who have received one or more doses of DTP and who experience a neurologic disorder, e.g., a seizure, temporally unassociated with the administration of vaccine but before the next scheduled dose, present a special problem. If the seizure or other disorder occurs before the first birthday and completion of the first three doses of the primary series of DTP, deferral of further doses of DTP or DT (but not OPV) is recommended until the infant's status has been clarified. The decision whether to use DTP or DT to complete the series should be made no later than the child's first birthday and should take into consideration the nature of the child's problem and the benefits and risks of the vaccine. If the seizure or other disorder occurs after the first birthday, the child's neurologic status should be evaluated to ensure the disorder is stable before a subsequent dose of DTP is given.[2]
4. **Infants and children with stable neurologic conditions.** Infants and children with stable neurologic conditions, including well-controlled seizures, may be vaccinated. The occurrence of single seizures (temporally unassociated with DTP) in infants and young children, while necessitating evaluation, need not contraindicate DTP immunization, particularly if the seizures can be satisfactorily explained.[2]
5. **Children with resolved or corrected neurologic disorders.** DTP administration is recommended for infants with certain neurologic problems that have clearly subsided without residua or have been corrected, such as neonatal hypocalcemic tetany or hydrocephalus (following placement of a shunt and without seizures).[2]

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (less than 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for one month;[16] otherwise, the patient should be vaccinated while still on therapy.[2]

If Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (DTP) has been administered to persons receiving immunosuppressive therapy, a recent injection of immune globulin or having an immunodeficiency disorder, an adequate immunologic response may not be obtained.

DTP should not be given to infants or children with any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

The simultaneous administration of DTP, oral polio virus vaccine (OPV), and/or measles-mumps-rubella vaccine (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately.[2,16] Therefore, if there is any doubt that a vaccine recipient will return for further vaccine doses, the ACIP recommends the simultaneous administration of all vaccines appropriate to the age and previous vaccination status of the recipient. This would especially include the simultaneous administration of DTP, OPV, and MMR to such persons at 15 months of age or older.[2]

PRECAUTIONS

GENERAL

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent side reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines (see CONTRAINDICATIONS), and a current knowledge of the literature concerning the use of the vaccine under consideration.

The vial of vaccine should be vigorously shaken to ensure a proper suspension of the antigen and adjuvant.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

PEDIATRIC USE

THIS VACCINE IS RECOMMENDED FOR IMMUNIZING CHILDREN 6 WEEKS THROUGH 6 YEARS (UP TO THE SEVENTH BIRTHDAY) OF AGE ONLY. Do NOT administer to persons 7 years of age and older.

INFORMATION FOR PATIENT

Parents should be fully informed of the benefits and risks of immunization with DTP.

Prior to administration of any dose of DTP, the parent or guardian should be asked about the recent health status of the infant or child to be injected.

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The physician should inform the parents or guardian about the significant adverse reactions that need to be monitored.

As part of the infant's or child's immuni[illegible]record, informed consent should be obtained and recorded. The lot number and manufacturer of the vaccin[illegible]istered should be recorded in the event of the occurrence of any symptoms and/or signs of an adverse re[illegible]on. Vaccine information sheets are available from the CDC or the State Health Department which may serve as guidelines.

WHEN AN INFANT OR CHILD IS RETURNED FOR THE NEXT DOSE IN THE SERIES, THE PARENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER PREVIOUS DOSE (see CONTRAINDICATIONS; ADVERSE REACTIONS).

ADVERSE REACTIONS

Not all adverse events following administration of DTP are causally related to DTP vaccine.

Adverse reactions which may be local and include pain, erythema, heat, edema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria, tetanus, or pertussis antigens. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses.[11] However, these observations were not noted by Barkin, R.M., et al.[12] Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6-10 per million doses).

Mild systemic reactions, such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following DTP than following DT, are usually self-limited, and need no therapy other than, perhaps, symptomatic treatment (e.g., antipyretics).[2] Rash, allergic reactions, and respiratory difficulties, including apnea, have been observed.

Moderate to severe systemic events, such as fever of 40.5°C (105°F) or higher, persistent, inconsolable crying lasting 3 hours or more, unusual high-pitched crying, collapse, or convulsions, occur relatively infrequently. More severe neurologic complications, such as a prolonged convulsion or an encephalopathy, occasionally fatal, have been reported to be associated with DTP administration.[2]

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in Table 1.[3,13,14]

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent.[13] If local redness of 2.5 cm or greater occurs, the likelihood of recurrence after another DTP dose increases significantly.[11]

In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England,[14] children 2-35 months of age with serious, acute neurologic disorders, such as encephalopathy or complicated convulsion(s), were more likely to have received DTP in the 7 days preceding onset than their age-, sex-, and neighborhood-matched controls. Among children known to be neurologically normal before entering the study, the relative risk (estimated by odds ratio) of a neurologic illness occurring within the 7-day period following receipt of DTP dose, compared to children not receiving DTP vaccine in the 7-day period before onset of their illness, was 3.3 ($p < 0.001$). Within this 7-day period, the risk was significantly increased for immunized children only within 3 days of vaccination (relative risk 4.2, $p < 0.001$). The relative risk for illness occurring 4-7 days after vaccination was 2.1 ($0.05 < p < 0.1$). The attributable risk estimates for a serious acute neurologic disorder within 7 days after DTP vaccine (regardless of outcome) was one in 110,000 doses of DTP, and for a permanent neurologic deficit, one in 310,000 doses. No specific clinical syndrome was identified. Overall, DTP vaccine accounted for only a small proportion of cases of serious neurologic disorders reported in the population studied.[2]

Although there are uncertainties in the reported studies, recent data suggest that infants and young children who have had previous convulsions (whether febrile or nonfebrile) are more likely to have seizures following DTP than those without such histories.[2,15]

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[2]

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid, particularly in adults who have received frequent (e.g., annual) boosters of tetanus toxoid. A few cases of peripheral neuropathy have been reported following tetanus toxoid administration, although a causal relationship has not been established.[2]

Sudden infant death syndrome (SIDS) has occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS.[18] It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2-6 months old and that approximately 85% of SIDS cases occur at ages 1-6 months, with the peak incidence occurring at 6 weeks-4 months of age. By chance alone, some SIDS victims can be expected to have recently received vaccine.[2]

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DTP or DT was not causally related to infantile spasms.[17] The incidence of onset of infantile spasms increases at 3-9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.[2]

TABLE 1.[3] Adverse events occurring within 48 hours of DTP immunizations

Event	Frequency*
Local	
Redness	1/3 doses
Swelling	2/5 doses
Pain	1/2 doses
Mild/moderate systemic	
Fever > 38°C (100.4°F)	1/2 doses
Drowsiness	1/3 doses
Fretfulness	1/2 doses
Vomiting	1/15 doses
Anorexia	1/5 doses
More serious systemic	
Persistent, inconsolable crying (duration ≥ 3 hours)	1/100 doses
High-pitched, unusual cry	1/900 doses
Fever ≥ 40.5°C (≥ 105°F)	1/330 doses
Collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,750 doses
Acute encephalopathy†	1/110,000 doses
Permanent neurologic deficit†	1/310,000 doses

*Number of adverse events per total number of doses regardless of dose number in DTP series.
†Occurring within 7 days of DTP immunization.

Reporting of Adverse Events

Reporting by parents and patients of all adverse events occurring within 4 weeks of antigen administration should be encouraged. Adverse events that require a visit to a health-care provider should be reported by health-care providers to manufacturers and local or state health departments. The information will be forwarded to an appropriate federal agency (the Office of Biologics Research and Review, FDA, or CDC).[2]

The following illnesses have been reported as temporally associated with the vaccine; neurological complications[18] including cochlear lesion,[19] brachial plexus neuropathies,[19,20] paralysis of the radial nerve,[21] paralysis of the recurrent nerve,[16] accommodation paresis, and EEG disturbances with encephalopathy.[13] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[22]

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, vaccine should not be administered.

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

SHAKE VIAL WELL *before withdrawing each dose. Vaccine contains a bacterial suspension. Vigorous agitation is required to resuspend the contents of the vial.*

Inject 0.5 ml intramuscularly. The vastus lateralis (mid-thigh laterally) is the preferred injection site for infants. The gluteus maximus should be avoided due to the potential for damage to the sciatic nerve. During the course of primary immunization, injections should not be made more than once at the same site.

Do NOT administer this product subcutaneously. Special care should be taken to ensure that the injection does not enter a blood vessel.

CONNAUGHT
A PASTEUR MÉRIEUX COMPANY

A.H.F.S. Category 80:08

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE)

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

DESCRIPTION

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP, for intramuscular use, combines diphtheria and tetanus toxoids, adsorbed with pertussis vaccine in a sterile isotonic sodium chloride solution containing sodium phosphate to control pH; each 0.5 ml injection contains not more than 0.25 mg of aluminum added in the form of aluminum potassium sulfate. Thimerosal (mercury derivative) 1:10,000 is added as a preservative. The vaccine, in suspension, is a turbid liquid, whitish in color. Each single dose of 0.5 ml is formulated to contain 6.7 Lf units of diphtheria toxoid and 5 Lf units of tetanus toxoid. The total human immunizing dose (the first three 0.5 ml doses given) contains an estimate of 12 units of pertussis vaccine.[1] Each component of the vaccine - diphtheria, tetanus and pertussis - meets the required potency standards.

CLINICAL PHARMACOLOGY

Simultaneous immunization against diphtheria, tetanus, and pertussis during infancy and childhood has been a routine practice in the United States since the late 1940s. This practice has played a major role in markedly reducing the incidence rates of cases and deaths from each of these diseases.[2]

DIPHTHERIA

Cornyebacterium diphtheriae may cause both a localized and a generalized disease. The systemic intoxication is caused by diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C. diphtheriae*.

At one time, diphtheria was common in the United States. More than 200,000 cases, primarily among children, were reported in 1921. Approximately 5% - 10% of cases were fatal; the highest case-fatality ratios were in the very young and the elderly. Reported cases of diphtheria of all types declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state. After 1979, cutaneous diphtheria was no longer reportable. From 1980 to 1983, only 15 cases of respiratory diphtheria were reported; 11 occurred among persons 20 years of age or older.[2]

The current rarity of diphtheria in the United States is due primarily to the high level of appropriate immunization among children (96% of children entering school have received three or more doses of Diphtheria and Tetanus Toxoids and Pertussis Vaccine [DTP]) and to an apparent reduction of the circulation of toxigenic strains of *C. diphtheriae*. Most cases occur among unimmunized or inadequately immunized persons. The age distribution of recent cases and the results of serosurveys indicate that many adults in the United States are not protected against diphtheria. Thus, it appears that in addition to continuing to immunize children more emphasis should be placed on adult immunization programs.[2]

Both toxigenic and non-toxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce toxin cause myocarditis and neuritis. Furthermore, toxigenic strains are more often associated with severe or fatal illness in noncutaneous (respiratory or other mucosal surface) infections and are more commonly recovered from respiratory than from cutaneous infections.[2]

C. diphtheriae can contaminate the skin of certain individuals, usually at the site of a wound. Although a sharply demarcated lesion with a pseudomembraneous base often results, the appearance may not be distinctive and the infection can be confirmed only by culture. Usually other bacterial species can also be isolated. Cutaneous diphtheria has most commonly affected indigent adults and certain groups of Native Americans.[2]

Complete immunization significantly reduces the risk of developing diphtheria, and immunized persons who develop disease have milder illnesses. Protection is thought to last at least 10 years. Immunization does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nose or on the skin.[2]

TETANUS

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*.

The occurrence of tetanus in the United States has decreased markedly because of the routine use of tetanus toxoid immunization. Nevertheless, the number of reported cases has remained relatively constant in the last decade at an annual average of 90 cases. In 1983, 91 tetanus cases were reported from 29 states. In recent years, approximately two-thirds of patients have been 50 years of age or older. The age distribution of recent cases and the results of serosurveys indicate that many United States adults are not protected against tetanus. The disease has occurred almost exclusively among persons who are unimmunized or inadequately immunized or whose immunization histories are unknown or uncertain.[2]

In 6% of tetanus cases reported during 1982 and 1983, no wound or other condition could be implicated. Non-acute skin lesions, such as ulcers, or medical conditions, such as abscesses, were reported in 17% of cases.[2]

Spores of *C. tetani* are ubiquitous. Serological tests indicate that naturally acquired immunity to tetanus toxin does not occur in the United States. Thus, universal primary immunization, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect all age groups. Tetanus toxoid is a highly effective antigen, and a completed primary series generally induces protective levels of serum antitoxin that persist for 10 or more years.[2]

PERTUSSIS

Pertussis is a disease of the respiratory tract caused by *Bordetella pertussis*. This gram-negative coccobacillus produces a variety of biologically active components which have been associated with a number of effects such as lymphocytosis, leukocytosis, sensitivity to histamine, changes in glucose and/or insulin levels, neurological effects, and adjuvant activity.[3] The role of each of the different components in either the pathogenesis of or the immunity to pertussis is not well understood.

General use of standardized pertussis vaccine has resulted in a substantial reduction in cases and deaths from pertussis disease. However, the annual number of reported cases has changed relatively little during the last 10 years, when annual averages of 1,835 cases and 10 fatalities have occurred. In 1983, 2,463 cases were reported; in 1981, the latest year for which final national mortality statistics are available from the National Center for Health Statistics, six deaths were recorded. More precise data do not exist, since many cases go unrecognized or unreported, and diagnostic tests for *B. pertussis* - culture and direct-immunofluorescence assay (DFA) - may be unavailable, difficult to perform, or incorrectly interpreted.[2]

For 1982 and 1983, 53% of reported illnesses from *B. pertussis* occurred among children under 1 year of age and 78% in children less than 5 years of age; 13 of 15 deaths reported to the Centers for Disease Control (CDC) occurred in children less than 1 year old. Before widespread use of DTP, about 20% of cases and 50% of pertussis-related deaths occurred among children less than 1 year old.[2]

Pertussis is highly communicable (attack rates of over 90% have been reported for unimmunized household contacts) and can cause severe disease, particularly in very young children. Of patients under 1 year of age reported to CDC during 1982 and 1983, 75% were hospitalized; approximately 22% had pneumonia; 2% had one or more seizures; and 0.7% died. Because of the substantial risks of complications of the disease, completion of a primary series of DTP early in life is recommended.[2]

In older children and adults, including in some instances those previously immunized, infection may result in nonspecific symptoms of bronchitis or an upper respiratory tract infection, and pertussis may not be diagnosed because classic signs, especially the inspiratory whoop, may be absent. Older preschool-aged children and school-aged siblings who are not fully immunized and develop pertussis can be important sources of infection for young infants, the group at highest risk of disease and disease severity. The importance of the infected adult in overall transmission remains to be defined.[2]

Controversy regarding use of pertussis vaccine led to a formal reevaluation of the benefits and risks of this vaccine. The analysis indicated that the benefits of the vaccine continue to outweigh its risks.[2,4]

Because the incidence and severity of pertussis decrease with age and because the vaccine may cause side effects and adverse reactions, pertussis immunization is not recommended for children after their seventh birthday.[2]

Evidence of the efficacy of pertussis vaccine can be provided by the recent British experience, where a reduction in the number of immunized individuals from 79% in 1973, to 31% in 1978 was associated with an epidemic of 102,500 pertussis cases and 36 deaths between late 1977 and 1980, and 1,440 cases per week reported during the winter of 1981-1982.[3] A similar situation occurred in Japan.[5,6]

The appropriate age for immunization of prematurely born infants is uncertain. Available data indicate that immunization with pertussis is recommended to begin at a chronological age of 2 months.[7,8]

As with any vaccine, vaccination with DTP may not protect 100% of susceptible individuals.

INDICATIONS AND USAGE

For active immunization of infants and children to age 7 years against diphtheria, tetanus and pertussis (whooping cough) simultaneously. DTP is recommended for primary immunization of infants and children up to 7 years of age. However, in places where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.

CONTRAINDICATIONS

Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.

Absolute contraindications: [2]

1. Allergic hypersensitivity to any component of the vaccine.

DTP should not be given [illegible] or children with any coagulation disorder that would contraindicate intramuscular injection unless the potential ben[illegible]ly outweighs the risk of administration.

The simultaneous administration of DTP, oral polio virus vaccine (OPV), and/or measles-mumps-rubella vaccine (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately.[2,10] Therefore, if there is any doubt that a vaccine recipient will return for further vaccine doses, the ACIP recommends the simultaneous administration of all vaccines appropriate to the age and previous vaccination status of the recipient. This would especially include the simultaneous administration of DTP, OPV, and MMR to such persons at 15 months of age or older.[2]

PRECAUTIONS

GENERAL

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylatic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent side reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines (see CONTRAINDICATIONS), and a current knowledge of the literature concerning the use of the vaccine under consideration.

The vial of vaccine should be vigorously shaken to ensure a proper suspension of the antigen and adjuvant.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

PEDIATRIC USE

THIS VACCINE IS RECOMMENDED FOR IMMUNIZING CHILDREN 6 WEEKS THROUGH 6 YEARS (UP TO THE SEVENTH BIRTHDAY) OF AGE ONLY. Do NOT administer to persons 7 years of age and older.

INFORMATION FOR PATIENT

Parents should be fully informed of the benefits and risks of immunization with DTP.

Prior to administration of any dose of DTP, the parent or guardian should be asked about the recent health status of the infant or child to be injected.

The physician should inform the parents or guardian about the significant adverse reactions that need to be monitored.

As part of the infant's or child's immunization record, informed consent should be obtained and recorded. The lot number and manufacturer of the vaccine administered should be recorded in the event of the occurrence of any symptoms and/or signs of an adverse reaction. Vaccine information sheets are available from the CDC or the State Health Department which may serve as guidelines.

WHEN AN INFANT OR CHILD IS RETURNED FOR THE NEXT DOSE IN THE SERIES, THE PARENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER PREVIOUS DOSE (see CONTRAINDICATIONS; ADVERSE REACTIONS).

ADVERSE REACTIONS

Not all adverse events following administration of DTP are causally related to DTP vaccine.

Adverse reactions which may be local and include pain, erythema, heat, edema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria, tetanus, or pertussis antigens. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses.[11] However, these observations were not noted by Barkin, R.M., et al.[12] Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6-10 per million doses).

Mild systemic reactions, such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following DTP than following DT, are usually self-limited, and need no therapy other than, perhaps, symptomatic treatment (e.g., antipyretics).[2] Rash, allergic reactions, and respiratory difficulties, including apnea, have been observed.

Moderate to severe systemic events, such as fever of 40.5°C (105°F) or higher, persistent, inconsolable crying lasting 3 hours or more, unusual high-pitched crying, collapse, or convulsions, occur relatively infrequently. More severe neurologic complications, such as a prolonged convulsion or an encephalopathy, occasionally fatal, have been reported to be associated with DTP administration.[2]

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in Table 1.[2,13,14]

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent.[13] If local redness of 2.5 cm or greater occurs, the likelihood of recurrence after another DTP dose increases significantly.[11]

In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England,[14] children 2 - 35 months of age with serious, acute neurologic disorders, such as encephalopathy or complicated convulsion(s), were more likely to have received DTP in the 7 days preceding onset than their age-, sex-, and neighborhood-matched controls. Among children known to be neurologically normal before entering the study, the relative risk (estimated by odds ratio) of a neurologic illness occurring within the 7-day period following receipt of DTP dose, compared to children not receiving DTP vaccine in the 7-day period before onset of their illness, was 3.3 ($p < 0.001$). Within this 7-day period, the risk was significantly increased for immunized children only within 3 days of vaccination (relative risk 4.2, $p < 0.001$). The relative risk for illness occurring 4 - 7 days after vaccination was 2.1 ($0.05 < p < 0.1$). The attributable risk estimates for a serious acute neurologic disorder within 7 days after DTP vaccine (regardless of outcome) was one in 110,000 doses of DTP, and for a permanent neurologic deficit, one in 310,000 doses. No specific clinical syndrome was identified. Overall, DTP vaccine accounted for only a small proportion of cases of serious neurologic disorders reported in the population studied.[2]

Although there are uncertainties in the reported studies, recent data suggest that infants and young children who have had previous convulsions (whether febrile or nonfebrile) are more likely to have seizures following DTP than those without such histories.[2,15]

Rarely, an anaphylatic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[2]

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2 - 8 hours after an injection), may follow receipt of tetanus toxoid, particularly in adults who have received frequent (e.g., annual) boosters of tetanus toxoid. A few cases of peripheral neuropathy have been reported following tetanus toxoid administration, although a causal relationship has not been established.[2]

Sudden infant death syndrome (SIDS) has occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS.[16] It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2 - 6 months old and that approximately 85% of SIDS cases occur at ages 1 - 6 months, with the peak incidence occurring at 6 weeks-4 months of age. By chance alone, some SIDS victims can be expected to have recently received vaccine.[2]

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DTP or DT was not causally related to infantile spasms.[17] The incidence of onset of infantile spasms increases at 3 - 9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.[2]

TABLE 1.[2] Adverse events occurring within 48 hours of DTP immunizations

Event	Frequency*
Local	
Redness	1/3 doses
Swelling	2/5 doses
Pain	1/2 doses
Mild/moderate systemic	
Fever > 38°C (100.4°F)	1/2 doses
Drowsiness	1/3 doses
Fretfulness	1/2 doses
Vomiting	1/15 doses
Anorexia	1/5 doses
More serious systemic	
Persistent, inconsolable crying (duration ≥3 hours)	1/100 doses
High-pitched, unusual cry	1/900 doses
Fever ≥40.5°C (≥105°F)	1/330 doses
Collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,750 doses
Acute encephalopathy†	1/110,000 doses
Permanent neurologic deficit†	1/310,000 doses

* Number of adverse events per total number of doses regardless of dose number in DTP series.
† Occurring within 7 days of DTP immunization.

Reporting of Adverse Events

Reporting by parents and patients of all adverse events occurring within 4 weeks of antigen administration should be encouraged. Adverse events that require a visit to a health-care provider should be reported by health-care providers to manufacturers and local or state health departments. The information will be forwarded to an appropriate federal agency (the Office of Biologics Research and Review, FDA, or CDC).[2]

The following illnesses have been reported as temporally associated with the vaccine; neurological complications[18] including cochlear lesion,[18] brachial plexus neuropathies,[19,20] paralysis of the radial nerve,[21] paralysis of the recurrent nerve,[19] accommodation paresis, and EEG disturbances with encephalopathy.[13] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[22]

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, vaccine should not be administered.

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylatic reaction occur due to any component of the vaccine.

3. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
4. Persisting, inconsolable crying lasting 3 hours or more or an unusual, high-pitched cry occurring within 48 hours.
5. Convulsion(s) with or without fever occurring within 7 days.
6. Encephalopathy occurring within 7 days; this includes severe alterations in consciousness with generalized or focal neurologic signs.

The presence of a neurologic condition characterized by changing developmental or neurologic findings, regardless of whether a definitive diagnosis has been made, is also considered *an absolute contraindication* to receipt of pertussis vaccine, because administration of DTP may coincide with or possibly even aggravate manifestations of the disease. Such disorders include uncontrolled epilepsy, infantile spasms, and progressive encephalopathy.[2]

Use of this product is also contraindicated if the child has a personal or family history of a seizure disorder. However, the ACIP does not accept family histories of convulsions or other central nervous system disorders as contraindications to pertussis vaccination.[2]

IT IS ALSO A CONTRAINDICATION TO ADMINISTER DTP TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL. IN ANY CASE, EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.[9]

WARNINGS

This vaccine must NOT be used for immunizing persons 7 years of age and older.

IMMUNIZATION SHOULD BE DEFERRED DURING THE COURSE OF ANY ACUTE ILLNESS. THE OCCURRENCE OF ANY TYPE OF NEUROLOGICAL SYMPTOMS OR SIGNS, INCLUDING ONE OR MORE CONVULSIONS (SEIZURES) FOLLOWING ADMINISTRATION OF THIS PRODUCT IS *AN ABSOLUTE CONTRAINDICATION* TO FURTHER USE. USE OF THIS PRODUCT IS ALSO CONTRAINDICATED IF THE CHILD HAS A PERSONAL OR FAMILY HISTORY OF A SEIZURE DISORDER.

THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A CONTRAINDICATION TO ADMINISTRATION OF DTP REGARDLESS OF WHETHER THE SUSPECTED NEUROLOGICAL DISORDER IS ASSOCIATED WITH OCCURRENCE OF SEIZURE ACTIVITY OF ANY TYPE.

The administration of DTP to children with proven or suspected underlying neurologic disorders, must be decided on an individual basis.

The ACIP recommends the following:

1. **Infants as yet unimmunized who are suspected of having underlying neurologic disease.** Possible latent central nervous system disorders that are suspected because of perinatal complications or other phenomena may become evident as they evolve over time. Because DTP administration may coincide with onset of overt manifestations of such disorders and result in confusion about causation, it is prudent to delay initiation of immunization with DTP or DT (but not OPV) until further observation and study have clarified the child's neurologic status. In addition, the effect of treatment, if any, can be assessed. The decision whether to commence immunization with DTP or DT should be made no later than the child's first birthday. In making this decision, it should be recognized that children with severe neurologic disorders may be at enhanced risk of exposure to pertussis from institutionalization or from attendance at clinics and special schools in which many of the children may be unimmunized. In addition, because of neurologic handicaps, these children may be in greater jeopardy from complications of the disease.[2]
2. **Infants and children with neurologic events temporally associated with DTP.** Infants and children who experience a seizure within 3 days of receipt of DTP or an encephalopathy within 7 days should not receive further pertussis vaccine, even though cause and effect may not be established (see CONTRAINDICATIONS).[2]
3. **Incompletely immunized children with neurologic events occurring between doses.** Infants and children who have received one or more doses of DTP and who experience a neurologic disorder, e.g., a seizure, temporally unassociated with the administration of vaccine but before the next scheduled dose, present a special problem. If the seizure or other disorder occurs before the first birthday and completion of the first three doses of the primary series of DTP, deferral of further doses of DTP or DT (but not OPV) is recommended until the infant's status has been clarified. The decision whether to use DTP or DT to complete the series should be made no later than the child's first birthday and should take into consideration the nature of the child's problem and the benefits and risks of the vaccine. If the seizure or other disorder occurs after the first birthday, the child's neurologic status should be evaluated to ensure the disorder is stable before a subsequent dose of DTP is given.[2]
4. **Infants and children with stable neurologic conditions.** Infants and children with stable neurologic conditions, including well-controlled seizures, may be vaccinated. The occurrence of single seizures (temporally unassociated with DTP) in infants and young children, while necessitating evaluation, need not contraindicate DTP immunization, particularly if the seizures can be satisfactorily explained.[2]
5. **Children with resolved or corrected neurologic disorders.** DTP administration is recommended for infants with certain neurologic problems that have clearly subsided without residua or have been corrected, such as neonatal hypocalcemic tetany or hydrocephalus (following placement of a shunt and without seizures).[2]

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (less than 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.[2]

If Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (DTP) has been administered to persons receiving immunosuppressive therapy, a recent injection of immune globulin or having an immunodeficiency disorder, an adequate immunologic response may not be obtained.

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to resuspend the contents of the vial.

Inject 0.5 ml intramuscularly. The vastus lateralis (mid-thigh laterally) is the preferred injection site for infants. The gluteus maximus should be avoided due to the potential for damage to the sciatic nerve. During the course of primary immunization, injections should not be made more than once at the same site.

Do NOT administer this product subcutaneously. Special care should be taken to ensure that the injection does not enter a blood vessel.

This vaccine is recommended for children 6 weeks through 6 years of age (up to the seventh birthday) ideally beginning when the infant is 6 weeks to 2 months of age in accordance with the following schedules indicated in Table 2.[2]

TABLE 2.[2] Routine diphtheria, tetanus, and pertussis immunization schedule summary for children under 7 years old - United States, 1985*

Dose	Age/Interval†	Product
Primary 1	6 weeks old or older	DTP†¶
Primary 2	4-8 weeks after first dose§	DTP ¶
Primary 3	4-8 weeks after second dose§	DTP ¶
Primary 4	6-12 months after third dose§	DTP ¶
Booster	4-6 years old, before entering kindergarten or elementary school (not necessary if fourth primary immunizing dose administered on or after fourth birthday)	DTP ¶
Additional boosters	Every 10 years after last dose	Td

* Important details are in the text.
† Customarily begun at 8 weeks of age, with second and third doses given at 8-week intervals.
§ Prolonging the interval dose does not require restarting series.
¶ DT, if pertussis vaccine is contraindicated. If the child is 1 year of age or older at the time the primary dose is given, a third dose 6-12 months after the second completes primary immunization with DT.

Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.

HOW SUPPLIED

Vial, 5 ml - Product No. 49281-280-10
Vial, 7.5 ml - Product No. 49281-280-84

STORAGE

Store between 2° — 8°C (35° — 46°F). DO NOT FREEZE. Temperature extremes may adversely affect resuspendability of this vaccine.

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CONNAUGHT LABORATORIES, INC.
Swiftwater, Pennsylvania 18370, U.S.A.

CONNAUGHT
A PASTEUR MÉRIEUX COMPANY

A.H.F.S. Category 80:08

...PHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE)

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

DESCRIPTION

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP, for intramuscular use, combines diphtheria and tetanus toxoids, adsorbed with pertussis vaccine in a sterile isotonic sodium chloride solution containing sodium phosphate to control pH; each 0.5 ml injection contains not more than 0.25 mg of aluminum added in the form of aluminum potassium sulfate. Thimerosal (mercury derivative) 1:10,000 is added as a preservative. The vaccine, in suspension, is a turbid liquid, whitish in color. Each single dose of 0.5 ml is formulated to contain 6.7 Lf units of diphtheria toxoid and 5 Lf units of tetanus toxoid. The total human immunizing dose (the first three 0.5 ml doses given) contains an estimate of 12 units of pertussis vaccine.[1] Each component of the vaccine - diphtheria, tetanus and pertussis - meets the required potency standards.

CLINICAL PHARMACOLOGY

Simultaneous immunization against diphtheria, tetanus, and pertussis during infancy and childhood has been a routine practice in the United States since the late 1940s. This practice has played a major role in markedly reducing the incidence rates of cases and deaths from each of these diseases.[2]

DIPHTHERIA

Cornyebacterium diphtheriae may cause both a localized and a generalized disease. The systemic intoxication is caused by diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C. diphtheriae*.

At one time, diphtheria was common in the United States. More than 200,000 cases, primarily among children, were reported in 1921. Approximately 5% - 10% of cases were fatal; the highest case-fatality ratios were in the very young and the elderly. Reported cases of diphtheria of all types declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state. After 1979, cutaneous diphtheria was no longer reportable. From 1980 to 1983, only 15 cases of respiratory diphtheria were reported; 11 occurred among persons 20 years of age or older.[2]

The current rarity of diphtheria in the United States is due primarily to the high level of appropriate immunization among children (96% of children entering school have received three or more doses of Diphtheria and Tetanus Toxoids and Pertussis Vaccine [DTP]) and to an apparent reduction of the circulation of toxigenic strains of *C. diphtheriae*. Most cases occur among unimmunized or inadequately immunized persons. The age distribution of recent cases and the results of serosurveys indicate that many adults in the United States are not protected against diphtheria. Thus, it appears that in addition to continuing to immunize children more emphasis should be placed on adult immunization programs.[2]

Both toxigenic and non-toxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce toxin cause myocarditis and neuritis. Furthermore, toxigenic strains are more often associated with severe or fatal illness in noncutaneous (respiratory or other mucosal surface) infections and are more commonly recovered from respiratory than from cutaneous infections.[2]

C. diphtheriae can contaminate the skin of certain individuals, usually at the site of a wound. Although a sharply demarcated lesion with a pseudomembraneous base often results, the appearance may not be distinctive and the infection can be confirmed only by culture. Usually other bacterial species can also be isolated. Cutaneous diphtheria has most commonly affected indigent adults and certain groups of Native Americans.[2]

...mplete immunization significantly reduces the risk of developing diphtheria, and immunized persons who develop disease ... milder illnesses. Protection is thought to last at least 10 years. Immunization does not, however, eliminate carriage of ...*diphtheriae* in the pharynx or nose or on the skin.[2]

TETANUS

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*.

The occurrence of tetanus in the United States has decreased markedly because of the routine use of tetanus toxoid immunization. Nevertheless, the number of reported cases has remained relatively constant in the last decade at an annual average of 90 cases. In 1983, 91 tetanus cases were reported from 29 states. In recent years, approximately two-thirds of patients have been 50 years of age or older. The age distribution of recent cases and the results of serosurveys indicate that many United States adults are not protected against tetanus. The disease has occurred almost exclusively among persons who are unimmunized or inadequately immunized or whose immunization histories are unknown or uncertain.[2]

In 6% of tetanus cases reported during 1982 and 1983, no wound or other condition could be implicated. Non-acute skin lesions, such as ulcers, or medical conditions, such as abscesses, were reported in 17% of cases.[2]

Spores of *C. tetani* are ubiquitous. Serological tests indicate that naturally acquired immunity to tetanus toxin does not occur in the United States. Thus, universal primary immunization, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect all age groups. Tetanus toxoid is a highly effective antigen, and a completed primary series generally induces protective levels of serum antitoxin that persist for 10 or more years.[2]

PERTUSSIS

Pertussis is a disease of the respiratory tract caused by *Bordetella pertussis*. This gram-negative coccobacillus produces a variety of biologically active components which have been associated with a number of effects such as lymphocytosis, leukocytosis, sensitivity to histamine, changes in glucose and/or insulin levels, neurological effects, and adjuvant activity.[3] The role of each of the different components in either the pathogenesis of or the immunity to pertussis is not well understood.

General use of standardized pertussis vaccine has resulted in a substantial reduction in cases and deaths from pertussis disease. However, the annual number of reported cases has changed relatively little during the last 10 years, when annual averages of 1,835 cases and 10 fatalities have occurred. In 1983, 2,463 cases were reported; in 1981, the latest year for which final national mortality statistics are available from the National Center for Health Statistics, six deaths were recorded. More precise data do not exist, since many cases go unrecognized or unreported, and diagnostic tests for *B. pertussis* - culture and direct-immunofluorescence assay (DFA) - may be unavailable, difficult to perform, or incorrectly interpreted.[2]

For 1982 and 1983, 53% of reported illnesses from *B. pertussis* occurred among children under 1 year of age and 78% in children less than 5 years of age; 13 of 15 deaths reported to the Centers for Disease Control (CDC) occurred in children less than 1 year old. Before widespread use of DTP, about 20% of cases and 50% of pertussis-related deaths occurred among children less than 1 year old.[2]

Pertussis is highly communicable (attack rates of over 90% have been reported for unimmunized household contacts) and can cause severe disease, particularly in very young children. Of patients under 1 year of age reported to CDC during 1982 and 1983, 75% were hospitalized; approximately 22% had pneumonia; 2% had one or more seizures; and 0.7% died. Because of the substantial risks of complications of the disease, completion of a primary series of DTP early in life is recommended.[2]

In older children and adults, including in some instances those previously immunized, infection may result in nonspecific symptoms of bronchitis or an upper respiratory tract infection, and pertussis may not be diagnosed because classic signs, especially the inspiratory whoop, may be absent. Older preschool-aged children and school-aged siblings who are not fully immunized and develop pertussis can be important sources of infection for young infants, the group at highest risk of disease and disease severity. The importance of the infected adult in overall transmission remains to be defined.[2]

Controversy regarding use of pertussis vaccine led to a formal reevaluation of the benefits and risks of this vaccine. The analysis indicated that the benefits of the vaccine continue to outweigh its risks.[2,4]

Because the incidence and severity of pertussis decrease with age and because the vaccine may cause side effects and adverse reactions, pertussis immunization is not recommended for children after their seventh birthday.[2]

Evidence of the efficacy of pertussis vaccine can be provided by the recent British experience, where a reduction in the number of immunized individuals from 79% in 1973, to 31% in 1978 was associated with an epidemic of 102,500 pertussis ...ases and 36 deaths between late 1977 and 1980, and 1,440 cases per week reported during the winter of 1981-1982.[3] A similar ...tion occurred in Japan.[5,6]

...propriate age for immunization of prematurely born infants is uncertain. Available data indicate that immunization with ...is recommended to begin at a chronological age of 2 months.[7,8]

As with any vaccine, vaccination with DTP may not protect 100% of susceptible individuals.

INDICATIONS AND USAGE

For active immunization of infants and children to age 7 years against diphtheria, tetanus and pertussis (whooping cough); ...ltaneously. DTP is recommended for primary immunization of infants and children up to 7 years of age. However, in ...ces where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine ...t to be administered, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) should be used. Immunization should ...e started at 6 weeks to 2 months of age and be completed before the seventh birthday.

CONTRAINDICATIONS

Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.

Absolute contraindications: [2]

1. Allergic hypersensitivity to any component of the vaccine.
2. Fever of 40.5°C (105°F) or greater within 48 hours.
3. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
4. Persisting, inconsolable crying lasting 3 hours or more or an unusual, high-pitched cry occurring within 48 hours.
5. Convulsion(s) with or without fever occurring within 7 days.
6. Encephalopathy occurring within 7 days; this includes severe alterations in consciousness with generalized or focal neurologic signs.

The presence of a neurologic condition characterized by changing developmental or neurologic findings, regardless of whether a definitive diagnosis has been made, is also considered *an absolute contraindication* to receipt of pertussis vaccine, because administration of DTP may coincide with or possibly even aggravate manifestations of the disease. Such disorders include uncontrolled epilepsy, infantile spasms, and progressive encephalopathy.[2]

Use of this product is also contraindicated if the child has a personal or family history of a seizure disorder. However, the ACIP does not accept family histories of convulsions or other central nervous system disorders as contraindications to pertussis vaccination.[2]

IT IS ALSO A CONTRAINDICATION TO ADMINISTER DTP TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL. IN ANY CASE, EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.[9]

WARNINGS

This vaccine must NOT be used for immunizing persons 7 years of age and older.

IMMUNIZATION SHOULD BE DEFERRED DURING THE COURSE OF ANY ACUTE ILLNESS. THE OCCURRENCE OF ANY TYPE OF NEUROLOGICAL SYMPTOMS OR SIGNS, INCLUDING ONE OR MORE CONVULSIONS (SEIZURES) FOLLOWING ADMINISTRATION OF THIS PRODUCT IS *AN ABSOLUTE CONTRAINDICATION* TO FURTHER USE. USE OF THIS PRODUCT IS ALSO CONTRAINDICATED IF THE CHILD HAS A PERSONAL OR FAMILY HISTORY OF A SEIZURE DISORDER.

THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A CONTRAINDICATION TO ADMINISTRATION OF DTP REGARDLESS OF WHETHER THE SUSPECTED NEUROLOGICAL DISORDER IS ASSOCIATED WITH OCCURRENCE OF SEIZURE ACTIVITY OF ANY TYPE.

The administration of DTP to children with proven or suspected underlying neurologic disorders, must be decided on an individual basis.

The ACIP recommends the following:

1. **Infants as yet unimmunized who are suspected of having underlying neurologic disease.** Possible latent central nervous system disorders that are suspected because of perinatal complications or other phenomena may become evident as they evolve over time. Because DTP administration may coincide with onset of overt manifestations of such disorders and result in confusion about causation, it is prudent to [illegible] not OPV...

DTP should not be given to infants or children with any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

The simultaneous administration of DTP, oral polio virus vaccine (OPV), and/or measles-mumps-rubella vaccine (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately.[2,10] Therefore, if there is any doubt that a vaccine recipient will return for further vaccine doses, the ACIP recommends the simultaneous administration of all vaccines appropriate to the age and previous vaccination status of the recipient. This would especially include the simultaneous administration of DTP, OPV, and MMR to such persons at 15 months of age or older.[2]

PRECAUTIONS

GENERAL

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylatic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent side reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines (see CONTRAINDICATIONS), and a current knowledge of the literature concerning the use of the vaccine under consideration.

The vial of vaccine should be vigorously shaken to ensure a proper suspension of the antigen and adjuvant.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

PEDIATRIC USE

THIS VACCINE IS RECOMMENDED FOR IMMUNIZING CHILDREN 6 WEEKS THROUGH 6 YEARS (UP TO THE SEVENTH BIRTHDAY) OF AGE ONLY. Do NOT administer to persons 7 years of age and older.

INFORMATION FOR PATIENT

Parents should be fully informed of the benefits and risks of immunization with DTP.

Prior to administration of any dose of DTP, the parent or guardian should be asked about the recent health status of the infant or child to be injected.

The physician should inform the parents or guardian about the significant adverse reactions that need to be monitored.

As part of the infant's or child's immunization record, informed consent should be obtained and recorded. The lot number and manufacturer of the vaccine administered should be recorded in the event of the occurrence of any symptoms and/or signs of an adverse reaction. Vaccine information sheets are available from the CDC or the State Health Department which may serve as guidelines.

WHEN AN INFANT OR CHILD IS RETURNED FOR THE NEXT DOSE IN THE SERIES, THE PARENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER PREVIOUS DOSE (see CONTRAINDICATIONS; ADVERSE REACTIONS).

ADVERSE REACTIONS

Not all adverse events following administration of DTP are causally related to DTP vaccine.

Adverse reactions which may be local and include pain, erythema, heat, edema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria, tetanus, or pertussis antigens. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses.[11] However, these observations were not noted by Barkin, R.M., et al.[12] Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6-10 per million doses).

Mild systemic reactions, such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following DTP than following DT, are usually self-limited, and need no therapy other than, perhaps, symptomatic treatment (e.g., antipyretics).[2] Rash, allergic reactions, and respiratory difficulties, including apnea, have been observed.

Moderate to severe systemic events, such as fever of 40.5°C (105°F) or higher, persistent, inconsolable crying lasting 3 hours or more, unusual high-pitched crying, collapse, or convulsions, occur relatively infrequently. More severe neurologic complications, such as a prolonged convulsion or an encephalopathy, occasionally fatal, have been reported to be associated with DTP administration.[2]

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in Table 1.[2,13,14]

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent.[13] If local redness of 2.5 cm or greater occurs, the likelihood of recurrence after another DTP dose increases significantly.[11]

In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England,[14] children 2 - 35 months of age with serious, acute neurologic disorders, such as encephalopathy or complicated convulsion(s), were more likely to have received DTP in the 7 days preceding onset than their age-, sex-, and neighborhood-matched controls. Among children known to be neurologically normal before entering the study, the relative risk (estimated by odds ratio) of a neurologic illness occurring within the 7-day period following receipt of DTP dose, compared to children not receiving DTP vaccine in the 7-day period before onset of their illness, was 3.3 ($p < 0.001$). Within this 7-day period, the risk was significantly increased for immunized children only within 3 days of vaccination (relative risk 4.2, $p < 0.001$). The relative risk for illness occurring 4 - 7 days after vaccination was 2.1 ($0.05 < p < 0.1$). The attributable risk estimates for a serious acute neurologic disorder within 7 days after DTP vaccine (regardless of outcome) was one in 110,000 doses of DTP, and for a permanent neurologic deficit, one in 310,000 doses. No specific clinical syndrome was identified. Overall, DTP vaccine accounted for only a small proportion of cases of serious neurologic disorders reported in the population studied.[2]

Although there are uncertainties in the reported studies, recent data suggest that infants and young children who have had previous convulsions (whether febrile or nonfebrile) are more likely to have seizures following DTP than those without such histories.[2,15]

Rarely, an anaphylatic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[2]

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2 - 8 hours after an injection), may follow receipt of tetanus toxoid, particularly in adults who have received frequent (e.g., annual) boosters of tetanus toxoid. A few cases of peripheral neuropathy have been reported following tetanus toxoid administration, although a causal relationship has not been established.[2]

Sudden infant death syndrome (SIDS) has occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS.[16] It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2 - 6 months old and that approximately 85% of SIDS cases occur at ages 1 - 6 months, with the peak incidence occurring at 6 weeks-4 months of age. By chance alone, some SIDS victims can be expected to have recently received vaccine.[2]

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DTP or DT was not causally related to infantile spasms.[17] The incidence of onset of infantile spasms increases at 3 - 9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.[2]

TABLE 1.[2] Adverse events occurring within 48 hours of DTP immunizations

Event	Frequency*
Local	
Redness	1/3 doses
Swelling	2/5 doses
Pain	1/2 doses
Mild/moderate systemic	
Fever > 38°C (100.4°F)	1/2 doses
Drowsiness	1/3 doses
Fretfulness	1/2 doses
Vomiting	1/15 doses
Anorexia	1/5 doses
More serious systemic	
Persistent, inconsolable crying (duration ≥3 hours)	1/100 doses
High-pitched, unusual cry	1/900 doses
Fever ≥40.5°C (≥105°F)	1/330 doses
Collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,750 doses
Acute encephalopathy†	1/110,000 doses
Permanent neurologic deficit†	1/310,000 doses

* Number of adverse events per total number of doses regardless of dose number in DTP series.
† Occurring within 7 days of DTP immunization.

Reporting of Adverse Events

Reporting by parents and patients of all adverse events occurring within 4 weeks of antigen administration should be encouraged. Adverse events that require a visit to a health-care provider should be reported by health-care providers to manufacturers and local or state health departments. The information will be forwarded to an appropriate federal agency (the Office of Biologics Research and Review, FDA, or CDC).[2]

The following illnesses have been reported as temporally associated with the vaccine; neurological complications[18] including cochlear lesion,[19] brachial plexus neuropathies,[19,20] paralysis of the radial nerve,[21] paralysis of the recurrent nerve,[19] accommodation paresis, and EEG disturbances with encephalopathy.[13] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[22]

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, vaccine should not be administered.

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylatic reaction occur due to any component of the vaccine.

SHAKE VIAL WELL *before withdrawing each dose. Vaccine contains a bacterial suspension. Vigorous agitation is required to resuspend the contents of the vial.*

Inject 0.5 ml intramuscularly. The vastus lateralis (mid-thigh laterally) is the preferred injection site for infants. The gluteus maximus should be avoided due to the potential for damage to the sciatic nerve. During the course of primary immunization, injections should not be made more than once at the same site.

Do NOT administer this product subcutaneously. Special care should be taken to ensure that the injection does not enter a blood vessel.

This vaccine is recommended for children 6 weeks through 6 years of age (up to the seventh birthday) ideally beginning when the infant is 6 weeks to 2 months of age in accordance with the following schedules indicated in Table 2.[2]

TABLE 2.[2] Routine diphtheria, tetanus, and pertussis immunization schedule summary for children under 7 years old - United States, 1985*

Dose	Age/Interval†	Product
Primary 1	6 weeks old or older	DTP†¶
Primary 2	4-8 weeks after first dose§	DTP ¶
Primary 3	4-8 weeks after second dose§	DTP ¶
Primary 4	6-12 months after third dose§	DTP ¶
Booster	4-6 years old, before entering kindergarten or elementary school (not necessary if fourth primary immunizing dose administered on or after fourth birthday)	DTP ¶
Additional boosters	Every 10 years after last dose	Td

* Important details are in the text.
† Customarily begun at 8 weeks of age, with second and third doses given at 8-week intervals.
§ Prolonging the interval dose does not require restarting series.
¶ DT, if pertussis vaccine is contraindicated. If the child is 1 year of age or older at the time the primary dose is given, a third dose 6-12 months after the second completes primary immunization with DT.

Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.

HOW SUPPLIED

Vial, 5 ml - Product No. 49281-280-10
Vial, 7.5 ml - Product No. 49281-280-84

CONNAUGHT
A PASTEUR MÉRIEUX COMPANY

A.H.F.S. Category 80:08

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE)

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

DESCRIPTION

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP, for intramuscular use, combines diphtheria and tetanus toxoids, adsorbed with pertussis vaccine in a sterile isotonic sodium chloride solution containing sodium phosphate to control pH; each 0.5 ml injection contains not more than 0.25 mg of aluminum added in the form of aluminum potassium sulfate. Thimerosal (mercury derivative) 1:10,000 is added as a preservative. The vaccine, in suspension, is a turbid liquid, whitish in color. Each single dose of 0.5 ml is formulated to contain 6.7 Lf units of diphtheria toxoid and 5 Lf units of tetanus toxoid. The total human immunizing dose (the first three 0.5 ml doses given) contains an estimate of 12 units of pertussis vaccine.[1] Each component of the vaccine - diphtheria, tetanus and pertussis - meets the required potency standards.

CLINICAL PHARMACOLOGY

Simultaneous immunization against diphtheria, tetanus, and pertussis during infancy and childhood has been a routine practice in the United States since the late 1940s. This practice has played a major role in markedly reducing the incidence rates of cases and deaths from each of these diseases.[2]

DIPHTHERIA

Cornyebacterium diphtheriae may cause both a localized and a generalized disease. The systemic intoxication is caused by diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C. diphtheriae*.

At one time, diphtheria was common in the United States. More than 200,000 cases, primarily among children, were reported in 1921. Approximately 5% - 10% of cases were fatal; the highest case-fatality ratios were in the very young and the elderly. Reported cases of diphtheria of all types declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state. After 1979, cutaneous diphtheria was no longer reportable. From 1980 to 1983, only 15 cases of respiratory diphtheria were reported; 11 occurred among persons 20 years of age or older.[2]

The current rarity of diphtheria in the United States is due primarily to the high level of appropriate immunization among children (96% of children entering school have received three or more doses of Diphtheria and Tetanus Toxoids and Pertussis Vaccine [DTP]) and to an apparent reduction of the circulation of toxigenic strains of *C. diphtheriae*. Most cases occur among unimmunized or inadequately immunized persons. The age distribution of recent cases and the results of serosurveys indicate that many adults in the United States are not protected against diphtheria. Thus, it appears that in addition to continuing to immunize children more emphasis should be placed on adult immunization programs.[2]

Both toxigenic and non-toxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce toxin cause myocarditis and neuritis. Furthermore, toxigenic strains are more often associated with severe or fatal illness in noncutaneous (respiratory or other mucosal surface) infections and are more commonly recovered from respiratory than from cutaneous infections.[2]

C. diphtheriae can contaminate the skin of certain individuals, usually at the site of a wound. Although a sharply demarcated lesion with a pseudomembraneous base often results, the appearance may not be distinctive and the infection can be confirmed only by culture. Usually other bacterial species can also be isolated. Cutaneous diphtheria has most commonly affected indigent adults and certain groups of Native Americans.[2]

Complete immunization significantly reduces the risk of developing diphtheria, and immunized persons who develop disease usually have milder illnesses. Protection is thought to last at least 10 years. Immunization does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nose or on the skin.[2]

TETANUS

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*.

The occurrence of tetanus in the United States has decreased markedly because of the routine use of tetanus toxoid immunization. Nevertheless, the number of reported cases has remained relatively constant in the last decade at an annual average of 90 cases. In 1983, 91 tetanus cases were reported from 29 states. In recent years, approximately two-thirds of patients have been 50 years of age or older. The age distribution of recent cases and the results of serosurveys indicate that many United States adults are not protected against tetanus. The disease has occurred almost exclusively among persons who are unimmunized or inadequately immunized or whose immunization histories are unknown or uncertain.[2]

In 6% of tetanus cases reported during 1982 and 1983, no wound or other condition could be implicated. Non-acute skin lesions, such as ulcers, or medical conditions, such as abscesses, were reported in 17% of cases.[2]

Spores of *C. tetani* are ubiquitous. Serological tests indicate that naturally acquired immunity to tetanus toxin does not occur in the United States. Thus, universal primary immunization, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect all age groups. Tetanus toxoid is a highly effective antigen, and a completed primary series generally induces protective levels of serum antitoxin that persist for 10 or more years.[2]

PERTUSSIS

Pertussis is a disease of the respiratory tract caused by *Bordetella pertussis*. This gram-negative coccobacillus produces a variety of biologically active components which have been associated with a number of effects such as lymphocytosis, leukocytosis, sensitivity to histamine, changes in glucose and/or insulin levels, neurological effects, and adjuvant activity.[3] The role of each of the different components in either the pathogenesis of or the immunity to pertussis is not well understood.

General use of standardized pertussis vaccine has resulted in a substantial reduction in cases and deaths from pertussis disease. However, the annual number of reported cases has changed relatively little during the last 10 years, when annual averages of 1,835 cases and 10 fatalities have occurred. In 1983, 2,463 cases were reported; in 1981, the latest year for which final national mortality statistics are available from the National Center for Health Statistics, six deaths were recorded. More precise data do not exist, since many cases go unrecognized or unreported, and diagnostic tests for *B. pertussis* - culture and direct-immunofluorescence assay (DFA) - may be unavailable, difficult to perform, or incorrectly interpreted.[2]

For 1982 and 1983, 53% of reported illnesses from *B. pertussis* occurred among children under 1 year of age and 78% in children less than 5 years of age; 13 of 15 deaths reported to the Centers for Disease Control (CDC) occurred in children less than 1 year old. Before widespread use of DTP, about 20% of cases and 50% of pertussis-related deaths occurred among children less than 1 year old.[2]

Pertussis is highly communicable (attack rates of over 90% have been reported for unimmunized household contacts) and can cause severe disease, particularly in very young children. Of patients under 1 year of age reported to CDC during 1982 and 1983, 75% were hospitalized; approximately 22% had pneumonia; 2% had one or more seizures; and 0.7% died. Because of the substantial risks of complications of the disease, completion of a primary series of DTP early in life is recommended.[2]

In older children and adults, including in some instances those previously immunized, infection may result in nonspecific symptoms of bronchitis or an upper respiratory tract infection, and pertussis may not be diagnosed because classic signs, especially the inspiratory whoop, may be absent. Older preschool-aged children and school-aged siblings who are not fully immunized and develop pertussis can be important sources of infection for young infants, the group at highest risk of disease and disease severity. The importance of the infected adult in overall transmission remains to be defined.[2]

Controversy regarding use of pertussis vaccine led to a formal reevaluation of the benefits and risks of this vaccine. The analysis indicated that the benefits of the vaccine continue to outweigh its risks.[2,4]

Because the incidence and severity of pertussis decrease with age and because the vaccine may cause side effects and adverse reactions, pertussis immunization is not recommended for children after their seventh birthday.[2]

Evidence of the efficacy of pertussis vaccine can be provided by the recent British experience, where a reduction in the number of immunized individuals from 79% in 1973, to 31% in 1978 was associated with an epidemic of 102,500 pertussis cases and 36 deaths between late 1977 and 1980, and 1,440 cases per week reported during the winter of 1981-1982.[3] A similar situation occurred in Japan.[5,6]

The appropriate age for immunization of prematurely born infants is uncertain. Available data indicate that immunization with DTP is recommended to begin at a chronological age of 2 months.[7,8]

As with any vaccine, vaccination with DTP may not protect 100% of susceptible individuals.

INDICATIONS AND USAGE

For active immunization of infants and children to age 7 years against diphtheria, tetanus and pertussis (whooping cough), simultaneously. DTP is recommended for primary immunization of infants and children up to 7 years of age. However, in cases where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.

CONTRAINDICATIONS

Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.

Absolute contraindications: [2]

1. Allergic hypersensitivity to any component of the vaccine.
2. Fever of 40.5°C (105°F) or greater within 48 hours.
3. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
4. Persisting, inconsolable crying lasting 3 hours or more or an unusual, high-pitched cry occurring within 48 hours.
5. Convulsion(s) with or without fever occurring within 7 days.
6. Encephalopathy occurring within 7 days; this includes severe alterations in consciousness with generalized or focal neurologic signs.

The presence of a neurologic condition characterized by changing developmental or neurologic findings, regardless of whether a definitive diagnosis has been made, is also considered *an absolute contraindication* to receipt of pertussis vaccine, because administration of DTP may coincide with or possibly even aggravate manifestations of the disease. Such disorders include uncontrolled epilepsy, infantile spasms, and progressive encephalopathy.[2]

Use of this product is also contraindicated if the child has a personal or family history of a seizure disorder. However, the ACIP does not accept family histories of convulsions or other central nervous system disorders as contraindications to pertussis vaccination.[2]

IT IS ALSO A CONTRAINDICATION TO ADMINISTER DTP TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL. IN ANY CASE, EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.[9]

WARNINGS

This vaccine must NOT be used for immunizing persons 7 years of age and older.

IMMUNIZATION SHOULD BE DEFERRED DURING THE COURSE OF ANY ACUTE ILLNESS. THE OCCURRENCE OF ANY TYPE OF NEUROLOGICAL SYMPTOMS OR SIGNS, INCLUDING ONE OR MORE CONVULSIONS (SEIZURES) FOLLOWING ADMINISTRATION OF THIS PRODUCT IS *AN ABSOLUTE CONTRAINDICATION* TO FURTHER USE. USE OF THIS PRODUCT IS ALSO CONTRAINDICATED IF THE CHILD HAS A PERSONAL OR FAMILY HISTORY OF A SEIZURE DISORDER.

THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A CONTRAINDICATION TO ADMINISTRATION OF DTP REGARDLESS OF WHETHER THE SUSPECTED NEUROLOGICAL DISORDER IS ASSOCIATED WITH OCCURRENCE OF SEIZURE ACTIVITY OF ANY TYPE.

The administration of DTP to children with proven or suspected underlying neurologic disorders, must be decided on an individual basis.

The ACIP recommends the following:

1. **Infants as yet unimmunized who are suspected of having underlying neurologic disease.** Possible latent central nervous system disorders that are suspected because of perinatal complications or other phenomena may become evident as they evolve over time. Because DTP administration may coincide with onset of overt manifestations of such disorders and result in confusion about causation, it is prudent to delay initiation of immunization with DTP or DT (but not OPV) until further observation and study have clarified the child's neurologic status. In addition, the effect of treatment, if any, can be assessed. The decision whether to commence immunization with DTP or DT should be made no later than the child's first birthday. In making this decision, it should be recognized that children with severe neurologic disorders may be at enhanced risk of exposure to pertussis from institutionalization or from attendance at clinics and special schools in which many of the children may be unimmunized. In addition, because of neurologic handicaps, these children may be in greater jeopardy from complications of the disease.[2]

   Infants and children with neurologic events temporally associated with DTP. Infants and children who experience a seizure within 3 days of receipt of DTP or an encephalopathy within 7 days should not receive further pertussis vaccine, even though cause and effect may not be established (see CONTRAINDICATIONS).[2]

2. **Incompletely immunized children with neurologic events occurring between doses.** Infants and children who have received one or more doses of DTP and who experience a neurologic disorder, e.g., a seizure, temporally unassociated with the administration of vaccine but before the next scheduled dose, present a special problem. If the seizure or other disorder occurs before the first birthday and completion of the first three doses of the primary series of DTP, deferral of further doses of DTP or DT (but not OPV) is recommended until the infant's status has been clarified. The decision whether to use DTP or DT to complete the series should be made no later than the child's first birthday and should take into consideration the nature of the child's problem and the benefits and risks of the vaccine. If the seizure or other disorder occurs after the first birthday, the child's neurologic status should be evaluated to ensure the disorder is stable before a subsequent dose of DTP is given.[2]

4. **Infants and children with stable neurologic conditions.** Infants and children with stable neurologic conditions, including well-controlled seizures, may be vaccinated. The occurrence of single seizures (temporally unassociated with DTP) in infants and young children, while necessitating evaluation, need not contraindicate DTP immunization, particularly if the seizures can be satisfactorily explained.[2]

5. **Children with resolved or corrected neurologic disorders.** DTP administration is recommended for infants with certain neurologic problems that have clearly subsided without residua or have been corrected, such as neonatal hypocalcemic tetany or hydrocephalus (following placement of a shunt and without seizures).[2]

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (less than 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.[2]

If Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (DTP) has been administered to persons receiving immunosuppressive therapy, a recent injection of immune globulin or having an immunodeficiency disorder, an adequate immunologic response may not be obtained.

separately.[2,10] Therefore, if there is any doubt that a vaccine recipient [illegible] mends the simultaneous administration of all vaccines appropriate to the age and previous vaccination status of the recipient. This would especially include the simultaneous administration of DTP, OPV, and MMR to such persons at 15 months of age or older.[2]

PRECAUTIONS

GENERAL

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylatic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent side reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines (see CONTRAINDICATIONS), and a current knowledge of the literature concerning the use of the vaccine under consideration.

The vial of vaccine should be vigorously shaken to ensure a proper suspension of the antigen and adjuvant.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

PEDIATRIC USE

THIS VACCINE IS RECOMMENDED FOR IMMUNIZING CHILDREN 6 WEEKS THROUGH 6 YEARS (UP TO THE SEVENTH BIRTHDAY) OF AGE ONLY. Do NOT administer to persons 7 years of age and older.

INFORMATION FOR PATIENT

Parents should be fully informed of the benefits and risks of immunization with DTP.

Prior to administration of any dose of DTP, the parent or guardian should be asked about the recent health status of the infant or child to be injected.

The physician should inform the parents or guardian about the significant adverse reactions that need to be monitored.

As part of the infant's or child's immunization record, informed consent should be obtained and recorded. The lot number and manufacturer of the vaccine administered should be recorded in the event of the occurrence of any symptoms and/or signs of an adverse reaction. Vaccine information sheets are available from the CDC or the State Health Department which may serve as guidelines.

WHEN AN INFANT OR CHILD IS RETURNED FOR THE NEXT DOSE IN THE SERIES, THE PARENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER PREVIOUS DOSE (see CONTRAINDICATIONS; ADVERSE REACTIONS).

ADVERSE REACTIONS

Not all adverse events following administration of DTP are causally related to DTP vaccine.

Adverse reactions which may be local and include pain, erythema, heat, edema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria, tetanus, or pertussis antigens. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses.[11] However, these observations were not noted by Barkin, R.M., et al.[12] Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6-10 per million doses).

Mild systemic reactions, such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following DTP than following DT, are usually self-limited, and need no therapy other than, perhaps, symptomatic treatment (e.g., antipyretics).[2] Rash, allergic reactions, and respiratory difficulties, including apnea, have been observed.

Moderate to severe systemic events, such as fever of 40.5°C (105°F) or higher, persistent, inconsolable crying lasting 3 hours or more, unusual high-pitched crying, collapse, or convulsions, occur relatively infrequently. More severe neurologic complications, such as a prolonged convulsion or an encephalopathy, occasionally fatal, have been reported to be associated with DTP administration.[2]

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in Table 1.[2,13,14]

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent.[13] If local redness of 2.5 cm or greater occurs, the likelihood of recurrence after another DTP dose increases significantly.[11]

In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England,[14] children 2 - 35 months of age with serious, acute neurologic disorders, such as encephalopathy or complicated convulsion(s), were more likely to have received DTP in the 7 days preceding onset than their age-, sex-, and neighborhood-matched controls. Among children known to be neurologically normal before entering the study, the relative risk (estimated by odds ratio) of a neurologic illness occurring within the 7-day period following receipt of DTP dose, compared to children not receiving DTP vaccine in the 7-day period before onset of their illness, was 3.3 ($p < 0.001$). Within this 7-day period, the risk was significantly increased for immunized children only within 3 days of vaccination (relative risk 4.2, $p < 0.001$). The relative risk for illness occurring 4 - 7 days after vaccination was 2.1 ($0.05 < p < 0.1$). The attributable risk estimates for a serious acute neurologic disorder within 7 days after DTP vaccine (regardless of outcome) was one in 110,000 doses of DTP, and for a permanent neurologic deficit, one in 310,000 doses. No specific clinical syndrome was identified. Overall, DTP vaccine accounted for only a small proportion of cases of serious neurologic disorders reported in the population studied.[2]

Although there are uncertainties in the reported studies, recent data suggest that infants and young children who have had previous convulsions (whether febrile or nonfebrile) are more likely to have seizures following DTP than those without such histories.[2,15]

Rarely, an anaphylatic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[2]

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2 - 8 hours after an injection), may follow receipt of tetanus toxoid, particularly in adults who have received frequent (e.g., annual) boosters of tetanus toxoid. A few cases of peripheral neuropathy have been reported following tetanus toxoid administration, although a causal relationship has not been established.[2]

Sudden infant death syndrome (SIDS) has occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS.[16] It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2 - 6 months old and that approximately 85% of SIDS cases occur at ages 1 - 6 months, with the peak incidence occurring at 6 weeks-4 months of age. By chance alone, some SIDS victims can be expected to have recently received vaccine.[2]

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DTP or DT was not causally related to infantile spasms.[17] The incidence of onset of infantile spasms increases at 3 - 9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.[2]

TABLE 1.[2] Adverse events occurring within 48 hours of DTP immunizations

Event	Frequency*
Local	
Redness	1/3 doses
Swelling	2/5 doses
Pain	1/2 doses
Mild/moderate systemic	
Fever > 38°C (100.4°F)	1/2 doses
Drowsiness	1/3 doses
Fretfulness	1/2 doses
Vomiting	1/15 doses
Anorexia	1/5 doses
More serious systemic	
Persistent, inconsolable crying (duration ≥3 hours)	1/100 doses
High-pitched, unusual cry	1/900 doses
Fever ≥40.5°C (≥105°F)	1/330 doses
Collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,750 doses
Acute encephalopathy†	1/110,000 doses
Permanent neurologic deficit†	1/310,000 doses

* Number of adverse events per total number of doses regardless of dose number in DTP series.
† Occurring within 7 days of DTP immunization.

Reporting of Adverse Events

Reporting by parents and patients of all adverse events occurring within 4 weeks of antigen administration should be encouraged. Adverse events that require a visit to a health-care provider should be reported by health-care providers to manufacturers and local or state health departments. The information will be forwarded to an appropriate federal agency (the Office of Biologics Research and Review, FDA, or CDC).[2]

The following illnesses have been reported as temporally associated with the vaccine; neurological complications[18] including cochlear lesion,[19] brachial plexus neuropathies,[19,20] paralysis of the radial nerve,[21] paralysis of the recurrent nerve,[19] accommodation paresis, and EEG disturbances with encephalopathy.[13] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[22]

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, vaccine should not be administered.

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylatic reaction occur due to any component of the vaccine.

SHAKE VIAL WELL *before withdrawing each dose. Vaccine contains a bacterial suspension. Vigorous agitation is required to resuspend the contents of the vial.*

Inject 0.5 ml intramuscularly. The vastus lateralis (mid-thigh laterally) is the preferred injection site for infants. The gluteus maximus should be avoided due to the potential for damage to the sciatic nerve. During the course of primary immunization, injections should not be made more than once at the same site.

Do NOT administer this product subcutaneously. Special care should be taken to ensure that the injection does not enter a blood vessel.

This vaccine is recommended for children 6 weeks through 6 years of age (up to the seventh birthday) ideally beginning when the infant is 6 weeks to 2 months of age in accordance with the following schedules indicated in Table 2.[2]

TABLE 2.[2] Routine diphtheria, tetanus, and pertussis immunization schedule summary for children under 7 years old - United States, 1985*

Dose	Age/Interval†	Product
Primary 1	6 weeks old or older	DTP†¶
Primary 2	4-8 weeks after first dose§	DTP ¶
Primary 3	4-8 weeks after second dose§	DTP ¶
Primary 4	6-12 months after third dose§	DTP ¶
Booster	4-6 years old, before entering kindergarten or elementary school (not necessary if fourth primary immunizing dose administered on or after fourth birthday)	DTP ¶
Additional boosters	Every 10 years after last dose	Td

* Important details are in the text.
† Customarily begun at 8 weeks of age, with second and third doses given at 8-week intervals.
§ Prolonging the interval dose does not require restarting series.
¶ DT, if pertussis vaccine is contraindicated. If the child is 1 year of age or older at the time the primary dose is given, a third dose 6-12 months after the second completes primary immunization with DT.

Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.

HOW SUPPLIED

Vial, 5 ml - Product No. 49281-280-10
Vial, 7.5 ml - Product No. 49281-280-84

STORAGE

Store between 2° — 8°C (35° — 46°F). DO NOT FREEZE. Temperature extremes may adversely affect resuspendability of this vaccine.

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Manufactured by:
CONNAUGHT LABORATORIES, INC.
Swiftwater, Pennsylvania 18370, U.S.A.

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CONNAUGHT

A.H.F.S. Category 80:08

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE)

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

DESCRIPTION

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP, for intramuscular use, combines diphtheria and tetanus toxoids, adsorbed with pertussis vaccine in a sterile isotonic sodium chloride solution containing sodium phosphate to control pH; each 0.5 ml injection contains not more than 0.25 mg of aluminum added in the form of aluminum potassium sulfate. Thimerosal (mercury derivative) 1:10,000 is added as a preservative. The vaccine, in suspension, is a turbid liquid, whitish in color. Each single dose of 0.5 ml is formulated to contain 6.7 Lf units of diphtheria toxoid and 5 Lf units of tetanus toxoid. The total human immunizing dose (the first three 0.5 ml doses given) contains an estimate of 12 units of pertussis vaccine.[1] Each component of the vaccine - diphtheria, tetanus and pertussis - meets the required potency standards.

CLINICAL PHARMACOLOGY

Simultaneous immunization against diphtheria, tetanus, and pertussis during infancy and childhood has been a routine practice in the United States since the late 1940s. This practice has played a major role in markedly reducing the incidence rates of cases and deaths from each of these diseases.[2]

DIPHTHERIA

Cornyebacterium diphtheriae may cause both a localized and a generalized disease. The systemic intoxication is caused by diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C. diphtheriae*.

At one time, diphtheria was common in the United States. More than 200,000 cases, primarily among children, were reported in 1921. Approximately 5%-10% of cases were fatal; the highest case-fatality ratios were in the very young and the elderly. Reported cases of diphtheria of all types declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state. After 1979, cutaneous diphtheria was no longer reportable. From 1980 to 1983, only 15 cases of respiratory diphtheria were reported; 11 occurred among persons 20 years of age or older.[2]

The current rarity of diphtheria in the United States is due primarily to the high level of appropriate immunization among children (96% of children entering school have received three or more doses of Diphtheria and Tetanus Toxoids and Pertussis Vaccine [DTP]) and to an apparent reduction of the circulation of toxigenic strains of *C. diphtheriae*. Most cases occur among unimmunized or inadequately immunized persons. The age distribution of recent cases and the results of serosurveys indicate that many adults in the United States are not protected against diphtheria. Thus, it appears that in addition to continuing to immunize children more emphasis should be placed on adult immunization programs.[2]

Both toxigenic and non-toxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce toxin cause myocarditis and neuritis. Furthermore, toxigenic strains are more often associated with severe or fatal illness in noncutaneous (respiratory or other mucosal surface) infections and are more commonly recovered from respiratory than from cutaneous infections.[2]

C. diphtheriae can contaminate the skin of certain individuals, usually at the site of a wound. Although a sharply demarcated lesion with a pseudomembraneous base often results, the appearance may not be distinctive and the infection can be confirmed only by culture. Usually other bacterial species can also be isolated. Cutaneous diphtheria has most commonly affected indigent adults and certain groups of Native Americans.[2]

Active immunization significantly reduces the risk of developing diphtheria, and immunized persons who develop disease have milder illnesses. Protection is thought to last at least 10 years. Immunization does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nose or on the skin.[2]

TETANUS

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*.

The occurrence of tetanus in the United States has decreased markedly because of the routine use of tetanus toxoid immunization. Nevertheless, the number of reported cases has remained relatively constant in the last decade at an annual average of 90 cases. In 1983, 91 tetanus cases were reported from 29 states. In recent years, approximately two-thirds of patients have been 50 years of age or older. The age distribution of recent cases and the results of serosurveys indicate that many United States adults are not protected against tetanus. The disease has occurred almost exclusively among persons who are unimmunized or inadequately immunized or whose immunization histories are unknown or uncertain.[2]

In 6% of tetanus cases reported during 1982 and 1983, no wound or other condition could be implicated. Non-acute skin lesions, such as ulcers, or medical conditions, such as abscesses, were reported in 17% of cases.[2]

Spores of *C. tetani* are ubiquitous. Serological tests indicate that naturally acquired immunity to tetanus toxin does not occur in the United States. Thus, universal primary immunization, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect all age groups. Tetanus toxoid is a highly effective antigen, and a completed primary series generally induces protective levels of serum antitoxin that persist for 10 or more years.[2]

PERTUSSIS

Pertussis is a disease of the respiratory tract caused by *Bordetella pertussis*. This gram-negative coccobacillus produces a variety of biologically active components which have been associated with a number of effects such as lymphocytosis, leukocytosis, sensitivity to histamine, changes in glucose and/or insulin levels, neurological effects, and adjuvant activity.[3] The role of each of the different components in either the pathogenesis of or the immunity to pertussis is not well understood.

General use of standardized pertussis vaccine has resulted in a substantial reduction in cases and deaths from pertussis disease. However, the annual number of reported cases has changed relatively little during the last 10 years, when annual averages of 1,835 cases and 10 fatalities have occurred. In 1983, 2,463 cases were reported; in 1981, the latest year for which final national mortality statistics are available from the National Center for Health Statistics, six deaths were recorded. More precise data do not exist, since many cases go unrecognized or unreported, and diagnostic tests for *B. pertussis* - culture and direct-immunofluorescence assay (DFA) - may be unavailable, difficult to perform, or incorrectly interpreted.[2]

For 1982 and 1983, 53% of reported illnesses from *B. pertussis* occurred among children under 1 year of age and 78% in children less than 5 years of age; 13 of 15 deaths reported to the Centers for Disease Control (CDC) occurred in children less than 1 year old. Before widespread use of DTP, about 20% of cases and 50% of pertussis-related deaths occurred among children less than 1 year old.[2]

Pertussis is highly communicable (attack rates of over 90% have been reported for unimmunized household contacts) and can cause severe disease, particularly in very young children. Of patients under 1 year of age reported to CDC during 1982 and 1983, 75% were hospitalized; approximately 22% had pneumonia; 2% had one or more seizures; and 0.7% died. Because of the substantial risks of complications of the disease, completion of a primary series of DTP early in life is recommended.[2]

In older children and adults, including in some instances those previously immunized, infection may result in nonspecific symptoms of bronchitis or an upper respiratory tract infection, and pertussis may not be diagnosed because classic signs, especially the inspiratory whoop, may be absent. Older preschool-aged children and schoolaged siblings who are not fully immunized and develop pertussis can be important sources of infection for younger infants, the group at highest risk of disease and disease severity. The importance of the infected adult in overall transmission remains to be defined.[2]

Controversy regarding use of pertussis vaccine led to a formal reevaluation of the benefits and risks of this vaccine. The analysis indicated that the benefits of the vaccine continue to outweigh its risks.[2,4]

Because the incidence and severity of pertussis decrease with age and because the vaccine may cause side effects and adverse reactions, pertussis immunization is not recommended for children after their seventh birthday.[2]

Evidence of the efficacy of pertussis vaccine can be provided by the recent British experience, where a reduction in the number of immunized individuals from 79% in 1973, to 31% in 1978 was associated with an epidemic of 102,500 pertussis cases and 36 deaths between late 1977 and 1980, and 1,440 cases per week reported during the winter of 1981-1982.[5] A similar situation occurred in Japan.[5,6]

PRECAUTIONS

GENERAL

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent side reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines (see CONTRAINDICATIONS), and a current knowledge of the literature concerning the use of the vaccine under consideration.

The vial of vaccine should be vigorously shaken to ensure a proper suspension of the antigen and adjuvant.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

PEDIATRIC USE

THIS VACCINE IS RECOMMENDED FOR IMMUNIZING CHILDREN 6 WEEKS THROUGH 6 YEARS (UP TO THE SEVENTH BIRTHDAY) OF AGE ONLY. Do NOT administer to persons 7 years of age and older.

INFORMATION FOR PATIENT

Parents should be fully informed of the benefits and risks of immunization with DTP.

Prior to administration of any dose of DTP, the parent or guardian should be asked about the recent health status of the infant or child to be injected.

The physician should inform the parents or guardian about the significant adverse reactions that need to be monitored.

As part of the infant's or child's immunization record, informed consent should be obtained and recorded. The lot number and manufacturer of the vaccine administered should be recorded in the event of the occurrence of any symptoms and/or signs of an adverse reaction. Vaccine information sheets are available from the CDC or the State Health Department which may serve as guidelines.

WHEN AN INFANT OR CHILD IS RETURNED FOR THE NEXT DOSE IN THE SERIES, THE PARENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER PREVIOUS DOSE (see CONTRAINDICATIONS; ADVERSE REACTIONS).

ADVERSE REACTIONS

Not all adverse events following administration of DTP are causally related to DTP vaccine.

Adverse reactions which may be local and include pain, erythema, heat, edema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria, tetanus, or pertussis antigens. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses.[11] However, these observations were not noted by Barkin, R.M., et al.[12] Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6-10 per million doses).

Mild systemic reactions, such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following DTP than following DT, are usually self-limited, and need no therapy other than, perhaps, symptomatic treatment (e.g., antipyretics).[2] Rash, allergic reactions, and respiratory difficulties, including apnea, have been observed.

Moderate to severe systemic events, such as fever of 40.5°C (105°F) or higher, persistent, inconsolable crying lasting 3 hours or more, unusual high-pitched crying, collapse, or convulsions, occur relatively infrequently. More severe neurologic complications, such as a prolonged convulsion or an encephalopathy, occasionally fatal, have been reported to be associated with DTP administration.[2]

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in Table 1.[2,13,14]

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent.[13] If local redness of 2.5 cm or greater occurs, the likelihood of recurrence after another DTP dose increases significantly.[11]

In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England,[14] children 2-35 months of age with serious, acute neurologic disorders, such as encephalopathy or complicated convulsion(s), were more likely to have received DTP in the 7 days preceding onset than their age-, sex-, and neighborhood-matched controls. Among children known to be neurologically normal before entering the study, the relative risk (estimated by odds ratio) of a neurologic illness occurring within the 7-day period following receipt of DTP dose, compared to children not receiving DTP vaccine in the 7-day period before onset of their illness, was 3.3 ($p < 0.001$). Within this 7-day period, the risk was significantly increased for immunized children only within 3 days of vaccination (relative risk 4.2, $p < 0.001$). The relative risk for illness occurring 4-7 days after vaccination was 2.1 ($0.05 < p < 0.1$). The attributable risk estimates for a serious acute neurologic disorder within 7 days after DTP vaccine (regardless of outcome) was one in 110,000 doses of DTP, and for a permanent neurologic deficit, one in 310,000 doses. No specific clinical syndrome was identified. Overall, DTP vaccine accounted for only a small proportion of cases of serious neurologic disorders reported in the population studied.[2]

Although there are uncertainties in the reported studies, recent data suggest that infants and young children who have had previous convulsions (whether febrile or nonfebrile) are more likely to have seizures following DTP than those without such histories.[2,15]

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[2]

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid, particularly in adults who have received frequent (e.g., annual) boosters of tetanus toxoid. A few cases of peripheral neuropathy have been reported following tetanus toxoid administration, although a causal relationship has not been established.[2]

Sudden infant death syndrome (SIDS) has occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS.[16] It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2-6 months old and that approximately 85% of SIDS cases occur at ages 1-6 months, with the peak incidence occurring at 6 weeks-4 months of age. By chance alone, some SIDS victims can be expected to have recently received vaccine.[2]

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DTP or DT was not causally related to infantile spasms.[17] The incidence of onset of infantile spasms increases at 3-9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.[2]

TABLE 1.[2] Adverse events occurring within 48 hours of DTP immunizations

Event	Frequency*
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Persistent, inconsolable crying (duration ≥ 3 hours)	1/100 doses
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Acute encephalopathy†	1/110,000 doses
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*Number of adverse events per total number of doses regardless of dose number in DTP series.
†Occurring within 7 days of DTP immunization.

Reporting of Adverse Events

Reporting by parents and patients of all adverse events occurring within 4 weeks of antigen administration should be encouraged. Adverse events that require a visit to a health-care provider should be reported by health-care providers to manufacturers and local or state health departments. The information will be forwarded to an ap-

INDICATIONS AND USAGE

For active immunization of infants and children to age 7 years against diphtheria, tetanus and pertussis (whooping cough) simultaneously. DTP is recommended for primary immunization of infants and children up to 7 years of age. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.

CONTRAINDICATIONS

Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.

Absolute contraindications:[2]

1. Allergic hypersensitivity to any component of the vaccine.
2. Fever of 40.5°C (105°F) or greater within 48 hours.
3. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
4. Persisting, inconsolable crying lasting 3 hours or more or an unusual, high-pitched cry occurring within 48 hours.
5. Convulsion(s) with or without fever occurring within 7 days.
6. Encephalopathy occurring within 7 days; this includes severe alterations in consciousness with generalized or focal neurologic signs.

The presence of a neurologic condition characterized by changing developmental or neurologic findings, regardless of whether a definitive diagnosis has been made, is also considered *an absolute contraindication* to receipt of pertussis vaccine, because administration of DTP may coincide with or possibly even aggravate manifestations of the disease. Such disorders include uncontrolled epilepsy, infantile spasms, and progressive encephalopathy.[2]

Use of this product is also contraindicated if the child has a personal or family history of a seizure disorder. However, the ACIP does not accept family histories of convulsions or other central nervous system disorders as contraindications to pertussis vaccination.[2]

IT IS ALSO A CONTRAINDICATION TO ADMINISTER DTP TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL. IN ANY CASE, EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.[9]

WARNINGS

This vaccine must NOT be used for immunizing persons 7 years of age and older.

IMMUNIZATION SHOULD BE DEFERRED DURING THE COURSE OF ANY ACUTE ILLNESS. THE OCCURRENCE OF ANY TYPE OF NEUROLOGICAL SYMPTOMS OR SIGNS, INCLUDING ONE OR MORE CONVULSIONS (SEIZURES) FOLLOWING ADMINISTRATION OF THIS PRODUCT IS *AN ABSOLUTE CONTRAINDICATION* TO FURTHER USE. USE OF THIS PRODUCT IS ALSO CONTRAINDICATED IF THE CHILD HAS A PERSONAL OR FAMILY HISTORY OF A SEIZURE DISORDER.

THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A CONTRAINDICATION TO ADMINISTRATION OF DTP REGARDLESS OF WHETHER THE SUSPECTED NEUROLOGICAL DISORDER IS ASSOCIATED WITH OCCURRENCE OF SEIZURE ACTIVITY OF ANY TYPE.

The administration of DTP to children with proven or suspected underlying neurologic disorders, must be decided on an individual basis.

The ACIP recommends the following:

1. **Infants as yet unimmunized who are suspected of having underlying neurologic disease.** Possible latent central nervous system disorders that are suspected because of perinatal complications or other phenomena may become evident as they evolve over time. Because DTP administration may coincide with onset of overt manifestations of such disorders and result in confusion about causation, it is prudent to delay initiation of immunization with DTP or DT (but not OPV) until further observation and study have clarified the child's neurologic status. In addition, the effect of treatment, if any, can be assessed. The decision whether to commence immunization with DTP or DT should be made no later than the child's first birthday. In making this decision, it should be recognized that children with severe neurologic disorders may be at enhanced risk of exposure to pertussis from institutionalization or from attendance at clinics and special schools in which many of the children may be unimmunized. In addition, because of neurologic handicaps, these children may be in greater jeopardy from complications of the disease.[2]
2. **Infants and children with neurologic events temporally associated with DTP.** Infants and children who experience a seizure within 3 days of receipt of DTP or an encephalopathy within 7 days should not receive further pertussis vaccine, even though cause and effect may not be established (see CONTRAINDICATIONS).[2]
3. **Incompletely immunized children with neurologic events occurring between doses.** Infants and children who have received one or more doses of DTP and who experience a neurologic disorder, e.g., a seizure, temporally unassociated with the administration of vaccine but before the next scheduled dose, present a special problem. If the seizure or other disorder occurs before the first birthday and completion of the first three doses of the primary series of DTP, deferral of further doses of DTP or DT (but not OPV) is recommended until the infant's status has been clarified. The decision whether to use DTP or DT to complete the series should be made no later than the child's first birthday and should take into consideration the nature of the child's problem and the benefits and risks of the vaccine. If the seizure or other disorder occurs after the first birthday, the child's neurologic status should be evaluated to ensure the disorder is stable before a subsequent dose of DTP is given.[2]
4. **Infants and children with stable neurologic conditions.** Infants and children with stable neurologic conditions, including well-controlled seizures, may be vaccinated. The occurrence of single seizures (temporally unassociated with DTP) in infants and young children, while necessitating evaluation, need not contraindicate DTP immunization, particularly if the seizures can be satisfactorily explained.[2]
5. **Children with resolved or corrected neurologic disorders.** DTP administration is recommended for infants with certain neurologic problems that have clearly subsided without residua or have been corrected, such as neonatal hypocalcemic tetany or hydrocephalus (following placement of a shunt and without seizures).[2]

mmunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corcosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term less than 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids hould not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunoppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient as been off therapy for one month;[16] otherwise, the patient should be vaccinated while still on therapy.[2]

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (DTP) has been administered to persons eceiving immunosuppressive therapy, a recent injection of immune globulin or having an immunodeficiency isorder, an adequate immunologic response may not be obtained.

TP should not be given to infants or children with any coagulation disorder that would contraindicate inamuscular injection unless the potential benefit clearly outweighs the risk of administration.

ne simultaneous administration of DTP, oral polio virus vaccine (OPV), and/or measles-mumps-rubella vaccine MR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines ne doses, the ACIP recommends the simultaneous administration of all vaccines appropriate to the age and evious vaccination status of the recipient. This would especially include the simultaneous administration of P, OPV, and MMR to such persons at 15 months of age or older.[2]

the recurrent nerve,[18] accommodation paresis, and EEG disturbances with encephalopathy.[19] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[22]

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, vaccine should not be administered.

Epinephrine injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

SHAKE VIAL WELL *before withdrawing each dose. Vaccine contains a bacterial suspension. Vigorous agitation is required to resuspend the contents of the vial.*

Inject 0.5 ml intramuscularly. The vastus lateralis (mid-thigh laterally) is the preferred injection site for infants. The gluteus maximus should be avoided due to the potential for damage to the sciatic nerve. During the course of primary immunization, injections should not be made more than once at the same site.

Do NOT administer this product subcutaneously. Special care should be taken to ensure that the injection does not enter a blood vessel.

This vaccine is recommended for children 6 weeks through 6 years of age (up to the seventh birthday) ideally beginning when the infant is 6 weeks to 2 months of age in accordance with the following schedules indicated in Table 2.[2]

TABLE 2.[2] Routine diphtheria, tetanus, and pertussis immunization schedule summary for children under 7 years old - United States, 1985*

Dose	Age/Interval†	Product
Primary 1	6 weeks old or older	DTP† ¶
Primary 2	4-8 weeks after first dose§	DTP ¶
Primary 3	4-8 weeks after second dose§	DTP ¶
Primary 4	6-12 months after third dose§	DTP ¶
Booster	4-6 years old, before entering kindergarten or elementary school (not necessary if fourth primary immunizing dose administered on or after fourth birthday)	DTP ¶
Additional boosters	Every 10 years after last dose	Td

* Important details are in the text.
† Customarily begun at 8 weeks of age, with second and third doses given at 8-week intervals.
§ Prolonging the interval dose does not require restarting series.
¶ DT, if pertussis vaccine is contraindicated. If the child is 1 year of age or older at the time the primary dose is given, a third dose 6-12 months after the second completes primary immunization with DT.

Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.

HOW SUPPLIED

Vial, 5 ml - Product No. 49281-280-10

Vial, 7.5 ml - Product No. 49281-280-84

STORAGE

Store between 2° - 8°C (35° - 46°F). DO NOT FREEZE. Temperature extremes may adversely affect resuspendability of this vaccine.

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due ... administration of ...

Connaught Laboratories, Inc.

Product Information as of July, 1986

Printed in U.S.A.
1629

CONNAUGHT
A PASTEUR MÉRIEUX COMPANY

A.H.F.S. Category 80:08

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP

(FOR PEDIATRIC USE)

Caution: *Federal (U.S.A.) law prohibits dispensing without prescription.*

DESCRIPTION

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) combines diphtheria and tetanus toxoids adsorbed with pertussis vaccine, for intramuscular use, in a sterile isotonic sodium chloride solution containing sodium phosphate buffer to control pH. The vaccine, after shaking, is a turbid liquid, whitish-gray in color. When used to reconstitute Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), ActHIB™ or OmniHIB™, the combined vaccines appear whitish in color.

Corynebacterium diphtheriae cultures are grown in a modified Mueller and Miller medium.[1] *Clostridium tetani* cultures are grown in a peptone-based medium. Both toxins are detoxified with formaldehyde. The detoxified materials are separately purified by serial ammonium sulfate fractionation and diafiltration.

The pertussis vaccine component is derived from *Bordetella pertussis* cultures grown on blood-free Bordet Gengou media. The pertussis organisms are harvested and inactivated with thimerosal and resuspended in physiological saline and thimerosal.

The toxoids are adsorbed to aluminum potassium sulfate (alum). The adsorbed diphtheria and tetanus toxoids are combined with pertussis vaccine concentrate, and diluted to a final volume using sterile phosphate-buffered physiological saline. Each 0.5 mL dose contains, by assay, not more than 0.17 mg of aluminum and not more than 100 µg (0.02%) of residual formaldehyde. Thimerosal (mercury derivative) 1:10,000 is added as a preservative.

Each 0.5 mL dose is formulated to contain 6.7 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid (both toxoids induce at least 2 units of antitoxin per mL in the guinea pig potency test).

The total human immunizing dose (the first three 0.5 mL doses administered) contains an estimate of 12 units of pertussis vaccine (4 protective units per single dose).[2] The potency of the pertussis component of each lot of DTP is tested in a mouse protection test.

At the time when Connaught Laboratories, Inc. (CLI) DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, each single dose of the 0.5 mL mixture is formulated to contain 6.7 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, an estimate of 4 protective units of pertussis vaccine, 10 µg of purified capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid, and 8.5% of sucrose.

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

CLINICAL PHARMACOLOGY

DIPHTHERIA

Corynebacterium diphtheriae may cause both localized and generalized disease. Systemic intoxication is caused by diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin.

At one time, diphtheria was common in the United States. More than 200,000 cases, primarily among young children, were reported in 1921. Approximately 5% to 10% of cases were fatal; the highest case-fatality ratios were recorded for the very young and the elderly. Reported cases of diphtheria of all types declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state. After 1979, cutaneous diphtheria was no longer a notifiable disease. From 1980 to 1989, only 24 cases of respiratory diphtheria were reported; two cases were fatal, and 18 (75%) occurred among persons 20 years of age or older.[2]

Diphtheria is currently a rare disease in the United States primarily because of the high level of appropriate vaccination among children (97% of children entering school have received ≥three doses of diphtheria and tetanus toxoids and pertussis vaccine adsorbed [DTP]) and because of an apparent reduction in the prevalence of toxigenic strains of *C. diphtheriae*. Most cases occur among unvaccinated or inadequately immunized persons.[2]

Both toxigenic and nontoxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce toxin cause myocarditis and neuritis. Toxigenic strains are more often associated with severe or fatal illness in noncutaneous (respiratory or other mucosal surface) infections and are more commonly recovered in association with respiratory than from cutaneous infections.[2]

A complete vaccination series substantially reduces the risk of developing diphtheria, and vaccinated persons who develop disease have a milder illness. Protection lasts at least 10 years. Vaccination does not, however, eliminate carriage of *C. diphtheriae* in the throat or nose or on the skin.[2]

TETANUS

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*.

The occurrence of tetanus in the United States has decreased dramatically from 560 reported cases in 1947 to a record low of 48 reported cases in 1987. Tetanus in the United States is primarily a disease of older adults. Of 99 tetanus patients with complete information reported to the Centers for Disease Control and Prevention (CDC) during 1987 and 1988, 63% were ≥50 years of age, while only six were <20 years of age. Overall, the case-fatality rate was 21%. In 1992, 45 cases were reported of which 82% were ≥50 years of age.[3] The disease continues to occur almost exclusively among persons who are unvaccinated or inadequately vaccinated or whose vaccination histories are unknown or uncertain.[2]

In 4% of tetanus cases reported during 1987 and 1988, no wound or other condition could be implicated. Non-acute skin lesions, such as ulcers, or medical conditions such as abscesses were reported in 14% of cases.[2]

Spores of *C. tetani* are ubiquitous. Serologic tests indicate that naturally acquired immunity to tetanus toxin does not occur in the United States.[2] Thus, universal primary vaccination, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect persons among all age-groups. Tetanus toxoid is a highly effective antigen, and a completed primary series generally induces protective levels of neutralizing antibodies to tetanus toxin that persist for ≥10 years.[2]

The potency of diphtheria and tetanus toxoids was determined on the basis of immunogenicity studies with a comparison to a serological correlate of protection (0.01 I.U./mL) established by the Panel on Review of Bacterial Vaccines & Toxoids.[4]

EFFICACY OF DIPHTHERIA AND TETANUS TOXOID VACCINES

Circulating protective levels of neutralizing antibodies to diphtheria and tetanus toxins can be induced by the administration of Diphtheria and Tetanus Toxoids Adsorbed USP (For Pediatric Use) (DT) or DTP.

A clinical study was performed in 20 children under one year of age to determine the serological responses and the adverse reactions when Connaught Laboratories, Inc. (CLI) DT was administered as a primary series of three doses. Protective levels of diphtheria and tetanus antitoxins that were equal to or greater than 0.01 I.U./mL were detected in 100% of the children following two doses of the vaccine. However, maternal antibody may have contributed to the total neutralizing antibody in some of these infants. Protective levels of antitoxin were observed in 100% of these infants following three doses of DT. No local or systemic reactions were observed in approximately half of the infants and only mild or moderate reactions were observed in the remainder of the DT study group.[5]

Another clinical study to evaluate serological responses and adverse reactions of CLI DT was performed in 40 children under one year of age. One group of 20 children received 0.5 mL doses of DTP, DT, DTP at two, four and six months of age, respectively. The second group of 20 children received 0.5 mL doses of DTP, DTP, and DT, respectively, at the same ages. The immunologic protection against diphtheria and tetanus as measured by toxin neutralizing antibodies induced by DT was comparable when administered as either a second or third dose.[6] The reaction rates following CLI whole-cell DTP vaccination closely correlated with the rates observed with other commercially available whole-cell DTP vaccines.[7] The incidence of adverse reactions was significantly lower following DT administration ($p < 0.05$). Although the number of vaccinees was small, no persistent screaming episodes or severe neurological reactions such as seizures or encephalopathy were observed with either vaccine in this study.[6]

PERTUSSIS

Disease caused by *Bordetella pertussis* was once a major cause of infant and childhood morbidity and mortality in the United States. Pertussis (whooping cough) became a nationally notifiable disease in 1922, and reports reached a peak of 265,269 cases and 7,518 deaths in 1934. The highest number of reported pertussis deaths (9,269) occurred in 1923. The introduction and widespread use of standardized whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids (DTP) in the late 1940s resulted in a substantial decline in pertussis disease, a decline which continued without interruption for nearly 30 years.[2]

By 1970, the annual reported incidence of pertussis had been reduced by 99%. During the 1970s the annual numbers of reported cases stabilized at an average of approximately 2,300 cases each year. During the 1980s, however, the annual numbers of reported cases gradually increased from 1,730 cases in 1980 to 4,517 cases in 1989. An average of eight pertussis-associated fatalities was reported each year throughout the 1980s.[2]

From 1989 to 1991, 11,446 cases of pertussis were reported for an unadjusted incidence per 100,000 population of 1.7 in 1989, 1.8 in 1990 and 1.1 in 1991. The incidence for 1992 was 1.6 per 100,000. Age specific incidence and hospitalization rates were highest in the first year of life, decreasing with increasing age. Trends of the past years suggest an increase in reported pertussis since 1976, with the peak year being 1990.[8]

During the period 1989 to 1991, of 3,900 reports of hospitalization, 1,115 had developed pneumonia, seizures occurred in 157 cases, encephalopathy was reported for 12, and there were 20 pertussis attributed deaths. These events were more frequently reported in children less than 6 months of age and were generally less frequent with increasing age.[7] Of patients 3 months through 4 years of age, where vaccination status was known, 65% of 4,471 patients had not received the recommended schedule of immunization and 39% had not received any pertussis containing vaccine.[8]

Among older children and adults, including those previously vaccinated, *B. pertussis* infection may result in symptoms of bronchitis or other upper-respiratory-tract infection. Pertussis may not be associated with classic signs, especially the inspiratory whoop. Older preschool children and school-age siblings who are not fully vaccinated and who develop pertussis can be important sources of infection for infants <1 year of age. Adults also play an important role in the transmission of pertussis to unvaccinated or incompletely vaccinated infants and young children.[2]

EFFICACY OF PERTUSSIS VACCINE

Although DTP has been evaluated as a control vaccine in a number of clinical trials of "acellular pertussis vaccines," no formal efficacy trial was performed prior to approval. Approval was based on historical and continuing evidence of protection (surveillance) in the population at risk. It was also shown that vaccines with acceptable mouse protection potencies induced protective serum agglutinin antibody titers.[4] The pertussis component of each lot of DTP is tested for potency by a mouse protection test.

In clinical trials, one dose of CLI whole-cell DTP vaccine was used to reconstitute one lyophilized single dose vial of ActHIB™ or OmniHIB™ with no diminution in anti-PRP response or diphtheria, tetanus and pertussis responses.

[illegible] when CLI DTP vaccine is used to reconstitute [illegible]

ADVERSE REACTIONS

Adverse reactions associated with the use of DTP include local redness, warmth, edema, induration with or without tenderness, as well as urticaria and rash. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses.[9]

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent.[10] If local redness 2.5 cm occurs, the likelihood of recurrence after another DTP dose increases significantly.[9]

Evidence does not indicate a causal relation between DTP vaccine and SIDS. Studies showing a temporal relation between these events are consistent with the expected occurrence of SIDS over the age range in which DTP immunization typically occurs.[12]

Deaths due to causes other than SIDS, including deaths due to serious infections, have occurred in infants following the administration of DTP. No association has been shown for hospitalizations due to infectious disease and receipt of DTP.[20]

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in TABLE 1:[2]

TABLE 1[2] ADVERSE EVENTS OCCURRING WITHIN 48 HOURS OF DTP VACCINATIONS

Event	Frequency*
Local	
Redness	1/3 doses
Swelling	2/5 doses
Pain	1/2 doses
Systemic	
Fever ≥38°C (100.4°F)	1/2 doses
Drowsiness	1/3 doses
Fretfulness	1/2 doses
Vomiting	1/15 doses
Anorexia	1/5 doses
Persistent, inconsolable crying (duration ≥3 hours)	1/100 doses
Fever ≥40.5°C (≥105°F)	1/330 doses
Nervous System	
Collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,750 doses

*Rate per total number of doses regardless of dose number in DTP series.

BODY SYSTEM AS A WHOLE

Mild systemic reactions such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following administration of DTP than following DT, are usually self-limited, and need no therapy other than symptomatic treatment such as acetaminophen.[2]

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) and death have been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[2]

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2 to 8 hours after an injection), may follow receipt of tetanus toxoid.[2]

Moderate to severe systemic events, include high fever (i.e., temperature of ≥40.5°C (105°F) and persistent, inconsolable crying lasting ≥3 hours. These events occur infrequently and appear to be without sequelae.[2]

Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6 to 10 per million doses).[2]

NERVOUS SYSTEM

The following neurologic illnesses have been reported as temporally associated with vaccine containing tetanus toxoid: neurological complications[21,22] including cochlear lesion,[23] brachial plexus neuropathies,[23,24] paralysis of the radial nerve,[23] paralysis of the recurrent nerve,[23] accommodation paresis, and EEG disturbances with encephalopathy.[19] The report from the IOM suggests that there is a causal relation between Guillain-Barré syndrome (GBS) and vaccines containing tetanus toxoid.[26] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid should be considered as a possible etiology.[19,27]

Short-lived convulsions (usually febrile), or collapse (hypotonic-hyporesponsive episode) occur infrequently and appear to be without sequelae.[2]

More severe neurologic events, such as a prolonged convulsion, or encephalopathy, although rare, have been reported in temporal association with DTP administration. An analysis of these data failed to show any cause and effect association.[2]

In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England, children 2 to 35 months of age with serious, acute neurologic disorders such as encephalopathy or complicated convulsion(s), were more likely to have received DTP in the 7 days preceding onset than their age-, sex-, and neighborhood-matched controls. Among children known to be neurologically normal before entering the study, the relative risk (estimated by odds ratio) of a neurologic illness occurring within the 7-day period following receipt of DTP dose, compared to children not receiving DTP in the 7-day period before onset of their illness, was 3.3 ($p < 0.001$).[2]

Within this 7-day period, the risk was significantly increased for immunized children only within 3 days of vaccination (relative risk 4.2, $p < 0.001$). The relative risk for illnesses occurring 4 to 7 days after vaccination was 2.1 ($p < 0.1$). Serious neurologic illnesses requiring hospitalization attributable to pertussis vaccine are rare. Final analysis of a comprehensive case-control study has estimated that the attributable risk of such illnesses is 1 in 140,000 doses administered. An earlier analysis had estimated this risk at 1/110,000 doses. In contrast, final analysis of the case-control study found that the risk of serious neurologic illness following pertussis disease was 1/11,000 pertussis cases. Repeated evaluations have shown that the benefits of vaccine outweigh the risks.[2,9]

The methods and results of the NCES have been thoroughly scrutinized since publication of the study. This reassessment by multiple groups has determined that the number of patients was too small and their classification subject to enough uncertainty to preclude drawing valid conclusions about whether a causal relation exists between pertussis vaccine and permanent neurologic damage. Preliminary data from a 10-year follow-up study of some of the children studied in the original NCES study also suggested a relation between symptoms following DTP vaccination and permanent neurologic disability. However, details are not available to evaluate this study adequately, and the same concerns remain about DTP vaccine precipitating initial manifestations of pre-existing neurologic disorders.[2]

An IOM report by the Committee to review the adverse consequences of pertussis and rubella vaccines concluded that evidence is consistent with a causal relation between DTP vaccine and acute encephalopathy, defined in the controlled studies reviewed as encephalopathy, encephalitis, or encephalomyelitis. On the basis of a review of the evidence bearing on this relation, the Committee concludes that the range of excess risk of acute encephalopathy following DTP immunization is consistent with that estimated for the NCES: 0.0 to 10.5 per million immunizations. The report also states that there is insufficient evidence to indicate a causal relation between DTP vaccine and permanent neurologic damage.[13]

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DT or DTP was not causally related to infantile spasms.[28] The incidence of onset of infantile spasms increases at 3 to 9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.[2]

A bulging fontanelle associated with increased intracranial pressure which occurred within 24 hours following DTP immunization has been reported. A causal relationship has not been established.[29,30,31]

CARDIOVASCULAR SYSTEM

An infant who developed myocarditis several hours after immunization has been reported.[32]

RESPIRATORY SYSTEM

Respiratory difficulties, including apnea, have been observed.

LOCAL

Rash and allergic reactions have been observed.

Sudden Infant Death Syndrome (SIDS) has temporally occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS.[33,34,35] It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2 to 6 months of age and that approximately 85% of SIDS cases occur at ages 1 to 6 months, with the peak incidence occurring at 6 weeks to 4 months of age. By chance alone, some SIDS victims can be expected to have recently received DTP.[33,34,35]

When CLI whole-cell DTP was administered concomitantly (at separate sites with separate syringes) with ActHIB™ or OmniHIB™, the systemic adverse experience profile was not different from that seen when CLI whole-cell DTP vaccine was administered alone.[10,11] ***(Refer to ActHIB™ package insert.)***

In general, the rates of minor systemic reactions after DTP was used to reconstitute ActHIB™ or OmniHIB™ were comparable to those usually reported after DTP vaccine alone.[6,19,29]

When CLI whole-cell DTP was used to reconstitute ActHIB™ or OmniHIB™ and administered to infants at 2, 4, and 6 months of age, the systemic adverse experience profile was comparable to that observed when the two vaccines were given separately. An increase in the rate of local reactions was observed in some instances within the 24-hour period after immunization.[10,11] ***(Refer to ActHIB™ package insert.)***

Reporting of Adverse Events

Reporting by parents or guardians of all adverse events occurring after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by health-care providers to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.[16,17,18]

Health-care providers also should report these events to the Director of Medical Affairs, Connaught Laboratories, Inc., Route 611, P.O. Box 187, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, the vaccine should not be administered.

SHAKE VIAL WELL *before withdrawing each dose. Vaccine contains a bacterial suspension. Vigorous agitation is required to resuspend the contents of the vial.* Discard if vaccine cannot be resuspended.

For Administration of DTP Vaccine Only:

The primary series for children less than 7 years of age is four doses of 0.5 mL each given intramuscularly. The customary age for the first dose is 2 months of age but may be given as young as 6 weeks of age and up to the seventh birthday.

Inject 0.5 mL intramuscularly only. The preferred injection sites are the anterolateral aspect of the thigh and the deltoid muscle of the upper arm. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk. During the course of primary immunizations, injections should not be made more than once at the same site.

The use of reduced volume (fractional doses) is not recommended. The effect of such practices on the frequency of serious adverse events and on protection against disease has not been determined.

Do NOT administer this product subcutaneously.

Special care should be taken to ensure that the injection does not enter a blood vessel.

PRIMARY IMMUNIZATION

This vaccine is recommended for children 6 weeks through 6 years (up to the seventh birthday) ideally beginning when the infant is 6 weeks to 2 months of age.

The primary series consists of four doses. For infants 6 weeks through 12 months of age, administer three 0.5 mL doses intramuscularly at least 4 to 8 weeks apart. The fourth dose is administered 6 to 12 months after the third injection.

BOOSTER IMMUNIZATION

For children between 4 and 6 years of age (preferably at time of kindergarten or elementary school entrance), a booster of 0.5 mL

...and adults, including those previously vaccinated, *B. pertussis* infection may result in symptoms of bronchitis or ...per-respiratory-tract infection. Pertussis may not be associated with classic signs, especially the inspiratory whoop. Older preschool children and school-age siblings who are not fully vaccinated and who develop pertussis can be important sources of infection for infants <1 year of age. Adults also play an important role in the transmission of pertussis to unvaccinated or incompletely vaccinated infants and young children.[2]

EFFICACY OF PERTUSSIS VACCINE

Although DTP has been evaluated as a control vaccine in a number of clinical trials of "acellular pertussis vaccines," no formal efficacy trial was performed prior to approval. Approval was based on historical and continuing evidence of protection (surveillance) in the population at risk. It was also shown that vaccines with acceptable mouse protection potencies induced protective serum agglutinin antibody titers.[4] The pertussis component of each lot of DTP is tested for potency by a mouse protection test.

In clinical trials, one dose of CLI whole-cell DTP vaccine was used to reconstitute one lyophilized single dose vial of ActHIB™ or OmniHIB™ with no diminution in anti-PRP response or diphtheria, tetanus and pertussis responses.

INDICATIONS AND USAGE

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) is recommended for active immunization of children up to age 7 years against diphtheria, tetanus, and pertussis (whooping cough) simultaneously. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, DT should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.[2,9]

Persons recovering from confirmed pertussis do not need additional doses of DTP but should receive additional doses of DT to complete the series.[2]

Available data indicate that the appropriate age for institution of immunizations in prematurely born infants is the usual chronological age of 2 months. Vaccine doses should not be reduced for preterm infants.[2,9]

If passive immunization is required, Tetanus Immune Globulin (Human) (TIG) and/or equine Diphtheria Antitoxin are the products of ...hoice for tetanus and diphtheria, respectively (see **DOSAGE AND ADMINISTRATION** section).

...en CLI DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, the combined vaccines are indicated for the active immunization ...nfants and children 2 months through 5 years of age for the prevention of invasive diseases caused by diphtheria, tetanus, pertussis ...d *H influenzae* type b.[10,11] ***(Refer to ActHIB™ package insert.)***

A single injection containing diphtheria, tetanus, pertussis and Haemophilus b conjugate antigens may be more acceptable to parents and may increase compliance with vaccination programs. Therefore, in those situations where, in the judgment of the physician, it is of benefit to administer a single injection of whole-cell DTP vaccine and Haemophilus b conjugate vaccine concomitantly, ***only CLI whole-cell DTP vaccine may be used for reconstitution of lyophilized ActHIB™ or OmniHIB™.*** Antibody levels associated with protection may not be achieved earlier than two weeks following the last recommended dose. (See **DOSAGE AND ADMINISTRATION** section.)

As with any vaccine, vaccination with DTP or combined vaccines CLI DTP and ActHIB™ or OmniHIB™ may not protect 100% of susceptible individuals.

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

This vaccine is NOT to be used for the treatment of diphtheria, tetanus, pertussis or H influenzae type b infection.

This vaccine should NOT be used for immunizing persons 7 years of age and older.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including thimerosal, a mercury derivative, is a contraindication for further use of this vaccine.

It is a contraindication to use this or any other related vaccine after an immediate anaphylactic reaction associated with a previous dose.

It is a contraindication to administer this vaccine in the presence of any evolving neurological condition.

...ncephalopathy after a previous dose is a contraindication to further use.

...munization should be deferred during the course of an acute illness. Vaccination of infants and children with severe, febrile illness ...ould generally be deferred until these persons have recovered. However, the presence of minor illnesses such as mild upper ...piratory infections with or without low-grade fever are not contraindications to further use.[2]

...lective immunization procedures should be deferred during an outbreak of poliomyelitis.[12]

WARNINGS

If any of the following events occur in temporal relation to receipt of DTP, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelae.[2]

THE FOLLOWING EVENTS WERE PREVIOUSLY CONSIDERED CONTRAINDICATIONS AND ARE NOW CONSIDERED WARNINGS:[2]

1. **Temperature of ≥40.5°C (105°F) within 48 hours not due to another identifiable cause:** Such a temperature is considered a warning because of the likelihood that fever following a subsequent dose of DTP vaccine also will be high. Because such febrile reactions are usually attributed to the pertussis component, vaccination with DT should not be discontinued.[2]
2. **Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours:** Although these uncommon events have not been recognized to cause death nor to induce permanent neurological sequelae, it is prudent to continue vaccination with DT, omitting the pertussis component.[2]
3. **Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours:** Follow-up of infants who have cried inconsolably following DTP vaccination has indicated that this reaction, though unpleasant, is without long-term sequelae and not associated with other reactions of greater significance.[2] Evidence is insufficient to indicate whether pertussis vaccine-associated protracted, inconsolable, or high-pitched crying or screaming does, or does not, lead to chronic neurologic damage.[13] Inconsolable crying occurs most frequently following the first dose and is less frequently reported following subsequent doses of DTP vaccine. However, crying for >30 minutes following DTP vaccination can be a predictor of increased likelihood of recurrence of persistent crying following subsequent doses. Children with persistent crying have had a higher rate of local reactions than children who had other DTP-associated reactions (including high fever, seizures, and hypotonic-hyporesponsive episodes), suggesting that prolonged crying was really a pain reaction.[2]
4. **Convulsions with or without fever occurring within three days:** Short-lived convulsions, with or without fever, have not been shown to cause permanent sequelae. Furthermore, the occurrence of prolonged febrile seizures (i.e., status epilepticus – any seizure lasting >30 minutes or recurrent seizures lasting a total of 30 minutes without the child fully regaining consciousness), irrespective of their cause, involving an otherwise normal child does not substantially increase the risk for subsequent febrile (brief or prolonged) or afebrile seizures. The risk is significantly increased (p=0.018) only among those children who are neurologically abnormal before their episode of status epilepticus.[2] Accordingly, although a convulsion following DTP vaccination has previously been considered a contraindication to further doses, under certain circumstances subsequent doses may be indicated, particularly if the risk of pertussis in the community is high. If a child has a seizure following the first or second dose of DTP, it is desirable to delay subsequent doses until the child's neurologic status is better defined. By the end of the first year of life, the presence of an underlying neurologic disorder has usually been determined, and appropriate treatment instituted. DT vaccine should not be administered before a decision has been made about whether to continue the DTP series. Regardless of which vaccine is given, it is prudent also to administer acetaminophen[2], 15 mg/kg of body weight, at the time of vaccination and every 4 hours subsequently for 24 hours.

Persons who experienced Arthus-type hypersensitivity reactions or a temperature of >103°F (39.4°C) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given even emergency doses of Td more frequently than every 10 years, even if they have a wound that is neither clean nor minor.[2]

DTP should not be given to children with any coagulation disorder, including thrombocytopenia, that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

Recent studies suggest that infants and children with a history of convulsions in first-degree family members (i.e., siblings and parents) have a 3.2-fold increased risk for neurologic events compared with those without such histories.[14] *However, the ACIP has concluded that a family history of convulsions in parents and siblings is not a contraindication to pertussis vaccination and that children with such family histories should receive pertussis vaccine according to the recommended schedule.*[2]

A recent review of all available data by the IOM found evidence is consistent with a causal relation between DTP vaccination and acute encephalopathy, but that there is insufficient evidence to indicate a causal relation between DTP vaccine and permanent neurologic damage.[13]

...nfants and children with recognized possible or potential underlying neurologic conditions seem to be at enhanced risk for the ...earance of manifestations of the underlying neurologic disorder within two or three days following vaccination.[2] Whether to ...minister DTP to children with proven or suspected underlying neurologic disorders must be decided on an individual basis. Important ...siderations include the current local incidence of pertussis, the near absence of diphtheria in the United States and the low risk of ...fection with *C. tetani*.[2]

Although these events were considered absolute contraindications in previous ACIP recommendations, there may be circumstances, such as a high incidence of pertussis, in which the potential benefits outweigh possible risks, particularly because these events are not associated with permanent sequelae.[2]

The administration of DTP to children with proven or suspected underlying neurologic disorders that are not actively evolving must be decided on an individual basis.

Only full doses (0.5 mL) of DTP vaccine should be given; if a specific contraindication to DTP exists, the vaccine should not be given.[2]

Controversy regarding the safety of pertussis vaccine during the 1970s led to several studies of the benefits and risks of this vaccination during the 1980s. These epidemiologic analyses clearly indicate that the benefits of pertussis vaccination outweigh any risks and have not shown a cause and effect with neurologic illness.[2,9]

Deaths have been reported in temporal association with the administration of DTP vaccine (see **ADVERSE REACTIONS** section).

When CLI DTP vaccine is used alone or to reconstitute ActHIB™ or OmniHIB™ and administered to immunosuppressed persons or persons receiving immunosuppressive therapy, the expected antibody responses may not be obtained. This includes patients with severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation.[15]

Administration of DTP and/or Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) is not contraindicated in individuals with HIV infection.[11]

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

...ECAUTIONS

...ENERAL

Care is to be taken by the health-care provider for the safe and effective use of DTP.

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines, previous immunization history, current health status (see **CONTRAINDICATIONS; WARNINGS** sections), and a current knowledge of the literature concerning the use of the vaccine under consideration. Immunosuppressed patients may not respond.

Prior to administration of DTP, health-care personnel should inform the parent or guardian of the patient the benefits and risks of immunization, and also inquire about the recent health status of the patient to be injected.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped and should be properly disposed.

INFORMATION FOR PATIENTS

As part of the child's immunization record, the date, lot number and manufacturer of the vaccine administered MUST be recorded.[16,17,18]

The health-care provider should inform the parent or guardian of the patient about the potential for adverse reactions that have been temporally associated with DTP administration. Parents or guardians should be instructed to report any serious adverse reactions to their health-care provider.

...IS EXTREMELY IMPORTANT WHEN THE CHILD RETURNS FOR THE NEXT DOSE IN THE SERIES, THAT THE PARENT OR GUARDIAN OF ...E PATIENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION ...ER THE PREVIOUS DOSE (SEE **CONTRAINDICATIONS; ADVERSE REACTIONS** SECTIONS).

...e health-care provider should inform the parent or guardian of the patient the importance of completing the immunization series.

The health-care provider should provide the Vaccine Information Materials (VIMs) which are required to be given with each immunization.

The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986.[16] The toll-free number for VAERS forms and information is 1-800-822-7967.

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records and to report occurrences of certain adverse events to the U.S. Department of Health and Human Services. Reportable events include those listed in the Act for each vaccine and events specified in the package insert as contraindications to further doses of the vaccine.[17,18]

DRUG INTERACTIONS

If DTP and TIG or Diphtheria Antitoxin are administered concurrently, separate syringes and separate sites should be used.

As with other intramuscular injections, use with caution in patients on anticoagulant therapy.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (<2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it is reasonable to defer vaccination until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.[2]

If DTP has been administered to persons receiving immunosuppressive therapy, a recent injection of immunoglobulin or having an ...mmunodeficiency disorder, an adequate immunologic response may not be obtained.

...RCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

...studies have been performed to evaluate carcinogenicity, mutagenic potential, or impact on fertility.

...REGNANCY

THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE AND OLDER.

PEDIATRIC USE

SAFETY AND EFFECTIVENESS OF DTP VACCINE OR AT THE TIME WHEN DTP VACCINE IS USED TO RECONSTITUTE ActHIB™ OR OmniHIB™ IN INFANTS BELOW THE AGE OF SIX WEEKS HAVE NOT BEEN ESTABLISHED. (See **DOSAGE AND ADMINISTRATION** section.)

This vaccine is recommended for immunizing children 6 weeks of age through 6 years of age (up to the seventh birthday). DTP is the preferred vaccine in this age group, but in those situations where an *absolute contraindication* to pertussis vaccination exists, or where in the opinion of the physician the pertussis vaccine should not be administered, DT is the appropriate alternative.

Full protection is achieved upon completion of primary immunization with either four doses of DTP, or three doses of DTP followed by a dose of an approved acellular DTP. A fifth dose of DTP or an approved acellular DTP is required.

THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE AND OLDER. For persons 7 years of age and older, the recommended vaccine is Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td).

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For Administration of DTP Vaccine Only:

The primary series for children less than 7 years of age is four doses of 0.5 mL each given intramuscularly. The customary age for the first dose is 2 months of age but may be given as young as 6 weeks of age and up to the seventh birthday.

Inject 0.5 mL intramuscularly only. The preferred injection sites are the anterolateral aspect of the thigh and the deltoid muscle of the upper arm. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk. During the course of primary immunizations, injections should not be made more than once at the same site.

The use of reduced volume (fractional doses) is not recommended. The effect of such practices on the frequency of serious adverse events and on protection against disease has not been determined.

Do NOT administer this product subcutaneously.

Special care should be taken to ensure that the injection does not enter a blood vessel.

PRIMARY IMMUNIZATION

This vaccine is recommended for children 6 weeks through 6 years (up to the seventh birthday) ideally beginning when the infant is 6 weeks to 2 months of age.

The primary series consists of four doses. For infants 6 weeks through 12 months of age, administer three 0.5 mL doses intramuscularly at least 4 to 8 weeks apart. The fourth dose is administered 6 to 12 months after the third injection.

BOOSTER IMMUNIZATION

For children between 4 and 6 years of age (preferably at time of kindergarten or elementary school entrance), a booster of 0.5 mL should be administered intramuscularly. Those who receive all four primary immunizing doses before their fourth birthday should receive a single dose of DTP just before entering kindergarten or elementary school. This booster dose is not necessary if the fourth dose in the primary series was administered after the fourth birthday. Thereafter, routine booster immunizations should be with Td, at intervals of 10 years. PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE) (DTP).

TABLE 2[2]

ROUTINE DIPHTHERIA, TETANUS, AND PERTUSSIS VACCINATION SCHEDULE
Summary For Children <7 Years Old – United States, 1991

Dose	Customary Age	Age/Interval†	Product
Primary 1	2 Months	6 weeks old or older	DTP†
Primary 2	4 Months	4-8 weeks after first dose*	DTP†
Primary 3	6 Months	4-8 weeks after second dose*	DTP†
Primary 4	15 Months	6-12 months after third dose*	DTP†
Booster	4-6 years old, before entering kindergarten or elementary school (not necessary if fourth primary vaccinating dose administered after fourth birthday)		DTP†
Additional Boosters		Every 10 years after last dose	Td

* Use DT if pertussis vaccine is contraindicated. If the child is ≥1 year of age at the time that primary dose three is due, a third dose 6 to 12 months after the second dose completes primary vaccination with DT.

† Prolonging the interval does not require restarting series.

Preterm infants should be vaccinated according to their chronological age from birth.[2,9]

Interruption of the recommended schedule with a delay between doses does not interfere with the final immunity achieved with DTP. There is no need to start the series over again, regardless of the time elapsed between doses.

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) can be interchangeably used with DTP for the fourth and fifth doses. However ActHIB™ cannot be reconstituted with DTaP.

The simultaneous administration of DTP, oral polio virus vaccine (OPV), and measles-mumps-rubella vaccine (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately. Simultaneous vaccination (at separate sites with separate syringes) with DTP, MMR, OPV, or inactivated poliovirus vaccine (IPV), and Haemophilus b conjugate vaccine (HbCV) is also acceptable.[2] The ACIP recommends the simultaneous administration, at separate sites with separate syringes, of all vaccines appropriate to the age and previous vaccination status of the recipients including the special circumstance of simultaneous administration of DTP, OPV, HbCV, and MMR at ≥15 months of age.[2]

If passive immunization is needed for tetanus, TIG is the product of choice. It provides longer protection than antitoxin of animal origin and causes few adverse reactions. The currently recommended prophylactic dose of TIG for wounds of average severity is 250 units intramuscularly. When tetanus toxoid and TIG are administered concurrently, separate syringes and separate sites should be used. The ACIP recommends the use of only adsorbed toxoid in this situation.[2]

WHEN RECONSTITUTING HAEMOPHILUS b CONJUGATE VACCINE (TETANUS TOXOID CONJUGATE), ActHIB™ or OmniHIB™

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

CLI whole-cell DTP vaccine also can be used for reconstitution of ActHIB™ or OmniHIB™. Cleanse both the DTP and ActHIB™ or OmniHIB™ vaccine vial rubber barriers with a suitable germicide prior to reconstitution. Thoroughly agitate the vial of CLI whole-cell DTP vaccine, then withdraw a 0.6 mL dose and inject into the vial of lyophilized ActHIB™ or *OmniHIB*™. After reconstitution and thorough agitation, ActHIB™ or OmniHIB™ will appear whitish in color. Using a new syringe, administer 0.5 mL dose of DTP/ActHIB™ or OmniHIB™ vaccines.

When CLI whole-cell DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, administer **intramuscularly only. Vaccine should be used immediately (i.e. within 30 minutes) after reconstitution.**

After reconstitution, each 0.5 mL dose is formulated to contain 6.7 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, an estimate of 4 protective units of pertussis vaccine, 10 µg of purified capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid, and 8.5% of sucrose. ***(Refer to ActHIB™ package insert.)***

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

Each dose of DTP/ActHIB™ or OmniHIB™ vaccines is administered intramuscularly in the outer aspect of the vastus lateralis (mid-thigh) or deltoid. The vaccine should not be injected into the gluteal area or areas where there may be a nerve trunk. During the course of primary immunizations, injections should not be made more than once at the same site.

When CLI DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, the combined vaccines are indicated for infants and children 2 months through 5 years of age for intramuscular administration in accordance with the schedule indicated in Table 3.[10]

TABLE 3[10]

RECOMMENDED IMMUNIZATION SCHEDULE
For Previously Unvaccinated Children

DOSE	AGE	IMMUNIZATION
First, Second and Third	At 2, 4 and 6 months	DTP or DTP/ActHIB™ or DTP/OmniHIB™
Fourth	At 15 to 18 months	DTP or DTP/ActHIB™ or DTP/*OmniHIB*™ or Acellular Pertussis (DTaP)
Fifth	4 to 6 years	DTP or Acellular Pertussis (DTaP)

* Acellular Pertussis (DTaP) should NOT be used to reconstitute ActHIB™/*OmniHIB*™. When administering DTaP for the fourth dose, *Haemophilus influenzae* type b vaccine also should be administered at this time in a separate syringe at a different site.

For Previously Unvaccinated Children

Immunization schedules should be considered on an individual basis for children not vaccinated according to the recommended schedule. Three doses of a product containing DTP, given at approximately 2-month intervals, are required followed by a fourth dose of a product containing DTP or DTaP approximately 12 months later and a fifth dose of a product containing DTP or DTaP at 4 to 6 years of age. If the fourth dose of a pertussis-containing vaccine is not given until after the fourth birthday, no further doses of a pertussis-containing vaccine are necessary.

The number of doses of a product containing *H influenzae* type b conjugate vaccine indicated depends on the age that immunization is begun. A child 7 to 11 months of age should receive 3 doses of a product containing *H influenzae* type b conjugate vaccine. A child 12 to 14 months of age should receive 2 doses of a product containing *H influenzae* type b conjugate vaccine. A child 15 to 59 months of age should receive 1 dose of a product containing *H influenzae* type b conjugate vaccine.

Preterm infants should be vaccinated according to their chronological age from birth.[9]

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved when CLI DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™. There is no need to start the series over again, regardless of the time elapsed between doses.

It is recommended that the same conjugate vaccine be used throughout each immunization schedule, consistent with the data supporting approval and licensure of the vaccine. Since ActHIB™ and OmniHIB™ are the same vaccine, these may be used interchangeably.

DO NOT INJECT INTRAVENOUSLY.

HOW SUPPLIED

DTP Vial, 2.5 mL – Product No. 49281-280-05
DTP Vial, 5 mL – Product No. 49281-280-10
DTP Vial, 7.5 mL – Product No. 49281-280-84

One 7.5 mL vial of Connaught Laboratories, Inc. Diphtheria and Tetanus Toxoids and Pertussis Vaccine as Diluent packaged with Vial, 1 Dose lyophilized Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) (10 x 1 Dose vials per package) – Product No. 49281-549-10

Administer vaccine immediately (i.e. within 30 minutes) after reconstitution.

STORAGE

Store between 2° – 8°C (35° – 46°F). DO NOT FREEZE. Temperature extremes may adversely affect resuspendability of this vaccine.

Store lyophilized vaccine packaged with vial containing Diphtheria and Tetanus Toxoids and Pertussis vaccine between 2° – 8°C (35° – 46°F). DO NOT FREEZE.

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CONNAUGHT
A PASTEUR MÉRIEUX COMPANY

A.H.F.S. Category 80:08

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP

(FOR PEDIATRIC USE)

Caution: *Federal (U.S.A.) law prohibits dispensing without prescription.*

DESCRIPTION

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) combines diphtheria and tetanus toxoids adsorbed with pertussis vaccine, for intramuscular use, in a sterile isotonic sodium chloride solution containing sodium phosphate buffer to control pH. The vaccine, after shaking, is a turbid liquid, whitish-gray in color. When used to reconstitute Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), ActHIB™ or OmniHIB™, the combined vaccines appear whitish in color.

Corynebacterium diphtheriae cultures are grown in a modified Mueller and Miller medium.[1] *Clostridium tetani* cultures are grown in a peptone-based medium. Both toxins are detoxified with formaldehyde. The detoxified materials are separately purified by serial ammonium sulfate fractionation and diafiltration.

The pertussis vaccine component is derived from *Bordetella pertussis* cultures grown on blood-free Bordet Gengou media. The pertussis organisms are harvested and inactivated with thimerosal and resuspended in physiological saline and thimerosal.

The toxoids are adsorbed to aluminum potassium sulfate (alum). The adsorbed diphtheria and tetanus toxoids are combined with pertussis vaccine concentrate, and diluted to a final volume using sterile phosphate-buffered physiological saline. Each 0.5 mL dose contains, by assay, not more than 0.17 mg of aluminum and not more than 100 µg (0.02%) of residual formaldehyde. Thimerosal (mercury derivative) 1:10,000 is added as a preservative.

Each 0.5 mL dose is formulated to contain 6.7 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid (both toxoids induce at least 2 units of antitoxin per mL in the guinea pig potency test).

The total human immunizing dose (the first three 0.5 mL doses administered) contains an estimate of 12 units of pertussis vaccine (4 protective units per single dose).[2] The potency of the pertussis component of each lot of DTP is tested in a mouse protection test.

At the time when Connaught Laboratories, Inc. (CLI) DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, each single dose of the 0.5 mL mixture is formulated to contain 6.7 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, an estimate of 4 protective units of pertussis vaccine, 10 µg of purified capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid, and 8.5% of sucrose.

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

CLINICAL PHARMACOLOGY

DIPHTHERIA

Corynebacterium diphtheriae may cause both localized and generalized disease. Systemic intoxication is caused by diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin.

At one time, diphtheria was common in the United States. More than 200,000 cases, primarily among young children, were reported in 1921. Approximately 5% to 10% of cases were fatal; the highest case-fatality ratios were recorded for the very young and the elderly. Reported cases of diphtheria of all types declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state. After 1979, cutaneous diphtheria was no longer a notifiable disease. From 1980 to 1989, only 24 cases of respiratory diphtheria were reported; two cases were fatal, and 18 (75%) occurred among persons 20 years of age or older.[2]

Diphtheria is currently a rare disease in the United States primarily because of the high level of appropriate vaccination among children (97% of children entering school have received ≥three doses of diphtheria and tetanus toxoids and pertussis vaccine adsorbed [DTP]) and because of an apparent reduction in the prevalence of toxigenic strains of *C. diphtheriae*. Most cases occur among unvaccinated or inadequately immunized persons.[2]

Both toxigenic and nontoxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce toxin cause myocarditis and neuritis. Toxigenic strains are more often associated with severe or fatal illness in noncutaneous (respiratory or other mucosal surface) infections and are more commonly recovered in association with respiratory than from cutaneous infections.[2]

A complete vaccination series substantially reduces the risk of developing diphtheria, and vaccinated persons who develop disease have milder illness. Protection lasts at least 10 years. Vaccination does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nose or on the skin.[2]

TETANUS

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*.

The occurrence of tetanus in the United States has decreased dramatically from 560 reported cases in 1947 to a record low of 48 reported cases in 1987. Tetanus in the United States is primarily a disease of older adults. Of 99 tetanus patients with complete information reported to the Centers for Disease Control and Prevention (CDC) during 1987 and 1988, 68% were ≥50 years of age, while only six were <20 years of age. Overall, the case-fatality rate was 21%. In 1992, 45 cases were reported of which 82% were ≥50 years of age.[3] The disease continues to occur almost exclusively among persons who are unvaccinated or inadequately vaccinated or whose vaccination histories are unknown or uncertain.[2]

In 4% of tetanus cases reported during 1987 and 1988, no wound or other condition could be implicated. Non-acute skin lesions, such as ulcers, or medical conditions such as abscesses were reported in 14% of cases.[2]

Spores of *C. tetani* are ubiquitous. Serologic tests indicate that naturally acquired immunity to tetanus toxin does not occur in the United States.[2] Thus, universal primary vaccination, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect persons among all age-groups. Tetanus toxoid is a highly effective antigen, and a completed primary series generally induces protective levels of neutralizing antibodies to tetanus toxin that persist for ≥10 years.[2]

The potency of diphtheria and tetanus toxoids was determined on the basis of immunogenicity studies with a comparison to a serological correlate of protection (0.01 I.U./mL) established by the Panel on Review of Bacterial Vaccines & Toxoids.[4]

EFFICACY OF DIPHTHERIA AND TETANUS TOXOID VACCINES

Circulating protective levels of neutralizing antibodies to diphtheria and tetanus toxins can be induced by the administration of Diphtheria and Tetanus Toxoids Adsorbed USP (For Pediatric Use) (DT) or DTP.

A clinical study was performed in 20 children under one year of age to determine the serological responses and the adverse reactions when Connaught Laboratories, Inc. (CLI) DT was administered as a primary series of three doses. Protective levels of diphtheria and tetanus antitoxins that were equal to or greater than 0.01 I.U./mL were detected in 100% of the children following two doses of the vaccine. However, maternal antibody may have contributed to the total neutralizing antibody in some of these infants. Protective levels of antitoxin were observed in 100% of these infants following three doses of DT. No local or systemic reactions were observed in approximately half of the infants and only mild or moderate reactions were observed in the remainder of the DT study group.[5]

Another clinical study to evaluate serological responses and adverse reactions of CLI DT was performed in 40 children under one year of age. One group of 20 children received 0.5 mL doses of DTP, DT, DTP at two, four and six months of age, respectively. The second group of 20 children received 0.5 mL doses of DTP, DTP, and DT, respectively, at the same ages. The immunologic protection against diphtheria and tetanus as measured by toxin neutralizing antibodies induced by DT was comparable when administered as either a second or third dose.[6] The reaction rates following CLI whole-cell DTP vaccination closely correlated with the rates observed with other commercially available whole-cell DTP vaccines.[7] The incidence of adverse reactions was significantly lower following DT administration ($p < 0.05$). Although the number of vaccinees was small, no persistent screaming episodes or severe neurological reactions such as seizures or encephalopathy were observed with either vaccine in this study.[6]

PERTUSSIS

Disease caused by *Bordetella pertussis* was once a major cause of infant and childhood morbidity and mortality in the United States. Pertussis (whooping cough) became a nationally notifiable disease in 1922, and reports reached a peak of 265,269 cases and 7,518 deaths in 1934. The highest number of reported pertussis deaths (9,269) occurred in 1923. The introduction and widespread use of standardized whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids (DTP) in the late 1940s resulted in a substantial decline in pertussis disease, a decline which continued without interruption for nearly 30 years.[2]

By 1970, the annual reported incidence of pertussis had been reduced by 99%. During the 1970s the annual numbers of reported cases stabilized at an average of approximately 2,300 cases each year. During the 1980s, however, the annual numbers of reported cases gradually increased from 1,730 cases in 1980 to 4,517 cases in 1989. An average of eight pertussis-associated fatalities was reported each year throughout the 1980s.[2]

From 1989 to 1991, 11,446 cases of pertussis were reported for an unadjusted incidence per 100,000 population of 1.7 in 1989, 1.8 in 1990 and 1.1 in 1991. The incidence for 1992 was 1.6 per 100,000. Age specific incidence and hospitalization rates were highest in the first year of life, decreasing with increasing age. Trends of the past years suggest an increase in reported pertussis since 1976, with the peak year being 1990.[8]

During the period 1989 to 1991, of 3,900 reports of hospitalization, 1,115 had developed pneumonia, seizures occurred in 157 cases, encephalopathy was reported for 12, and there were 20 pertussis attributed deaths. These events were more frequently reported in children less than 6 months of age and were generally less frequent with increasing age.[7] Of patients 3 months through 4 years of age, where vaccination status was known, 65% of 4,471 patients had not received the recommended schedule of immunization and 39% had not received any pertussis containing vaccine.[3]

Among older children and adults, including those previously vaccinated, *B. pertussis* infection may result in symptoms of bronchitis or upper-respiratory-tract infection. Pertussis may not be associated with classic signs, especially the inspiratory whoop. Older preschool children and school-age siblings who are not fully vaccinated and who develop pertussis can be important sources of infection for infants <1 year of age. Adults also play an important role in the transmission of pertussis to unvaccinated or incompletely vaccinated infants and young children.[2]

EFFICACY OF PERTUSSIS VACCINE

Although DTP has been evaluated as a control vaccine in a number of clinical trials of "acellular pertussis vaccines," no formal efficacy trial was performed prior to approval. Approval was based on historical and continuing evidence of protection (surveillance) in the population at risk. It was also shown that vaccines with acceptable mouse protection potencies induced protective serum agglutinin antibody titers.[4] The pertussis component of each lot of DTP is tested for potency by a mouse protection test.

In clinical trials, one dose of CLI whole-cell DTP vaccine was used to reconstitute one lyophilized single dose vial of ActHIB™ or OmniHIB™ with no diminution in anti-PRP response or diphtheria, tetanus and pertussis responses.

INDICATIONS AND USAGE

[illegible] Adsorbed USP (For Pediatric Use) is recommended for active immunization of

In clinical trials, one dose of CLI whole-cell DTP vaccine was used to reconstitute one lyophilized single dose vial of ActHIB™ or OmniHIB™ with no diminution in anti-PRP response or diphtheria, tetanus and pertussis responses.

INDICATIONS AND USAGE

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) is recommended for active immunization of children up to age 7 years against diphtheria, tetanus, and pertussis (whooping cough) simultaneously. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, DT should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.[2,9]

Persons recovering from confirmed pertussis do not need additional doses of DTP but should receive additional doses of DT to complete the series.[2]

Available data indicate that the appropriate age for institution of immunizations in prematurely born infants is the usual chronological age of 2 months. Vaccine doses should not be reduced for preterm infants.[2,9]

If passive immunization is required, Tetanus Immune Globulin (Human) (TIG) and/or equine Diphtheria Antitoxin are the products of choice for tetanus and diphtheria, respectively (see **DOSAGE AND ADMINISTRATION** section).

When CLI DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, the combined vaccines are indicated for the active immunization of infants and children 2 months through 5 years of age for the prevention of invasive diseases caused by diphtheria, tetanus, pertussis and *H influenzae* type b.[10,11] ***(Refer to ActHIB™ package insert.)***

A single injection containing diphtheria, tetanus, pertussis and Haemophilus b conjugate antigens may be more acceptable to parents and may increase compliance with vaccination programs. Therefore, in those situations where, in the judgment of the physician, it is of benefit to administer a single injection of whole-cell DTP vaccine and Haemophilus b conjugate vaccine concomitantly, ***only CLI whole-cell DTP vaccine may be used for reconstitution of lyophilized ActHIB™ or OmniHIB™.*** Antibody levels associated with protection may not be achieved earlier than two weeks following the last recommended dose. (See **DOSAGE AND ADMINISTRATION** section.)

As with any vaccine, vaccination with DTP or combined vaccines CLI DTP and ActHIB™ or OmniHIB™ may not protect 100% of susceptible individuals.

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

This vaccine is NOT to be used for the treatment of diphtheria, tetanus, pertussis or H influenzae type b infection.

This vaccine should NOT be used for immunizing persons 7 years of age and older.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including thimerosal, a mercury derivative, is a contraindication for further use of this vaccine.

It is a contraindication to use this or any other related vaccine after an immediate anaphylactic reaction associated with a previous dose.

It is a contraindication to administer this vaccine in the presence of any evolving neurological condition.

Encephalopathy after a previous dose is a contraindication to further use.

Immunization should be deferred during the course of an acute illness. Vaccination of infants and children with severe, febrile illness should generally be deferred until these persons have recovered. However, the presence of minor illnesses such as mild upper respiratory infections with or without low-grade fever are not contraindications to further use.[2]

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.[12]

WARNINGS

If any of the following events occur in temporal relation to receipt of DTP, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelae.[2]

THE FOLLOWING EVENTS WERE PREVIOUSLY CONSIDERED CONTRAINDICATIONS AND ARE NOW CONSIDERED WARNINGS:[2]

1. **Temperature of ≥40.5°C (105°F) within 48 hours not due to another identifiable cause:** Such a temperature is considered a warning because of the likelihood that fever following a subsequent dose of DTP vaccine also will be high. Because such febrile reactions are usually attributed to the pertussis component, vaccination with DT should not be discontinued.[2]
2. **Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours:** Although these uncommon events have not been recognized to cause death nor to induce permanent neurological sequelae, it is prudent to continue vaccination with DT, omitting the pertussis component.[2]
3. **Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours:** Follow-up of infants who have cried inconsolably following DTP vaccination has indicated that this reaction, though unpleasant, is without long-term sequelae and not associated with other reactions of greater significance.[2] Evidence is insufficient to indicate whether pertussis vaccine-associated protracted, inconsolable, or high-pitched crying or screaming does, or does not, lead to chronic neurologic damage.[13] Inconsolable crying occurs most frequently following the first dose and is less frequently reported following subsequent doses of DTP vaccine. However, crying for >30 minutes following DTP vaccination can be a predictor of increased likelihood of recurrence of persistent crying following subsequent doses. Children with persistent crying have had a higher rate of local reactions than children who had other DTP-associated reactions (including high fever, seizures, and hypotonic-hyporesponsive episodes), suggesting that prolonged crying was really a pain reaction.[2]
4. **Convulsions with or without fever occurring within three days:** Short-lived convulsions, with or without fever, have not been shown to cause permanent sequelae. Furthermore, the occurrence of prolonged febrile seizures (i.e., status epilepticus – any seizure lasting >30 minutes or recurrent seizures lasting a total of 30 minutes without the child fully regaining consciousness), irrespective of their cause, involving an otherwise normal child does not substantially increase the risk for subsequent febrile (brief or prolonged) or afebrile seizures. The risk is significantly increased (p=0.018) only among those children who are neurologically abnormal before their episode of status epilepticus.[2] Accordingly, although a convulsion following DTP vaccination has previously been considered a contraindication to further doses, under certain circumstances subsequent doses may be indicated, particularly if the risk of pertussis in the community is high. If a child has a seizure following the first or second dose of DTP, it is desirable to delay subsequent doses until the child's neurologic status is better defined. By the end of the first year of life, the presence of an underlying neurologic disorder has usually been determined, and appropriate treatment instituted. DT vaccine should not be administered before a decision has been made about whether to continue the DTP series. Regardless of which vaccine is given, it is prudent also to administer acetaminophen[2], 15 mg/kg of body weight, at the time of vaccination and every 4 hours subsequently for 24 hours.

Persons who experienced Arthus-type hypersensitivity reactions or a temperature of >103°F (39.4°C) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given even emergency doses of Td more frequently than every 10 years, even if they have a wound that is neither clean nor minor.[2]

DTP should not be given to children with any coagulation disorder, including thrombocytopenia, that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

Recent studies suggest that infants and children with a history of convulsions in first-degree family members (i.e., siblings and parents) have a 3.2-fold increased risk for neurologic events compared with those without such histories.[14] *However, the ACIP has concluded that a family history of convulsions in parents and siblings is not a contraindication to pertussis vaccination and that children with such family histories should receive pertussis vaccine according to the recommended schedule.*[2]

A recent review of all available data by the IOM found evidence is consistent with a causal relation between DTP vaccination and acute encephalopathy, but that there is insufficient evidence to indicate a causal relation between DTP vaccine and permanent neurologic damage.[13]

Infants and children with recognized possible or potential underlying neurologic conditions seem to be at enhanced risk for the appearance of manifestations of the underlying neurologic disorder within two or three days following vaccination.[2] Whether to administer DTP to children with proven or suspected underlying neurologic disorders must be decided on an individual basis. Important considerations include the current local incidence of pertussis, the near absence of diphtheria in the United States and the low risk of infection with *C. tetani*.[2]

Although these events were considered absolute contraindications in previous ACIP recommendations, there may be circumstances, such as a high incidence of pertussis, in which the potential benefits outweigh possible risks, particularly because these events are not associated with permanent sequelae.[2]

The administration of DTP to children with proven or suspected underlying neurologic disorders that are not actively evolving must be decided on an individual basis.

Only full doses (0.5 mL) of DTP vaccine should be given; if a specific contraindication to DTP exists, the vaccine should not be given.[2]

Controversy regarding the safety of pertussis vaccine during the 1970s led to several studies of the benefits and risks of this vaccination during the 1980s. These epidemiologic analyses clearly indicate that the benefits of pertussis vaccination outweigh any risks and have not shown a cause and effect with neurologic illness.[2,9]

Deaths have been reported in temporal association with the administration of DTP vaccine (see **ADVERSE REACTIONS** section).

When CLI DTP vaccine is used alone or to reconstitute ActHIB™ or OmniHIB™ and administered to immunosuppressed persons or persons receiving immunosuppressive therapy, the expected antibody responses may not be obtained. This includes patients with severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation.[15]

Administration of DTP and/or Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) is not contraindicated in individuals with HIV infection.[11]

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

PRECAUTIONS

GENERAL

Care is to be taken by the health-care provider for the safe and effective use of DTP.

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines, previous immunization history, current health status (see **CONTRAINDICATIONS; WARNINGS** sections), and a current knowledge of the literature concerning the use of the vaccine under consideration. Immunosuppressed patients may not respond.

Prior to administration of DTP, health-care personnel should inform the parent or guardian of the patient the benefits and risks of immunization, and also inquire about the recent health status of the patient to be injected.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped and should be properly disposed.

INFORMATION FOR PATIENTS

As part of the child's immunization record, the date, lot number and manufacturer of the vaccine administered MUST be recorded.[16,17,18]

The health-care provider should inform the parent or guardian of the patient about the potential for adverse reactions that have been temporally associated with DTP administration. Parents or guardians should be instructed to report any serious adverse reactions to their health-care provider.

IT IS EXTREMELY IMPORTANT WHEN THE CHILD RETURNS FOR THE NEXT DOSE IN THE SERIES, THAT THE PARENT OR GUARDIAN OF THE PATIENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER THE PREVIOUS DOSE (SEE **CONTRAINDICATIONS; ADVERSE REACTIONS** SECTIONS).

The health-care provider should inform the parent or guardian of the patient the importance of completing the immunization series.

The health-care provider should provide the Vaccine Information Materials (VIMs) which are required to be given with each immunization.

The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986.[16] The toll-free number for VAERS forms and information is 1-800-822-7967.

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records and to report occurrences of certain adverse events to the U.S. Department of Health and Human Services. Reportable events include those listed in the Act for each vaccine and events specified in the package insert as contraindications to further doses of the vaccine.[17,18]

DRUG INTERACTIONS

If DTP and TIG or Diphtheria Antitoxin are administered concurrently, separate syringes and separate sites should be used.

As with other intramuscular injections, use with caution in patients on anticoagulant therapy.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (<2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it is reasonable to defer vaccination until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.[2]

If DTP has been administered to persons receiving immunosuppressive therapy, a recent injection of immunoglobulin or having an immunodeficiency disorder, an adequate immunologic response may not be obtained.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

No studies have been performed to evaluate carcinogenicity, mutagenic potential, or impact on fertility.

PREGNANCY

THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE AND OLDER.

PEDIATRIC USE

SAFETY AND EFFECTIVENESS OF DTP VACCINE OR AT THE TIME WHEN DTP VACCINE IS USED TO RECONSTITUTE ActHIB™ OR OmniHIB™ IN INFANTS BELOW THE AGE OF SIX WEEKS HAVE NOT BEEN ESTABLISHED. (See **DOSAGE AND ADMINISTRATION** section.)

This vaccine is recommended for immunizing children 6 weeks of age through 6 years of age (up to the seventh birthday). DTP is the preferred vaccine in this age group, but in those situations where an *absolute contraindication* to pertussis vaccination exists, or where in the opinion of the physician the pertussis vaccine should not be administered, DT is the appropriate alternative.

Full protection is achieved upon completion of primary immunization with either four doses of DTP, or three doses of DTP followed by a dose of an approved acellular DTP. A fifth dose of DTP or an approved acellular DTP is required.

THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE AND OLDER. For persons 7 years of age and older, the recommended vaccine is Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td).

ADVERSE REACTIONS

Adverse reactions associated with the use of DTP include local redness, warmth, edema, induration with or without tenderness, as well as urticaria and rash. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses.[6]

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent.[19] If local redness 2.5 cm occurs, the likelihood of recurrence after another DTP dose increases significantly.[6]

Evidence does not indicate a causal relation between DTP vaccine and SIDS. Studies showing a temporal relation between these events are consistent with the expected occurrence of SIDS over the age range in which DTP immunization typically occurs.[13]

Deaths due to causes other than SIDS, including deaths due to serious infections, have occurred in infants following the administration of DTP. No association has been shown for hospitalizations due to infectious disease and receipt of DTP.[20]

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in TABLE 1.[2]

TABLE 1[2] ADVERSE EVENTS OCCURRING WITHIN 48 HOURS OF DTP VACCINATIONS

Event	Frequency*
Local	
Redness	1/3 doses
Swelling	2/5 doses
Pain	1/2 doses
Systemic	
Fever ≥38°C (100.4°F)	1/3 doses
Drowsiness	1/2 doses
Fretfulness	1/15 doses
Vomiting	1/5 doses
Anorexia	
Persistent, inconsolable crying (duration ≥3 hours)	1/100 doses
Fever ≥40.5°C (≥105°F)	1/330 doses
Nervous System	
Collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,750 doses

*Rate per total number of doses regardless of dose number in DTP series.

BODY SYSTEM AS A WHOLE

Mild systemic reactions such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following administration of DTP than following DT, are usually self-limited, and need no therapy other than symptomatic treatment such as acetaminophen.[2]

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) and death have been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[2]

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2 to 8 hours after an injection), may follow receipt of tetanus toxoid.[2]

Moderate to severe systemic events, include high fever (i.e., temperature of ≥40.5°C (105°F) and persistent, inconsolable crying lasting ≥3 hours. These events occur infrequently and appear to be without sequelae.[2]

Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6 to 10 per million doses).[2]

NERVOUS SYSTEM

The following neurologic illnesses have been reported as temporally associated with vaccine containing tetanus toxoid: neurological complications[21,22] including cochlear lesion,[23] brachial plexus neuropathies,[23,24] paralysis of the radial nerve,[25] paralysis of the recurrent nerve,[23] accommodation paresis, and EEG disturbances with encephalopathy.[19] The report from the IOM suggests that there is a causal relation between Guillain-Barré syndrome (GBS) and vaccines containing tetanus toxoid.[26] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid should be considered as a possible etiology.[19,27]

Short-lived convulsions (usually febrile), or collapse (hypotonic-hyporesponsive episode) occur infrequently and appear to be without sequelae.[2]

More severe neurologic events, such as a prolonged convulsion, or encephalopathy, although rare, have been reported in temporal association with DTP administration. An analysis of these data failed to show any cause and effect association.[2]

In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England, children 2 to 35 months of age with serious, acute neurologic disorders such as encephalopathy or complicated convulsion(s), were more likely to have received DTP in the 7 days preceding onset than their age-, sex-, and neighborhood-matched controls. Among children known to be neurologically normal before entering the study, the relative risk (estimated by odds ratio) of a neurologic illness occurring within the 7-day period following receipt of DTP dose, compared to children not receiving DTP in the 7-day period before onset of their illness, was 3.3 ($p < 0.001$).[2]

Within this 7-day period, the risk was significantly increased for immunized children only within 3 days of vaccination (relative risk 4.2, $p < 0.001$). The relative risk for illnesses occurring 4 to 7 days after vaccination was 2.1 ($p < 0.1$). Serious neurologic illnesses requiring hospitalization attributable to pertussis vaccine are rare. Final analysis of a comprehensive case-control study has estimated that the attributable risk of such illnesses is 1 in 140,000 doses administered. An earlier analysis had estimated this risk at 1/110,000 doses. In contrast, final analysis of the case-control study found that the risk of serious neurologic illness following pertussis disease was 1/11,000 pertussis cases. Repeated evaluations have shown that the benefits of vaccine outweigh the risks.[2,9]

The methods and results of the NCES have been thoroughly scrutinized since publication of the study. This reassessment by multiple groups has determined that the number of patients was too small and their classification subject to enough uncertainty to preclude drawing valid conclusions about whether a causal relation exists between pertussis vaccine and permanent neurologic damage. Preliminary data from a 10-year follow-up study of some of the children studied in the original NCES study also suggested a relation between symptoms following DTP vaccination and permanent neurologic disability. However, details are not available to evaluate this study adequately, and the same concerns remain about DTP vaccine precipitating initial manifestations of pre-existing neurologic disorders.[2]

An IOM report by the Committee to review the adverse consequences of pertussis and rubella vaccines concluded that evidence is consistent with a causal relation between DTP vaccine and acute encephalopathy, defined in the controlled studies reviewed as encephalopathy, encephalitis, or encephalomyelitis. On the basis of a review of the evidence bearing on this relation, the Committee concludes that the range of excess risk of acute encephalopathy following DTP immunization is consistent with that estimated for the NCES: 0.0 to 10.5 per million immunizations. The report also states that there is insufficient evidence to indicate a causal relation between DTP vaccine and permanent neurologic damage.[13]

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DT or DTP was not causally related to infantile spasms.[28] The incidence of onset of infantile spasms increases at 3 to 9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.[2]

A bulging fontanelle associated with increased intracranial pressure which occurred within 24 hours following DTP immunization has been reported. A causal relationship has not been established.[29,30,31]

CARDIOVASCULAR SYSTEM

An infant who developed myocarditis several hours after immunization has been reported.[32]

RESPIRATORY SYSTEM

Respiratory difficulties, including apnea, have been observed.

LOCAL

Rash and allergic reactions have been observed.

Sudden Infant Death Syndrome (SIDS) has temporally occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS.[33,34,35] It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2 to 6 months of age and that approximately 85% of SIDS cases occur at ages 1 to 6 months, with the peak incidence occurring at 6 weeks to 4 months of age. By chance alone, some SIDS victims can be expected to have recently received DTP.[33,34,35]

When CLI whole-cell DTP was administered concomitantly (at separate sites with separate syringes) with ActHIB™ or OmniHIB™, the systemic adverse experience profile was not different from that seen when CLI whole-cell DTP vaccine was administered alone.[10,11] ***(Refer to ActHIB™ package insert.)***

In general, the rates of minor systemic reactions after DTP was used to reconstitute ActHIB™ or OmniHIB™ were comparable to those usually reported after DTP vaccine alone.[6,14,36]

When CLI whole-cell DTP was used to reconstitute ActHIB™ or OmniHIB™ and administered to infants at 2, 4, and 6 months of age, the systemic adverse experience profile was comparable to that observed when the two vaccines were given separately. An increase in the rate of local reactions was observed in some instances within the 24-hour period after immunization.[10,11] ***(Refer to ActHIB™ package insert.)***

Reporting of Adverse Events

Reporting by parents or guardians of all adverse events occurring after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by health-care providers to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.[16,17,18]

Health-care providers also should report these events to the Director of Medical Affairs, Connaught Laboratories, Inc., Route 611, P.O. Box 187, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, the vaccine should not be administered.

SHAKE VIAL WELL *before withdrawing each dose. Vaccine contains a bacterial suspension. Vigorous agitation is required to resuspend the contents of the vial.* Discard if vaccine cannot be resuspended.

For Administration of DTP Vaccine Only:

The primary series for children less than 7 years of age is four doses of 0.5 mL each given intramuscularly. The customary age for the first dose is 2 months of age but may be given as young as 6 weeks of age and up to the seventh birthday.

Inject 0.5 mL intramuscularly only. The preferred injection sites are the anterolateral aspect of the thigh and the deltoid muscle of the upper arm. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk. During the course of primary immunizations, injections should not be made more than once at the same site.

The use of reduced volume (fractional doses) is not recommended. The effect of such practices on the frequency of serious adverse events and on protection against disease has not been determined.

Do NOT administer this product subcutaneously.

Special care should be taken to ensure that the injection does not enter a blood vessel.

PRIMARY IMMUNIZATION

This vaccine is recommended for children 6 weeks through 6 years (up to the seventh birthday) ideally beginning when the infant is 6 weeks to 2 months of age.

The primary series consists of four doses. For infants 6 weeks through 12 months of age, administer three 0.5 mL doses intramuscularly at least 4 to 8 weeks apart. The fourth dose is administered 6 to 12 months after the third injection.

BOOSTER IMMUNIZATION

For children between 4 and 6 years of age (preferably at time of kindergarten or elementary school entrance), a booster of 0.5 mL should be administered intramuscularly. Those who receive all four primary immunizing doses before their fourth birthday should receive a single dose of DTP just before entering kindergarten or elementary school. This booster dose is not necessary if the fourth dose in the primary series was administered after the fourth birthday. Thereafter, routine booster immunizations should be with Td, at intervals of 10 years. PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE) (DTP).

BOOSTER IMMUNIZATION
For children between 4 and 6 years of age (preferably at time of kindergarten or elementary school entrance), a booster of 0.5 mL should be administered intramuscularly. Those who receive all four primary immunizing doses before their fourth birthday should receive a single dose of DTP just before entering kindergarten or elementary school. This booster dose is not necessary if the fourth dose in the primary series was administered after the fourth birthday. Thereafter, routine booster immunizations should be with Td, at intervals of 10 years. PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DIPHTHERIA AND TETANUS TOXOIDS *AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE) (DTP).*

TABLE 2[2] **ROUTINE DIPHTHERIA, TETANUS, AND PERTUSSIS VACCINATION SCHEDULE**
Summary For Children <7 Years Old – United States, 1991

Dose	Customary Age	Age/Interval†	Product
Primary 1	2 Months	6 weeks old or older	DTP†
Primary 2	4 Months	4-8 weeks after first dose*	DTP†
Primary 3	6 Months	4-8 weeks after second dose*	DTP†
Primary 4	15 Months	6-12 months after third dose*	DTP†
Booster	4-6 years old, before entering kindergarten or elementary school (not necessary if fourth primary vaccinating dose administered after fourth birthday)		DTP†
Additional Boosters		Every 10 years after last dose	Td

* Use DT if pertussis vaccine is contraindicated. If the child is ≥1 year of age at the time that primary dose three is due, a third dose 6 to 12 months after the second dose completes primary vaccination with DT.
† *Prolonging the interval does not require restarting series.*

Preterm infants should be vaccinated according to their chronological age from birth.[2,9]

Interruption of the recommended schedule with a delay between doses does not interfere with the final immunity achieved with DTP. There is no need to start the series over again, regardless of the time elapsed between doses.

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) can be interchangeably used with DTP for the fourth and fifth doses. However ActHIB™ cannot be reconstituted with DTaP.

The simultaneous administration of DTP, oral polio virus vaccine (OPV), and measles-mumps-rubella vaccine (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately. Simultaneous vaccination (at separate sites with separate syringes) with DTP, MMR, OPV, or inactivated poliovirus vaccine (IPV), and Haemophilus b conjugate vaccine (HbCV) is also acceptable.[2] The ACIP recommends the simultaneous administration, at separate sites with separate syringes, of all vaccines appropriate to the age and previous vaccination status of the recipients including the special circumstance of simultaneous administration of DTP, OPV, HbCV, and MMR at ≥15 months of age.[2]

If passive immunization is needed for tetanus, TIG is the product of choice. It provides longer protection than antitoxin of animal origin and causes few adverse reactions. The currently recommended prophylactic dose of TIG for wounds of average severity is 250 units intramuscularly. When tetanus toxoid and TIG are administered concurrently, separate syringes and separate sites should be used. The ACIP recommends the use of only adsorbed toxoid in this situation.[2]

WHEN RECONSTITUTING HAEMOPHILUS b CONJUGATE VACCINE (TETANUS TOXOID CONJUGATE), ActHIB™ or OmniHIB™

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

CLI whole-cell DTP vaccine also can be used for reconstitution of ActHIB™ or OmniHIB™. Cleanse both the DTP and ActHIB™ or OmniHIB™ vaccine vial rubber barriers with a suitable germicide prior to reconstitution. Thoroughly agitate the vial of CLI whole-cell DTP vaccine, then withdraw a 0.6 mL dose and inject into the vial of lyophilized ActHIB™ or OmniHIB™. After reconstitution and thorough agitation, ActHIB™ or OmniHIB™ will appear whitish in color. Using a new syringe, administer 0.5 mL dose of DTP/ActHIB™ *or OmniHIB™ vaccines.*

When CLI whole-cell DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, administer **intramuscularly only. Vaccine should be used immediately (i.e. within 30 minutes) after reconstitution.**

After reconstitution, each 0.5 mL dose is formulated to contain 6.7 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, an estimate of 4 protective units of pertussis vaccine, 10 µg of purified capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid, and 8.5% of sucrose. ***(Refer to ActHIB™ package insert.)***

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

Each dose of DTP/ActHIB™ or OmniHIB™ vaccines is administered intramuscularly in the outer aspect of the vastus lateralis (mid-thigh) or deltoid. The vaccine should not be injected into the gluteal area or areas where there may be a nerve trunk.. During the course of primary immunizations, injections should not be made more than once at the same site.

When CLI DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, the combined vaccines are indicated for infants and children 2 months through 5 years of age for intramuscular administration in accordance with the schedule indicated in Table 3.[10]

TABLE 3[10] **RECOMMENDED IMMUNIZATION SCHEDULE**
For Previously Unvaccinated Children

DOSE	AGE	IMMUNIZATION
First, Second and Third	At 2, 4 and 6 months	DTP or DTP/ActHIB™ or DTP/OmniHIB™
Fourth	At 15 to 18 months	DTP or DTP/ActHIB™ or DTP/OmniHIB™ or Acellular Pertussis (DTaP)
Fifth	4 to 6 years	DTP or Acellular Pertussis (DTaP)

* Acellular Pertussis (DTaP) should NOT be used to reconstitute ActHIB™/OmniHIB™. When administering DTaP for the fourth dose, *Haemophilus influenzae* type b vaccine also should be administered at this time in a separate syringe at a different site.

For Previously Unvaccinated Children
Immunization schedules should be considered on an individual basis for children not vaccinated according to the recommended schedule. Three doses of a product containing DTP, given at approximately 2-month intervals, are required followed by a fourth dose of a product containing DTP or DTaP approximately 12 months later and a fifth dose of a product containing DTP or DTaP at 4 to 6 years of age. If the fourth dose of a pertussis-containing vaccine is not given until after the fourth birthday, no further doses of a pertussis-containing vaccine are necessary.

The number of doses of a product containing *H influenzae* type b conjugate vaccine indicated depends on the age that immunization is begun. A child 7 to 11 months of age should receive 3 doses of a product containing *H influenzae* type b conjugate vaccine. A child 12 to 14 months of age should receive 2 doses of a product containing *H influenzae* type b conjugate vaccine. A child 15 to 59 months of age should receive 1 dose of a product containing *H influenzae* type b conjugate vaccine.

Preterm infants should be vaccinated according to their chronological age from birth.[9]

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved when CLI DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™. There is no need to start the series over again, regardless of the time elapsed between doses.

It is recommended that the same conjugate vaccine be used throughout each immunization schedule, consistent with the data supporting approval and licensure of the vaccine. Since ActHIB™ and OmniHIB™ are the same vaccine, these may be used interchangeably.

DO NOT INJECT INTRAVENOUSLY.

HOW SUPPLIED
DTP Vial, 2.5 mL – Product No. 49281-280-05
DTP Vial, 5 mL – Product No. 49281-280-10
DTP Vial, 7.5 mL – Product No. 49281-280-84

One 7.5 mL vial of Connaught Laboratories, Inc. Diphtheria and Tetanus Toxoids and Pertussis Vaccine as Diluent packaged with Vial, 1 Dose lyophilized Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) (10 x 1 Dose vials per package) – Product No. 49281-549-10

Administer vaccine immediately (i.e. within 30 minutes) after reconstitution.

STORAGE
Store between 2° – 8°C (35° – 46°F). DO NOT FREEZE. Temperature extremes may adversely affect resuspendability of this vaccine.

Store lyophilized vaccine packaged with vial containing Diphtheria and Tetanus Toxoids and Pertussis vaccine between 2° – 8°C (35° – 46°F). DO NOT FREEZE.

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Product information
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Swiftwater, Pennsylvania 18370, U.S.A.

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CONNAUGHT
A PASTEUR MÉRIEUX COMPANY

A.H.F.S. Category 80:08

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP

(FOR PEDIATRIC USE)

Caution: *Federal (U.S.A.) law prohibits dispensing without prescription.*

DESCRIPTION

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) combines diphtheria and tetanus toxoids adsorbed with pertussis vaccine, for intramuscular use, in a sterile isotonic sodium chloride solution containing sodium phosphate buffer to control pH. The vaccine, after shaking, is a turbid liquid, whitish-gray in color. When used to reconstitute Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), ActHIB™ or OmniHIB™, the combined vaccines appear whitish in color.

Corynebacterium diphtheriae cultures are grown in a modified Mueller and Miller medium.[1] *Clostridium tetani* cultures are grown in a peptone-based medium. Both toxins are detoxified with formaldehyde. The detoxified materials are separately purified by serial ammonium sulfate fractionation and diafiltration.

The pertussis vaccine component is derived from *Bordetella pertussis* cultures grown on blood-free Bordet Gengou media. The pertussis organisms are harvested and inactivated with thimerosal and resuspended in physiological saline and thimerosal.

The toxoids are adsorbed to aluminum potassium sulfate (alum). The adsorbed diphtheria and tetanus toxoids are combined with pertussis vaccine concentrate, and diluted to a final volume using sterile phosphate-buffered physiological saline. Each 0.5 mL dose contains, by assay, not more than 0.17 mg of aluminum and not more than 100 µg (0.02%) of residual formaldehyde. Thimerosal (mercury derivative) 1:10,000 is added as a preservative.

Each 0.5 mL dose is formulated to contain 6.7 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid (both toxoids induce at least 2 units of antitoxin per mL in the guinea pig potency test).

The total human immunizing dose (the first three 0.5 mL doses administered) contains an estimate of 12 units of pertussis vaccine (4 protective units per single dose).[2] The potency of the pertussis component of each lot of DTP is tested in a mouse protection test.

At the time when Connaught Laboratories, Inc. (CLI) DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, each single dose of the 0.5 mL mixture is formulated to contain 6.7 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, an estimate of 4 protective units of pertussis vaccine, 10 µg of purified capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid, and 8.5% of sucrose.

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

CLINICAL PHARMACOLOGY

DIPHTHERIA

Corynebacterium diphtheriae may cause both localized and generalized disease. Systemic intoxication is caused by diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin.

At one time, diphtheria was common in the United States. More than 200,000 cases, primarily among young children, were reported in 1921. Approximately 5% to 10% of cases were fatal; the highest case-fatality ratios were recorded for the very young and the elderly. Reported cases of diphtheria of all types declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state. After 1979, cutaneous diphtheria was no longer a notifiable disease. From 1980 to 1989, only 24 cases of respiratory diphtheria were reported; two cases were fatal, and 18 (75%) occurred among persons 20 years of age or older.[2]

Diphtheria is currently a rare disease in the United States primarily because of the high level of appropriate vaccination among children (97% of children entering school have received ≥three doses of diphtheria and tetanus toxoids and pertussis vaccine adsorbed [DTP]) and because of an apparent reduction in the prevalence of toxigenic strains of *C. diphtheriae*. Most cases occur among unvaccinated or inadequately immunized persons.[2]

Both toxigenic and nontoxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce toxin cause myocarditis and neuritis. Toxigenic strains are more often associated with severe or fatal illness in noncutaneous (respiratory or other mucosal surface) infections and are more commonly recovered in association with respiratory than from cutaneous infections.[2]

A complete vaccination series substantially reduces the risk of developing diphtheria, and vaccinated persons who develop disease have milder illness. Protection lasts at least 10 years. Vaccination does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nose or on the skin.[2]

TETANUS

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*.

The occurrence of tetanus in the United States has decreased dramatically from 560 reported cases in 1947 to a record low of 48 reported cases in 1987. Tetanus in the United States is primarily a disease of older adults. Of 99 tetanus patients with complete information reported to the Centers for Disease Control and Prevention (CDC) during 1987 and 1988, 68% were ≥50 years of age, while only six were <20 years of age. Overall, the case-fatality rate was 21%. In 1992, 45 cases were reported of which 82% were ≥50 years of age.[3] The disease continues to occur almost exclusively among persons who are unvaccinated or inadequately vaccinated or whose vaccination histories are unknown or uncertain.[2]

In 4% of tetanus cases reported during 1987 and 1988, no wound or other condition could be implicated. Non-acute skin lesions, such as ulcers, or medical conditions such as abscesses were reported in 14% of cases.[2]

Spores of *C. tetani* are ubiquitous. Serologic tests indicate that naturally acquired immunity to tetanus toxin does not occur in the United States.[2] Thus, universal primary vaccination, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect persons among all age-groups. Tetanus toxoid is a highly effective antigen, and a completed primary series generally induces protective levels of neutralizing antibodies to tetanus toxin that persist for ≥10 years.[2]

The potency of diphtheria and tetanus toxoids was determined on the basis of immunogenicity studies with a comparison to a serological correlate of protection (0.01 I.U./mL) established by the Panel on Review of Bacterial Vaccines & Toxoids.[4]

EFFICACY OF DIPHTHERIA AND TETANUS TOXOID VACCINES

Circulating protective levels of neutralizing antibodies to diphtheria and tetanus toxins can be induced by the administration of Diphtheria and Tetanus Toxoids Adsorbed USP (For Pediatric Use) (DT) or DTP.

A clinical study was performed in 20 children under one year of age to determine the serological responses and the adverse reactions when Connaught Laboratories, Inc. (CLI) DT was administered as a primary series of three doses. Protective levels of diphtheria and tetanus antitoxins that were equal to or greater than 0.01 I.U./mL were detected in 100% of the children following two doses of the vaccine. However, maternal antibody may have contributed to the total neutralizing antibody in some of these infants. Protective levels of antitoxin were observed in 100% of these infants following three doses of DT. No local or systemic reactions were observed in approximately half of the infants and only mild or moderate reactions were observed in the remainder of the DT study group.[5]

Another clinical study to evaluate serological responses and adverse reactions of CLI DT was performed in 40 children under one year of age. One group of 20 children received 0.5 mL doses of DTP, DT, DTP at two, four and six months of age, respectively. The second group of 20 children received 0.5 mL doses of DTP, DTP, and DT, respectively, at the same ages. The immunologic protection against diphtheria and tetanus as measured by toxin neutralizing antibodies induced by DT was comparable when administered as either a second or third dose.[6] The reaction rates following CLI whole-cell DTP vaccination closely correlated with the rates observed with other commercially available whole-cell DTP vaccines.[7] The incidence of adverse reactions was significantly lower following DT administration ($p < 0.05$). Although the number of vaccinees was small, no persistent screaming episodes or severe neurological reactions such as seizures or encephalopathy were observed with either vaccine in this study.[6]

PERTUSSIS

Disease caused by *Bordetella pertussis* was once a major cause of infant and childhood morbidity and mortality in the United States. Pertussis (whooping cough) became a nationally notifiable disease in 1922, and reports reached a peak of 265,269 cases and 7,518 deaths in 1934. The highest number of reported pertussis deaths (9,269) occurred in 1923. The introduction and widespread use of standardized whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids (DTP) in the late 1940s resulted in a substantial decline in pertussis disease, a decline which continued without interruption for nearly 30 years.[2]

By 1970, the annual reported incidence of pertussis had been reduced by 99%. During the 1970s the annual numbers of reported cases stabilized at an average of approximately 2,300 cases each year. During the 1980s, however, the annual numbers of reported cases gradually increased from 1,730 cases in 1980 to 4,517 cases in 1989. An average of eight pertussis-associated fatalities was reported each year throughout the 1980s.[2]

From 1989 to 1991, 11,446 cases of pertussis were reported for an unadjusted incidence per 100,000 population of 1.7 in 1989, 1.8 in 1990 and 1.1 in 1991. The incidence for 1992 was 1.6 per 100,000. Age specific incidence and hospitalization rates were highest in the first year of life, decreasing with increasing age. Trends of the past years suggest an increase in reported pertussis since 1976, with the peak year being 1990.[8]

During the period 1989 to 1991, of 3,900 reports of hospitalization, 1,115 had developed pneumonia, seizures occurred in 157 cases, encephalopathy was reported for 12, and there were 20 pertussis attributed deaths. These events were more frequently reported in children less than 6 months of age and were generally less frequent with increasing age.[2] Of patients 3 months through 4 years of age, where vaccination status was known, 65% of 4,471 patients had not received the recommended schedule of immunization and 39% had not received any pertussis containing vaccine.[3]

Among older children and adults, including those previously vaccinated, *B. pertussis* infection may result in symptoms of bronchitis or upper-respiratory-tract infection. Pertussis may not be associated with classic signs, especially the inspiratory whoop. Older preschool children and school-age siblings who are not fully vaccinated and who develop pertussis can be important sources of infection for infants <1 year of age. Adults also play an important role in the transmission of pertussis to unvaccinated or incompletely vaccinated infants and young children.[2]

EFFICACY OF PERTUSSIS VACCINE

Although DTP has been evaluated as a control vaccine in a number of clinical trials of "acellular pertussis vaccines," no formal efficacy trial was performed prior to approval. Approval was based on historical and continuing evidence of protection (surveillance) in the population at risk. It was also shown that vaccines with acceptable mouse protection potencies induced protective serum agglutinin antibody titers.[4] The pertussis component of each lot of DTP is tested for potency by a mouse protection test.

In clinical trials, one dose of CLI whole-cell DTP vaccine was used to reconstitute one lyophilized single dose vial of ActHIB™ or OmniHIB™ with no diminution in anti-PRP response or diphtheria, tetanus and pertussis responses.

INDICATIONS AND USAGE

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) is recommended for active immunization of children up to age 7 years against diphtheria, tetanus, and pertussis (whooping cough) simultaneously. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, DT should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.[2,9]

Persons recovering from confirmed pertussis do not need additional doses of DTP but should receive additional doses of DT to complete the series.[2]

Available data indicate that the appropriate age for institution of immunizations in prematurely born infants is the usual chronological age of 2 months. Vaccine doses should not be reduced for preterm infants.[2,9]

If passive immunization is required, Tetanus Immune Globulin (Human) (TIG) and/or equine Diphtheria Antitoxin are the products of choice for tetanus and diphtheria, respectively (see **DOSAGE AND ADMINISTRATION** section).

When CLI DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, the combined vaccines are indicated for the active immunization of infants and children 2 months through 5 years of age for the prevention of invasive diseases caused by diphtheria, tetanus, pertussis and *H influenzae* type b.[10,11] ***(Refer to ActHIB™ package insert.)***

ADVERSE REACTIONS

Adverse reactions associated with the use of DTP include local redness, warmth, edema, induration with or without tenderness, as well as urticaria and rash. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses.[6]

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent.[19] If local redness 2.5 cm occurs, the likelihood of recurrence after another DTP dose increases significantly.[6]

Evidence does not indicate a causal relation between DTP vaccine and SIDS. Studies showing a temporal relation between these events are consistent with the expected occurrence of SIDS over the age range in which DTP immunization typically occurs.[13]

Deaths due to causes other than SIDS, including deaths due to serious infections, have occurred in infants following the administration of DTP. No association has been shown for hospitalizations due to infectious disease and receipt of DTP.[20]

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in TABLE 1.[2]

TABLE 1[2] **ADVERSE EVENTS OCCURRING WITHIN 48 HOURS OF DTP VACCINATIONS**

Event	Frequency*
Local	
Redness	1/3 doses
Swelling	2/5 doses
Pain	1/2 doses
Systemic	
Fever ≥38°C (100.4°F)	1/2 doses
Drowsiness	1/3 doses
Fretfulness	1/2 doses
Vomiting	1/15 doses
Anorexia	1/5 doses
Persistent, inconsolable crying (duration ≥3 hours)	1/100 doses
Fever ≥40.5°C (≥105°F)	1/330 doses
Nervous System	
Collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,750 doses

*Rate per total number of doses regardless of dose number in DTP series.

BODY SYSTEM AS A WHOLE

Mild systemic reactions such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following administration of DTP than following DT, are usually self-limited, and need no therapy other than symptomatic treatment such as acetaminophen.[2]

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) and death have been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[2]

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2 to 8 hours after an injection), may follow receipt of tetanus toxoid.[2]

Moderate to severe systemic events, include high fever (i.e., temperature of ≥40.5°C (105°F) and persistent, inconsolable crying lasting ≥3 hours. These events occur infrequently and appear to be without sequelae.[2]

Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6 to 10 per million doses).[2]

NERVOUS SYSTEM

The following neurologic illnesses have been reported as temporally associated with vaccine containing tetanus toxoid: neurological complications[21,22] including cochlear lesion,[23] brachial plexus neuropathies,[23,24] paralysis of the radial nerve,[25] paralysis of the recurrent nerve,[23] accommodation paresis, and EEG disturbances with encephalopathy.[19] The report from the IOM suggests that there is a causal relation between Guillain-Barré syndrome (GBS) and vaccines containing tetanus toxoid.[26] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid should be considered as a possible etiology.[19,27]

Short-lived convulsions (usually febrile), or collapse (hypotonic-hyporesponsive episode) occur infrequently and appear to be without sequelae.[2]

More severe neurologic events, such as a prolonged convulsion, or encephalopathy, although rare, have been reported in temporal association with DTP administration. An analysis of these data failed to show any cause and effect association.[2]

In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England, children 2 to 35 months of age with serious, acute neurologic disorders such as encephalopathy or complicated convulsion(s), were more likely to have received DTP in the 7 days preceding onset than their age-, sex-, and neighborhood-matched controls. Among children known to be neurologically normal before entering the study, the relative risk (estimated by odds ratio) of a neurologic illness occurring within the 7-day period following receipt of DTP dose, compared to children not receiving DTP in the 7-day period before onset of their illness, was 3.3 ($p < 0.001$).[2]

Within this 7-day period, the risk was significantly increased for immunized children only within 3 days of vaccination (relative risk 4.2, $p < 0.001$). The relative risk for illnesses occurring 4 to 7 days after vaccination was 2.1 ($p < 0.1$). Serious neurologic illnesses requiring hospitalization attributable to pertussis vaccine are rare. Final analysis of a comprehensive case-control study has estimated that the attributable risk of such illnesses is 1 in 140,000 doses administered. An earlier analysis had estimated this risk at 1/110,000 doses. In contrast, final analysis of the case-control study found that the risk of serious neurologic illness following pertussis disease was 1/11,000 pertussis cases. Repeated evaluations have shown that the benefits of vaccine outweigh the risks.[2,9]

The methods and results of the NCES have been thoroughly scrutinized since publication of the study. This reassessment by multiple groups has determined that the number of patients was too small and their classification subject to enough uncertainty to preclude drawing valid conclusions about whether a causal relation exists between pertussis vaccine and permanent neurologic damage. Preliminary data from a 10-year follow-up study of some of the children studied in the original NCES study also suggested a relation between symptoms following DTP vaccination and permanent neurologic disability. However, details are not available to evaluate this study adequately, and the same concerns remain about DTP vaccine precipitating initial manifestations of pre-existing neurologic disorders.[2]

An IOM report by the Committee to review the adverse consequences of pertussis and rubella vaccines concluded that evidence is consistent with a causal relation between DTP vaccine and acute encephalopathy, defined in the controlled studies reviewed as encephalopathy, encephalitis, or encephalomyelitis. On the basis of a review of the evidence bearing on this relation, the Committee concludes that the range of excess risk of acute encephalopathy following DTP immunization is consistent with that estimated for the NCES: 0.0 to 10.5 per million immunizations. The report also states that there is insufficient evidence to indicate a causal relation between DTP vaccine and permanent neurologic damage.[13]

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DT or DTP was not causally related to infantile spasms.[28] The incidence of onset of infantile spasms increases at 3 to 9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.[2]

A bulging fontanelle associated with increased intracranial pressure which occurred within 24 hours following DTP immunization has been reported. A causal relationship has not been established.[29,30,31]

CARDIOVASCULAR SYSTEM

An infant who developed myocarditis several hours after immunization has been reported.[32]

RESPIRATORY SYSTEM

Respiratory difficulties, including apnea, have been observed.

LOCAL

Rash and allergic reactions have been observed.

Sudden Infant Death Syndrome (SIDS) has temporally occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS.[33,34,35] It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2 to 6 months of age and that approximately 85% of SIDS cases occur at ages 1 to 6 months, with the peak incidence occurring at 6 weeks to 4 months of age. By chance alone, some SIDS victims can be expected to have recently received DTP.[33,34,35]

When CLI whole-cell DTP was administered concomitantly (at separate sites with separate syringes) with ActHIB™ or OmniHIB™, the systemic adverse experience profile was not different from that seen when CLI whole-cell DTP vaccine was administered alone.[10,11] ***(Refer to ActHIB™ package insert.)***

In general, the rates of minor systemic reactions after DTP was used to reconstitute ActHIB™ or OmniHIB™ were comparable to those usually reported after DTP vaccine alone.[6,19,36]

When CLI whole-cell DTP was used to reconstitute ActHIB™ or OmniHIB™ and administered to infants at 2, 4, and 6 months of age, the systemic adverse experience profile was comparable to that observed when the two vaccines were given separately. An increase in the rate of local reactions was observed in some instances within the 24-hour period after immunization.[10,11] ***(Refer to ActHIB™ package insert.)***

Reporting of Adverse Events

Reporting by parents or guardians of all adverse events occurring after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by health-care providers to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.[16,17,18]

Health-care providers also should report these events to the Director of Medical Affairs, Connaught Laboratories, Inc., Route 611, P.O. Box 187, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, the vaccine should not be administered.

SHAKE VIAL WELL *before withdrawing each dose. Vaccine contains a bacterial suspension. Vigorous agitation is required to resuspend the contents of the vial.* Discard if vaccine cannot be resuspended.

For Administration of DTP Vaccine Only:

The primary series for children less than 7 years of age is four doses of 0.5 mL each given intramuscularly. The customary age for the first dose is 2 months of age but may be given as young as 6 weeks of age and up to the seventh birthday.

Inject 0.5 mL intramuscularly only. The preferred injection sites are the anterolateral aspect of the thigh and the deltoid muscle of the upper arm. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk. During the course of primary immunizations, injections should not be made more than once at the same site.

The use of reduced volume (fractional doses) is not recommended. The effect of such practices on the frequency of serious adverse events and on protection against disease has not been determined.

Do NOT administer this product subcutaneously.

Special care should be taken to ensure that the injection does not enter a blood vessel.

PRIMARY IMMUNIZATION

This vaccine is recommended for children 6 weeks through 6 years (up to the seventh birthday) ideally beginning when the infant is 6 weeks to 2 months of age.

The primary series consists of four doses. For infants 6 weeks through 12 months of age, administer three 0.5 mL doses intramuscularly at least 4 to 8 weeks apart. The fourth dose is administered 6 to 12 months after the third injection.

BOOSTER IMMUNIZATION

For children between 4 and 6 years of age (preferably at time of kindergarten or elementary school entrance), a booster of 0.5 mL should be administered intramuscularly. Those who receive all four primary immunizing doses before their fourth birthday should receive a single dose of DTP just before entering kindergarten or elementary school. This booster dose is not necessary if the fourth dose in the primary series was administered after the fourth birthday. Thereafter, routine booster immunizations should be with Td, at intervals of 10 years. PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE) (DTP).

TABLE 2[2] **ROUTINE DIPHTHERIA, TETANUS, AND PERTUSSIS VACCINATION SCHEDULE**
Summary For Children <7 Years Old – United States, 1991

Dose	Customary Age

A clinical study was performed in 20 children under one year of age to determine the serological responses and the adverse reactions when Connaught Laboratories, Inc. (CLI) DT was administered as a primary series of three doses. Protective levels of diphtheria and tetanus antitoxins that were equal to or greater than 0.01 I.U./mL were detected in 100% of the children following two doses of the vaccine. However, maternal antibody may have contributed to the total neutralizing antibody in some of these infants. Protective levels of antitoxin were observed in 100% of these infants following three doses of DT. No local or systemic reactions were observed in approximately half of the infants and only mild or moderate reactions were observed in the remainder of the DT study group.[5]

Another clinical study to evaluate serological responses and adverse reactions of CLI DT was performed in 40 children under one year of age. One group of 20 children received 0.5 mL doses of DTP, DT, DTP at two, four and six months of age, respectively. The second group of 20 children received 0.5 mL doses of DTP, DTP, and DT, respectively, at the same ages. The immunologic protection against diphtheria and tetanus as measured by toxin neutralizing antibodies induced by DT was comparable when administered as either a second or third dose.[6] The reaction rates following CLI whole-cell DTP vaccination closely correlated with the rates observed with other commercially available whole-cell DTP vaccines.[7] The incidence of adverse reactions was significantly lower following DT administration ($p < 0.05$). Although the number of vaccinees was small, no persistent screaming episodes or severe neurological reactions such as seizures or encephalopathy were observed with either vaccine in this study.[6]

PERTUSSIS

Disease caused by *Bordetella pertussis* was once a major cause of infant and childhood morbidity and mortality in the United States. Pertussis (whooping cough) became a nationally notifiable disease in 1922, and reports reached a peak of 265,269 cases and 7,518 deaths in 1934. The highest number of reported pertussis deaths (9,269) occurred in 1923. The introduction and widespread use of standardized whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids (DTP) in the late 1940s resulted in a substantial decline in pertussis disease, a decline which continued without interruption for nearly 30 years.[2]

By 1970, the annual reported incidence of pertussis had been reduced by 99%. During the 1970s the annual numbers of reported cases stabilized at an average of approximately 2,300 cases each year. During the 1980s, however, the annual numbers of reported cases gradually increased from 1,730 cases in 1980 to 4,517 cases in 1989. An average of eight pertussis-associated fatalities was reported each year throughout the 1980s.[2]

From 1989 to 1991, 11,446 cases of pertussis were reported for an unadjusted incidence per 100,000 population of 1.7 in 1989, 1.8 in 1990 and 1.1 in 1991. The incidence for 1992 was 1.6 per 100,000. Age specific incidence and hospitalization rates were highest in the first year of life, decreasing with increasing age. Trends of the past years suggest an increase in reported pertussis since 1976, with the peak year being 1990.[8]

During the period 1989 to 1991, of 3,900 reports of hospitalization, 1,115 had developed pneumonia, seizures occurred in 157 cases, encephalopathy was reported for 12, and there were 20 pertussis attributed deaths. These events were more frequently reported in children less than 6 months of age and were generally less frequent with increasing age.[7] Of patients 3 months through 4 years of age, where vaccination status was known, 65% of 4,471 patients had not received the recommended schedule of immunization and 39% had not received any pertussis containing vaccine.[3]

Among older children and adults, including those previously vaccinated, *B. pertussis* infection may result in symptoms of bronchitis or upper-respiratory-tract infection. Pertussis may not be associated with classic signs, especially the inspiratory whoop. Older preschool children and school-age siblings who are not fully vaccinated and who develop pertussis can be important sources of infection for infants <1 year of age. Adults also play an important role in the transmission of pertussis to unvaccinated or incompletely vaccinated infants and young children.[2]

EFFICACY OF PERTUSSIS VACCINE

Although DTP has been evaluated as a control vaccine in a number of clinical trials of "acellular pertussis vaccines," no formal efficacy trial was performed prior to approval. Approval was based on historical and continuing evidence of protection (surveillance) in the population at risk. It was also shown that vaccines with acceptable mouse protection potencies induced protective serum agglutinin antibody titers.[4] The pertussis component of each lot of DTP is tested for potency by a mouse protection test.

In clinical trials, one dose of CLI whole-cell DTP vaccine was used to reconstitute one lyophilized single dose vial of ActHIB™ or OmniHIB™ with no diminution in anti-PRP response or diphtheria, tetanus and pertussis responses.

INDICATIONS AND USAGE

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) is recommended for active immunization of children up to age 7 years against diphtheria, tetanus, and pertussis (whooping cough) simultaneously. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, DT should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.[2,9]

Persons recovering from confirmed pertussis do not need additional doses of DTP but should receive additional doses of DT to complete the series.[2]

Available data indicate that the appropriate age for institution of immunizations in prematurely born infants is the usual chronological age of 2 months. Vaccine doses should not be reduced for preterm infants.[2,9]

If passive immunization is required, Tetanus Immune Globulin (Human) (TIG) and/or equine Diphtheria Antitoxin are the products of choice for tetanus and diphtheria, respectively (see **DOSAGE AND ADMINISTRATION** section).

When CLI DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, the combined vaccines are indicated for the active immunization of infants and children 2 months through 5 years of age for the prevention of invasive diseases caused by diphtheria, tetanus, pertussis and *H influenzae* type b.[10,11] ***(Refer to ActHIB™ package insert.)***

A single injection containing diphtheria, tetanus, pertussis and Haemophilus b conjugate antigens may be more acceptable to parents and may increase compliance with vaccination programs. Therefore, in those situations where, in the judgment of the physician, it is of benefit to administer a single injection of whole-cell DTP vaccine and Haemophilus b conjugate vaccine concomitantly, ***only CLI whole-cell DTP vaccine may be used for reconstitution of lyophilized ActHIB™ or OmniHIB™.*** Antibody levels associated with protection may not be achieved earlier than two weeks following the last recommended dose. (See **DOSAGE AND ADMINISTRATION** section.)

As with any vaccine, vaccination with DTP or combined vaccines CLI DTP and ActHIB™ or OmniHIB™ may not protect 100% of susceptible individuals.

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

This vaccine is NOT to be used for the treatment of diphtheria, tetanus, pertussis or H influenzae type b infection.

This vaccine should NOT be used for immunizing persons 7 years of age and older.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including thimerosal, a mercury derivative, is a contraindication for further use of this vaccine.

It is a contraindication to use this or any other related vaccine after an immediate anaphylactic reaction associated with a previous dose.

It is a contraindication to administer this vaccine in the presence of any evolving neurological condition.

Encephalopathy after a previous dose is a contraindication to further use.

Immunization should be deferred during the course of an acute illness. Vaccination of infants and children with severe, febrile illness should generally be deferred until these persons have recovered. However, the presence of minor illnesses such as mild upper respiratory infections with or without low-grade fever are not contraindications to further use.[2]

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.[12]

WARNINGS

If any of the following events occur in temporal relation to receipt of DTP, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelae.[2]

THE FOLLOWING EVENTS WERE PREVIOUSLY CONSIDERED CONTRAINDICATIONS AND ARE NOW CONSIDERED WARNINGS:[2]

1. **Temperature of ≥40.5°C (105°F) within 48 hours not due to another identifiable cause:** Such a temperature is considered a warning because of the likelihood that fever following a subsequent dose of DTP vaccine also will be high. Because such febrile reactions are usually attributed to the pertussis component, vaccination with DT should not be discontinued.[2]
2. **Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours:** Although these uncommon events have not been recognized to cause death nor to induce permanent neurological sequelae, it is prudent to continue vaccination with DT, omitting the pertussis component.[2]
3. **Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours:** Follow-up of infants who have cried inconsolably following DTP vaccination has indicated that this reaction, though unpleasant, is without long-term sequelae and not associated with other reactions of greater significance.[2] Evidence is insufficient to indicate whether pertussis vaccine-associated protracted, inconsolable, or high-pitched crying or screaming does, or does not, lead to chronic neurologic damage.[13] Inconsolable crying occurs most frequently following the first dose and is less frequently reported following subsequent doses of DTP vaccine. However, crying for >30 minutes following DTP vaccination can be a predictor of increased likelihood of recurrence of persistent crying following subsequent doses. Children with persistent crying have had a higher rate of local reactions than children who had other DTP-associated reactions (including high fever, seizures, and hypotonic-hyporesponsive episodes), suggesting that prolonged crying was really a pain reaction.[2]
4. **Convulsions with or without fever occurring within three days:** Short-lived convulsions, with or without fever, have not been shown to cause permanent sequelae. Furthermore, the occurrence of prolonged febrile seizures (i.e., status epilepticus – any seizure lasting >30 minutes or recurrent seizures lasting a total of 30 minutes without the child fully regaining consciousness), irrespective of their cause, involving an otherwise normal child does not substantially increase the risk for subsequent febrile (brief or prolonged) or afebrile seizures. The risk is significantly increased ($p=0.018$) only among those children who are neurologically abnormal before their episode of status epilepticus.[2] Accordingly, although a convulsion following DTP vaccination has previously been considered a contraindication to further doses, under certain circumstances subsequent doses may be indicated, particularly if the risk of pertussis in the community is high. If a child has a seizure following the first or second dose of DTP, it is desirable to delay subsequent doses until the child's neurologic status is better defined. By the end of the first year of life, the presence of an underlying neurologic disorder has usually been determined, and appropriate treatment instituted. DT vaccine should not be administered before a decision has been made about whether to continue the DTP series. Regardless of which vaccine is given, it is prudent also to administer acetaminophen[2], 15 mg/kg of body weight, at the time of vaccination and every 4 hours subsequently for 24 hours.

Persons who experienced Arthus-type hypersensitivity reactions or a temperature of >103°F (39.4°C) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given even emergency doses of Td more frequently than every 10 years, even if they have a wound that is neither clean nor minor.[2]

DTP should not be given to children with any coagulation disorder, including thrombocytopenia, that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

Recent studies suggest that infants and children with a history of convulsions in first-degree family members (i.e., siblings and parents) have a 3.2-fold increased risk for neurologic events compared with those without such histories.[14] *However, the ACIP has concluded that a family history of convulsions in parents and siblings is not a contraindication to pertussis vaccination and that children with such family histories should receive pertussis vaccine according to the recommended schedule.*[2]

A recent review of all available data by the IOM found evidence is consistent with a causal relation between DTP vaccination and acute encephalopathy, but that there is insufficient evidence to indicate a causal relation between DTP vaccine and permanent neurologic damage.[13]

Infants and children with recognized possible or potential underlying neurologic conditions seem to be at enhanced risk for the appearance of manifestations of the underlying neurologic disorder within two or three days following vaccination.[2] Whether to administer DTP to children with proven or suspected underlying neurologic disorders must be decided on an individual basis. Important considerations include the current local incidence of pertussis, the near absence of diphtheria in the United States and the low risk of infection with *C. tetani*.[2]

Although these events were considered absolute contraindications in previous ACIP recommendations, there may be circumstances, such as a high incidence of pertussis, in which the potential benefits outweigh possible risks, particularly because these events are not associated with permanent sequelae.[2]

The administration of DTP to children with proven or suspected underlying neurologic disorders that are not actively evolving must be decided on an individual basis.

Only full doses (0.5 mL) of DTP vaccine should be given; if a specific contraindication to DTP exists, the vaccine should not be given.[2]

Controversy regarding the safety of pertussis vaccine during the 1970s led to several studies of the benefits and risks of this vaccination during the 1980s. These epidemiologic analyses clearly indicate that the benefits of pertussis vaccination outweigh any risks and have not shown a cause and effect with neurologic illness.[2,9]

Deaths have been reported in temporal association with the administration of DTP vaccine (see **ADVERSE REACTIONS** section).

When CLI DTP vaccine is used alone or to reconstitute ActHIB™ or OmniHIB™ and administered to immunosuppressed persons or persons receiving immunosuppressive therapy, the expected antibody responses may not be obtained. This includes patients with severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation.[15]

Administration of DTP and/or Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) is not contraindicated in individuals with HIV infection.[11]

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

PRECAUTIONS

GENERAL

Care is to be taken by the health-care provider for the safe and effective use of DTP.

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines, previous immunization history, current health status (see **CONTRAINDICATIONS; WARNINGS** sections), and a current knowledge of the literature concerning the use of the vaccine under consideration. Immunosuppressed patients may not respond.

Prior to administration of DTP, health-care personnel should inform the parent or guardian of the patient the benefits and risks of immunization, and also inquire about the recent health status of the patient to be injected.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped and should be properly disposed.

INFORMATION FOR PATIENTS

As part of the child's immunization record, the date, lot number and manufacturer of the vaccine administered MUST be recorded.[16,17,18]

The health-care provider should inform the parent or guardian of the patient about the potential for adverse reactions that have been temporally associated with DTP administration. Parents or guardians should be instructed to report any serious adverse reactions to their health-care provider.

IT IS EXTREMELY IMPORTANT WHEN THE CHILD RETURNS FOR THE NEXT DOSE IN THE SERIES, THAT THE PARENT OR GUARDIAN OF THE PATIENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER THE PREVIOUS DOSE (SEE **CONTRAINDICATIONS; ADVERSE REACTIONS** SECTIONS).

The health-care provider should inform the parent or guardian of the patient the importance of completing the immunization series.

The health-care provider should provide the Vaccine Information Materials (VIMs) which are required to be given with each immunization.

The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986.[16] The toll-free number for VAERS forms and information is 1-800-822-7967.

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records and to report occurrences of certain adverse events to the U.S. Department of Health and Human Services. Reportable events include those listed in the Act for each vaccine and events specified in the package insert as contraindications to further doses of the vaccine.[17,18]

DRUG INTERACTIONS

If DTP and TIG or Diphtheria Antitoxin are administered concurrently, separate syringes and separate sites should be used.

As with other intramuscular injections, use with caution in patients on anticoagulant therapy.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (<2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it is reasonable to defer vaccination until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.[2]

If DTP has been administered to persons receiving immunosuppressive therapy, a recent injection of immunoglobulin or having an immunodeficiency disorder, an adequate immunologic response may not be obtained.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

No studies have been performed to evaluate carcinogenicity, mutagenic potential, or impact on fertility.

PREGNANCY

THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE AND OLDER.

PEDIATRIC USE

SAFETY AND EFFECTIVENESS OF DTP VACCINE OR AT THE TIME WHEN DTP VACCINE IS USED TO RECONSTITUTE ActHIB™ OR OmniHIB™ IN INFANTS BELOW THE AGE OF SIX WEEKS HAVE NOT BEEN ESTABLISHED. (See **DOSAGE AND ADMINISTRATION** section.)

This vaccine is recommended for immunizing children 6 weeks of age through 6 years of age (up to the seventh birthday). DTP is the preferred vaccine in this age group, but in those situations where an *absolute contraindication* to pertussis vaccination exists, or where in the opinion of the physician the pertussis vaccine should not be administered, DT is the appropriate alternative.

Full protection is achieved upon completion of primary immunization with either four doses of DTP, or three doses of DTP followed by a dose of an approved acellular DTP. A fifth dose of DTP or an approved acellular DTP is required.

THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE AND OLDER. For persons 7 years of age and older, the recommended vaccine is Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td).

CARDIOVASCULAR SYSTEM

An infant who developed myocarditis several hours after immunization has been reported.[32]

RESPIRATORY SYSTEM

Respiratory difficulties, including apnea, have been observed.

LOCAL

Rash and allergic reactions have been observed.

Sudden Infant Death Syndrome (SIDS) has temporally occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS.[33,34,35] It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2 to 6 months of age and that approximately 85% of SIDS cases occur at ages 1 to 6 months, with the peak incidence occurring at 6 weeks to 4 months of age. By chance alone, some SIDS victims can be expected to have recently received DTP.[33,34,35]

When CLI whole-cell DTP was administered concomitantly (at separate sites with separate syringes) with ActHIB™ or OmniHIB™, the systemic adverse experience profile was not different from that seen when CLI whole-cell DTP vaccine was administered alone.[10,11] ***(Refer to ActHIB™ package insert.)***

In general, the rates of minor systemic reactions after DTP was used to reconstitute ActHIB™ or OmniHIB™ were comparable to those usually reported after DTP vaccine alone.[6,19,36]

When CLI whole-cell DTP was used to reconstitute ActHIB™ or OmniHIB™ and administered to infants at 2, 4, and 6 months of age, the systemic adverse experience profile was comparable to that observed when the two vaccines were given separately. An increase in the rate of local reactions was observed in some instances within the 24-hour period after immunization.[10,11] ***(Refer to ActHIB™ package insert.)***

Reporting of Adverse Events

Reporting by parents or guardians of all adverse events occurring after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by health-care providers to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.[16,17,18]

Health-care providers also should report these events to the Director of Medical Affairs, Connaught Laboratories, Inc., Route 611, P.O. Box 187, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, the vaccine should not be administered.

SHAKE VIAL WELL *before withdrawing each dose. Vaccine contains a bacterial suspension. Vigorous agitation is required to resuspend the contents of the vial.* Discard if vaccine cannot be resuspended.

For Administration of DTP Vaccine Only:

The primary series for children less than 7 years of age is four doses of 0.5 mL each given intramuscularly. The customary age for the first dose is 2 months of age but may be given as young as 6 weeks of age and up to the seventh birthday.

Inject 0.5 mL intramuscularly only. The preferred injection sites are the anterolateral aspect of the thigh and the deltoid muscle of the upper arm. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk. During the course of primary immunizations, injections should not be made more than once at the same site.

The use of reduced volume (fractional doses) is not recommended. The effect of such practices on the frequency of serious adverse events and on protection against disease has not been determined.

Do NOT administer this product subcutaneously.

Special care should be taken to ensure that the injection does not enter a blood vessel.

PRIMARY IMMUNIZATION

This vaccine is recommended for children 6 weeks through 6 years (up to the seventh birthday) ideally beginning when the infant is 6 weeks to 2 months of age.

The primary series consists of four doses. For infants 6 weeks through 12 months of age, administer three 0.5 mL doses intramuscularly at least 4 to 8 weeks apart. The fourth dose is administered 6 to 12 months after the third injection.

BOOSTER IMMUNIZATION

For children between 4 and 6 years of age (preferably at time of kindergarten or elementary school entrance), a booster of 0.5 mL should be administered intramuscularly. Those who receive all four primary immunizing doses before their fourth birthday should receive a single dose of DTP just before entering kindergarten or elementary school. This booster dose is not necessary if the fourth dose in the primary series was administered after the fourth birthday. Thereafter, routine booster immunizations should be with Td, at intervals of 10 years. PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE) (DTP).

TABLE 2[2]

ROUTINE DIPHTHERIA, TETANUS, AND PERTUSSIS VACCINATION SCHEDULE
Summary For Children <7 Years Old – United States, 1991

Dose	Customary Age	Age/Interval†	Product
Primary 1	2 Months	6 weeks old or older	DTP†
Primary 2	4 Months	4-8 weeks after first dose*	DTP†
Primary 3	6 Months	4-8 weeks after second dose*	DTP†
Primary 4	15 Months	6-12 months after third dose*	DTP†
Booster	4-6 years old, before entering kindergarten or elementary school (not necessary if fourth primary vaccinating dose administered after fourth birthday)		DTP†
Additional Boosters		Every 10 years after last dose	Td

* Use DT if pertussis vaccine is contraindicated. If the child is ≥1 year of age at the time that primary dose three is due, a third dose 6 to 12 months after the second dose completes primary vaccination with DT.

† Prolonging the interval does not require restarting series.

Preterm infants should be vaccinated according to their chronological age from birth.[2,9]

Interruption of the recommended schedule with a delay between doses does not interfere with the final immunity achieved with DTP. There is no need to start the series over again, regardless of the time elapsed between doses.

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) can be interchangeably used with DTP for the fourth and fifth doses. However ActHIB™ cannot be reconstituted with DTaP.

The simultaneous administration of DTP, oral polio virus vaccine (OPV), and measles-mumps-rubella vaccine (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately. Simultaneous vaccination (at separate sites with separate syringes) with DTP, MMR, OPV, or inactivated poliovirus vaccine (IPV), and Haemophilus b conjugate vaccine (HbCV) is also acceptable.[2] The ACIP recommends the simultaneous administration, at separate sites with separate syringes, of all vaccines appropriate to the age and previous vaccination status of the recipients including the special circumstance of simultaneous administration of DTP, OPV, HbCV, and MMR at ≥15 months of age.[2]

If passive immunization is needed for tetanus, TIG is the product of choice. It provides longer protection than antitoxin of animal origin and causes few adverse reactions. The currently recommended prophylactic dose of TIG for wounds of average severity is 250 units intramuscularly. When tetanus toxoid and TIG are administered concurrently, separate syringes and separate sites should be used. The ACIP recommends the use of only adsorbed toxoid in this situation.[2]

WHEN RECONSTITUTING HAEMOPHILUS b CONJUGATE VACCINE (TETANUS TOXOID CONJUGATE), ActHIB™ or OmniHIB™

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

CLI whole-cell DTP vaccine also can be used for reconstitution of ActHIB™ or OmniHIB™. Cleanse both the DTP and ActHIB™ or OmniHIB™ vaccine vial rubber barriers with a suitable germicide prior to reconstitution. Thoroughly agitate the vial of CLI whole-cell DTP vaccine, then withdraw a 0.6 mL dose and inject into the vial of lyophilized *ActHIB™ or OmniHIB™. After reconstitution and* thorough agitation, *ActHIB™ or OmniHIB™ will appear whitish in color. Using a* new syringe, *administer 0.5 mL dose of DTP/ActHIB™* or OmniHIB™ vaccines.

When CLI whole-cell DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, administer **intramuscularly only. Vaccine should be used immediately (i.e. within 30 minutes) after reconstitution.**

After reconstitution, each 0.5 mL dose is formulated to contain 6.7 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, an estimate of 4 protective units of pertussis vaccine, 10 µg of purified capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid, and 8.5% of sucrose. ***(Refer to ActHIB™ package insert.)***

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

Each dose of DTP/ActHIB™ or OmniHIB™ vaccines is administered intramuscularly in the outer aspect of the vastus lateralis (mid-thigh) or deltoid. The vaccine should not be injected into the gluteal area or areas where there may be a nerve trunk. During the course of primary immunizations, *injections should not be made more than once at the same site.*

When CLI DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, the combined vaccines are indicated for infants and children 2 months through 5 years of age for intramuscular administration in accordance with the schedule indicated in Table 3.[10]

TABLE 3[10]

RECOMMENDED IMMUNIZATION SCHEDULE
For Previously Unvaccinated Children

DOSE	AGE	IMMUNIZATION
First, Second and Third	At 2, 4 and 6 months	DTP or DTP/ActHIB™ or DTP/OmniHIB™
Fourth	At 15 to 18 months	DTP or DTP/ActHIB™ or DTP/OmniHIB™ or Acellular Pertussis (DTaP)
Fifth	4 to 6 years	DTP or Acellular Pertussis (DTaP)

* Acellular Pertussis (DTaP) should NOT be used to reconstitute ActHIB™/OmniHIB™. When administering DTaP for the fourth dose, *Haemophilus influenzae* type b vaccine also should be administered at this time in a separate syringe at a different site.

For Previously Unvaccinated Children

Immunization schedules should be considered on an individual basis for children not vaccinated according to the recommended schedule. Three doses of a product containing DTP, given at approximately 2-month intervals, are required followed by a fourth dose of a product containing DTP or DTaP approximately 12 months later and a fifth dose of a product containing DTP or DTaP at 4 to 6 years of age. If the fourth dose of a pertussis-containing vaccine is not given until after the fourth birthday, no further doses of a pertussis-containing vaccine are necessary.

The number of doses of a product containing *H influenzae* type b conjugate vaccine indicated depends on the age that immunization is begun. A child 7 to 11 months of age should receive 3 doses of a product containing *H influenzae* type b conjugate vaccine. A child 12 to 14 months of age should receive 2 doses of a product containing *H influenzae* type b conjugate vaccine. A child 15 to 59 months of age should receive 1 dose of a product containing *H influenzae* type b conjugate vaccine.

Preterm infants should be vaccinated according to their chronological age from birth.[9]

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved when CLI DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™. There is no need to start the series over again, regardless of the time elapsed between doses.

It is recommended that the same conjugate vaccine be used throughout each immunization schedule, consistent with the data supporting approval and licensure of the vaccine. Since ActHIB™ and OmniHIB™ are the same vaccine, these may be used interchangeably.

DO NOT INJECT INTRAVENOUSLY.

HOW SUPPLIED

DTP Vial, 2.5 mL – Product No. 49281-280-05
DTP Vial, 5 mL – Product No. 49281-280-10
DTP Vial, 7.5 mL – Product No. 49281-280-84

One 7.5 mL vial of Connaught Laboratories, Inc. Diphtheria and Tetanus Toxoids and Pertussis Vaccine as Diluent packaged with Vial, 1 Dose lyophilized Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) (10 x 1 Dose vials per package) – Product No. 49281-549-10

Administer vaccine immediately (i.e. within 30 minutes) after reconstitution.

STORAGE

Store between 2° – 8°C (35° – 46°F). DO NOT FREEZE. Temperature extremes may adversely affect resuspendability of this vaccine.

Store lyophilized vaccine packaged with vial *containing Diphtheria and Tetanus Toxoids and Pertussis vaccine between 2° – 8°C* (35° – 46°F). DO NOT FREEZE.

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Product information
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Manufactured by:
CONNAUGHT LABORATORIES, INC.
Swiftwater, Pennsylvania 18370, U.S.A.

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CONNAUGHT
A PASTEUR MÉRIEUX COMPANY

A.H.F.S. Category 80:08

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP

(FOR PEDIATRIC USE)

Caution: *Federal (U.S.A.) law prohibits dispensing without prescription.*

DESCRIPTION

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) combines diphtheria and tetanus toxoids adsorbed with pertussis vaccine, for intramuscular use, in a sterile isotonic sodium chloride solution containing sodium phosphate buffer to control pH. The vaccine, after shaking, is a turbid liquid, whitish-gray in color. When used to reconstitute Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), ActHIB™ or OmniHIB™, the combined vaccines appear whitish in color.

Corynebacterium diphtheriae cultures are grown in a modified Mueller and Miller medium.[1] *Clostridium tetani* cultures are grown in a peptone-based medium. Both toxins are detoxified with formaldehyde. The detoxified materials are separately purified by serial ammonium sulfate fractionation and diafiltration.

The pertussis vaccine component is derived from *Bordetella pertussis* cultures grown on blood-free Bordet Gengou media. The pertussis organisms are harvested and inactivated with thimerosal and resuspended in physiological saline and thimerosal.

The toxoids are adsorbed to aluminum potassium sulfate (alum). The adsorbed diphtheria and tetanus toxoids are combined with pertussis vaccine concentrate, and diluted to a final volume using sterile phosphate-buffered physiological saline. Each 0.5 mL dose contains, by assay, not more than 0.17 mg of aluminum and not more than 100 µg (0.02%) of residual formaldehyde. Thimerosal (mercury derivative) 1:10,000 is added as a preservative.

Each 0.5 mL dose is formulated to contain 6.7 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid (both toxoids induce at least 2 units of antitoxin per mL in the guinea pig potency test).

The total human immunizing dose (the first three 0.5 mL doses administered) contains an estimate of 12 units of pertussis vaccine (4 protective units per single dose).[2] The potency of the pertussis component of each lot of DTP is tested in a mouse protection test.

At the time when Connaught Laboratories, Inc. (CLI) DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, each single dose of the 0.5 mL mixture is formulated to contain 6.7 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, an estimate of 4 protective units of pertussis vaccine, 10 µg of purified capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid, and 8.5% of sucrose.

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

CLINICAL PHARMACOLOGY

DIPHTHERIA

Corynebacterium diphtheriae may cause both localized and generalized disease. Systemic intoxication is caused by diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin.

At one time, diphtheria was common in the United States. More than 200,000 cases, primarily among young children, were reported in 1921. Approximately 5% to 10% of cases were fatal; the highest case-fatality ratios were recorded for the very young and the elderly. Reported cases of diphtheria of all types declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state. After 1979, cutaneous diphtheria was no longer a notifiable disease. From 1980 to 1989, only 24 cases of respiratory diphtheria were reported; two cases were fatal, and 18 (75%) occurred among persons 20 years of age or older.[2]

Diphtheria is currently a rare disease in the United States primarily because of the high level of appropriate vaccination among children (97% of children entering school have received ≥three doses of diphtheria and tetanus toxoids and pertussis vaccine adsorbed [DTP]) and because of an apparent reduction in the prevalence of toxigenic strains of *C. diphtheriae*. Most cases occur among unvaccinated or inadequately immunized persons.[2]

Both toxigenic and nontoxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce toxin cause myocarditis and neuritis. Toxigenic strains are more often associated with severe or fatal illness in noncutaneous (respiratory or other mucosal surface) infections and are more commonly recovered in association with respiratory than from cutaneous infections.[2]

A complete vaccination series substantially reduces the risk of developing diphtheria, and vaccinated persons who develop disease have milder illness. Protection lasts at least 10 years. Vaccination does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nose or on the skin.[2]

TETANUS

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*.

The occurrence of tetanus in the United States has decreased dramatically from 560 reported cases in 1947 to a record low of 48 reported cases in 1987. Tetanus in the United States is primarily a disease of older adults. Of 99 tetanus patients with complete information reported to the Centers for Disease Control and Prevention (CDC) during 1987 and 1988, 68% were ≥50 years of age, while only six were <20 years of age. Overall, the case-fatality rate was 21%. In 1992, 45 cases were reported of which 82% were ≥50 years of age.[3] The disease continues to occur almost exclusively among persons who are unvaccinated or inadequately vaccinated or whose vaccination histories are unknown or uncertain.[2]

In 4% of tetanus cases reported during 1987 and 1988, no wound or other condition could be implicated. Non-acute skin lesions, such as ulcers, or medical conditions such as abscesses were reported in 14% of cases.[2]

Spores of *C. tetani* are ubiquitous. Serologic tests indicate that naturally acquired immunity to tetanus toxin does not occur in the United States.[2] Thus, universal primary vaccination, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect persons among all age-groups. Tetanus toxoid is a highly effective antigen, and a completed primary series generally induces protective levels of neutralizing antibodies to tetanus toxin that persist for ≥10 years.[2]

The potency of diphtheria and tetanus toxoids was determined on the basis of immunogenicity studies with a comparison to a serological correlate of protection (0.01 I.U./mL) established by the Panel on Review of Bacterial Vaccines & Toxoids.[4]

EFFICACY OF DIPHTHERIA AND TETANUS TOXOID VACCINES

Circulating protective levels of neutralizing antibodies to diphtheria and tetanus toxins can be induced by the administration of Diphtheria and Tetanus Toxoids Adsorbed USP (For Pediatric Use) (DT) or DTP.

A clinical study was performed in 20 children under one year of age to determine the serological responses and the adverse reactions when Connaught Laboratories, Inc. (CLI) DT was administered as a primary series of three doses. Protective levels of diphtheria and tetanus antitoxins that were equal to or greater than 0.01 I.U./mL were detected in 100% of the children following two doses of the vaccine. However, maternal antibody may have contributed to the total neutralizing antibody in some of these infants. Protective levels of antitoxin were observed in 100% of these infants following three doses of DT. No local or systemic reactions were observed in approximately half of the infants and only mild or moderate reactions were observed in the remainder of the DT study group.[5]

Another clinical study to evaluate serological responses and adverse reactions of CLI DT was performed in 40 children under one year of age. One group of 20 children received 0.5 mL doses of DTP, DT, DTP at two, four and six months of age, respectively. The second group of 20 children received 0.5 mL doses of DTP, DTP, and DT, respectively, at the same ages. The immunologic protection against diphtheria and tetanus as measured by toxin neutralizing antibodies induced by DT was comparable when administered as either a second or third dose.[6] The reaction rates following CLI whole-cell DTP vaccination closely correlated with the rates observed with other commercially available whole-cell DTP vaccines.[7] The incidence of adverse reactions was significantly lower following DT administration ($p < 0.05$). Although the number of vaccinees was small, no persistent screaming episodes or severe neurological reactions such as seizures or encephalopathy were observed with either vaccine in this study.[6]

PERTUSSIS

Disease caused by *Bordetella pertussis* was once a major cause of infant and childhood morbidity and mortality in the United States. Pertussis (whooping cough) became a nationally notifiable disease in 1922, and reports reached a peak of 265,269 cases and 7,518 deaths in 1934. The highest number of reported pertussis deaths (9,269) occurred in 1923. The introduction and widespread use of standardized whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids (DTP) in the late 1940s resulted in a substantial decline in pertussis disease, a decline which continued without interruption for nearly 30 years.[2]

By 1970, the annual reported incidence of pertussis had been reduced by 99%. During the 1970s the annual numbers of reported cases stabilized at an average of approximately 2,300 cases each year. During the 1980s, however, the annual numbers of reported cases gradually increased from 1,730 cases in 1980 to 4,517 cases in 1989. An average of eight pertussis-associated fatalities was reported each year throughout the 1980s.[2]

From 1989 to 1991, 11,446 cases of pertussis were reported for an unadjusted incidence per 100,000 population of 1.7 in 1989, 1.8 in 1990 and 1.1 in 1991. The incidence for 1992 was 1.6 per 100,000. Age specific incidence and hospitalization rates were highest in the first year of life, decreasing with increasing age. Trends of the past years suggest an increase in reported pertussis since 1976, with the peak year being 1990.[8]

During the period 1989 to 1991, of 3,900 reports of hospitalization, 1,115 had developed pneumonia, seizures occurred in 157 cases, encephalopathy was reported for 12, and there were 20 pertussis attributed deaths. These events were more frequently reported in children less than 6 months of age and were generally less frequent with increasing age.[7] Of patients 3 months through 4 years of age, where vaccination status was known, 65% of 4,471 patients had not received the recommended schedule of immunization and 39% had not received any pertussis containing vaccine.[3]

Among older children and adults, including those previously vaccinated, *B. pertussis* infection may result in symptoms of bronchitis or upper-respiratory-tract infection. Pertussis may not be associated with classic signs, especially the inspiratory whoop. Older preschool children and school-age siblings who are not fully vaccinated and who develop pertussis can be important sources of infection for infants <1 year of age. Adults also play an important role in the transmission of pertussis to unvaccinated or incompletely vaccinated infants and young children.[2]

EFFICACY OF PERTUSSIS VACCINE

Although DTP has been evaluated as a control vaccine in a number of clinical trials of "acellular pertussis vaccines," no formal efficacy trial was performed prior to approval. Approval was based on historical and continuing evidence of protection (surveillance) in the population at risk. It was also shown that vaccines with acceptable mouse protection potencies induced protective serum agglutinin antibody titers.[4] The pertussis component of each lot of DTP is tested for potency by a mouse protection test.

In clinical trials, one dose of CLI whole-cell DTP vaccine was used to reconstitute one lyophilized single dose vial of ActHIB™ or OmniHIB™ with no diminution in anti-PRP response or diphtheria, tetanus and pertussis responses.

INDICATIONS AND USAGE

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) is recommended for active immunization of children up to age 7 years against diphtheria, tetanus, and pertussis (whooping cough) simultaneously. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, DT should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.[2,9]

Persons recovering from confirmed pertussis do not need additional doses of DTP but should receive additional doses of DT to complete the series.[2]

Available data indicate that the appropriate age for institution of immunizations in prematurely born infants is the usual chronological age of 2 months. Vaccine doses should not be reduced for preterm infants.[2,9]

If passive immunization is required, Tetanus Immune Globulin (Human) (TIG) and/or equine Diphtheria Antitoxin are the products of

ADVERSE REACTIONS

Adverse reactions associated with the use of DTP include local redness, warmth, edema, induration with or without tenderness, as well as urticaria and rash. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses.[6]

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent.[19] If local redness 2.5 cm occurs, the likelihood of recurrence after another DTP dose increases significantly.[6]

Evidence does not indicate a causal relation between DTP vaccine and SIDS. Studies showing a temporal relation between these events are consistent with the expected occurrence of SIDS over the age range in which DTP immunization typically occurs.[13]

Deaths due to causes other than SIDS, including deaths due to serious infections, have occurred in infants following the administration of DTP. No association has been shown for hospitalizations due to infectious disease and receipt of DTP.[20]

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in TABLE 1.[2]

TABLE 1[2] **ADVERSE EVENTS OCCURRING WITHIN 48 HOURS OF DTP VACCINATIONS**

Event	Frequency*
Local	
Redness	1/3 doses
Swelling	2/5 doses
Pain	1/2 doses
Systemic	
Fever ≥38°C (100.4°F)	1/2 doses
Drowsiness	1/3 doses
Fretfulness	1/2 doses
Vomiting	1/15 doses
Anorexia	1/5 doses
Persistent, inconsolable crying (duration ≥3 hours)	1/100 doses
Fever ≥40.5°C (≥105°F)	1/330 doses
Nervous System	
Collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,750 doses

*Rate per total number of doses regardless of dose number in DTP series.

BODY SYSTEM AS A WHOLE

Mild systemic reactions such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following administration of DTP than following DT, are usually self-limited, and need no therapy other than symptomatic treatment such as acetaminophen.[2]

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) and death have been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[2]

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2 to 8 hours after an injection), may follow receipt of tetanus toxoid.[2]

Moderate to severe systemic events, include high fever (i.e., temperature of ≥40.5°C (105°F) and persistent, inconsolable crying lasting ≥3 hours. These events occur infrequently and appear to be without sequelae.[2]

Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6 to 10 per million doses).[2]

NERVOUS SYSTEM

The following neurologic illnesses have been reported as temporally associated with vaccine containing tetanus toxoid: neurological complications[21,22] including cochlear lesion,[23] brachial plexus neuropathies,[23,24] paralysis of the radial nerve,[25] paralysis of the recurrent nerve,[23] accommodation paresis, and EEG disturbances with encephalopathy.[19] The report from the IOM suggests that there is a causal relation between Guillain-Barré syndrome (GBS) and vaccines containing tetanus toxoid.[26] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid should be considered as a possible etiology.[19,27]

Short-lived convulsions (usually febrile), or collapse (hypotonic-hyporesponsive episode) occur infrequently and appear to be without sequelae.[2]

More severe neurologic events, such as a prolonged convulsion, or encephalopathy, although rare, have been reported in temporal association with DTP administration. An analysis of these data failed to show any cause and effect association.[2]

In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England, children 2 to 35 months of age with serious, acute neurologic disorders such as encephalopathy or complicated convulsion(s), were more likely to have received DTP in the 7 days preceding onset than their age-, sex-, and neighborhood-matched controls. Among children known to be neurologically normal before entering the study, the relative risk (estimated by odds ratio) of a neurologic illness occurring within the 7-day period following receipt of DTP dose, compared to children not receiving DTP in the 7-day period before onset of their illness, was 3.3 ($p < 0.001$).[2]

Within this 7-day period, the risk was significantly increased for immunized children only within 3 days of vaccination (relative risk 4.2, $p < 0.001$). The relative risk for illnesses occurring 4 to 7 days after vaccination was 2.1 ($p < 0.1$). Serious neurologic illnesses requiring hospitalization attributable to pertussis vaccine are rare. Final analysis of a comprehensive case-control study has estimated that the attributable risk of such illnesses is 1 in 140,000 doses administered. An earlier analysis had estimated this risk at 1/110,000 doses. In contrast, final analysis of the case-control study found that the risk of serious neurologic illness following pertussis disease was 1/11,000 pertussis cases. Repeated evaluations have shown that the benefits of vaccine outweigh the risks.[2,9]

The methods and results of the NCES have been thoroughly scrutinized since publication of the study. This reassessment by multiple groups has determined that the number of patients was too small and their classification subject to enough uncertainty to preclude drawing valid conclusions about whether a causal relation exists between pertussis vaccine and permanent neurologic damage. Preliminary data from a 10-year follow-up study of some of the children studied in the original NCES study also suggested a relation between symptoms following DTP vaccination and permanent neurologic disability. However, details are not available to evaluate this study adequately, and the same concerns remain about DTP vaccine precipitating initial manifestations of pre-existing neurologic disorders.[2]

An IOM report by the Committee to review the adverse consequences of pertussis and rubella vaccines concluded that evidence is consistent with a causal relation between DTP vaccine and acute encephalopathy, defined in the controlled studies reviewed as encephalopathy, encephalitis, or encephalomyelitis. On the basis of a review of the evidence bearing on this relation, the Committee concludes that the range of excess risk of acute encephalopathy following DTP immunization is consistent with that estimated for the NCES: 0.0 to 10.5 per million immunizations. The report also states that there is insufficient evidence to indicate a causal relation between DTP vaccine and permanent neurologic damage.[13]

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DT or DTP was not causally related to infantile spasms.[28] The incidence of onset of infantile spasms increases at 3 to 9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.[2]

A bulging fontanelle associated with increased intracranial pressure which occurred within 24 hours following DTP immunization has been reported. A causal relationship has not been established.[29,30,31]

CARDIOVASCULAR SYSTEM

An infant who developed myocarditis several hours after immunization has been reported.[32]

RESPIRATORY SYSTEM

Respiratory difficulties, including apnea, have been observed.

LOCAL

Rash and allergic reactions have been observed.

Sudden Infant Death Syndrome (SIDS) has temporally occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS.[33,34,35] It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2 to 6 months of age and that approximately 85% of SIDS cases occur at ages 1 to 6 months, with the peak incidence occurring at 6 weeks to 4 months of age. By chance alone, some SIDS victims can be expected to have recently received DTP.[33,34,35]

When CLI whole-cell DTP was administered concomitantly (at separate sites with separate syringes) with ActHIB™ or OmniHIB™, the systemic adverse experience profile was not different from that seen when CLI whole-cell DTP vaccine was administered alone.[10,11] ***(Refer to ActHIB™ package insert.)***

In general, the rates of minor systemic reactions after DTP was used to reconstitute ActHIB™ or OmniHIB™ were comparable to those usually reported after DTP vaccine alone.[6,19,36]

When CLI whole-cell DTP was used to reconstitute ActHIB™ or OmniHIB™ and administered to infants at 2, 4, and 6 months of age, the systemic adverse experience profile was comparable to that observed when the two vaccines were given separately. An increase in the rate of local reactions was observed in some instances within the 24-hour period after immunization.[10,11] ***(Refer to ActHIB™ package insert.)***

Reporting of Adverse Events

Reporting by parents or guardians of all adverse events occurring after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by health-care providers to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.[16,17,18]

Health-care providers also should report these events to the Director of Medical Affairs, Connaught Laboratories, Inc., Route 611, P.O. Box 187, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, the vaccine should not be administered.

SHAKE VIAL WELL *before withdrawing each dose. Vaccine contains a bacterial suspension. Vigorous agitation is required to resuspend the contents of the vial.* Discard if vaccine cannot be resuspended.

For Administration of DTP Vaccine Only:

The primary series for children less than 7 years of age is four doses of 0.5 mL each given intramuscularly. The customary age for the first dose is 2 months of age but may be given as young as 6 weeks of age and up to the seventh birthday.

Inject 0.5 mL intramuscularly only. The preferred injection sites are the anterolateral aspect of the thigh and the deltoid muscle of the upper arm. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk. During the course of primary immunizations, injections should not be made more than once at the same site.

The use of reduced volume (fractional doses) is not recommended. The effect of such practices on the frequency of serious adverse events and on protection against disease has not been determined.

Do NOT administer this product subcutaneously.

Special care should be taken to ensure that the injection does not enter a blood vessel.

PRIMARY IMMUNIZATION

This vaccine is recommended for children 6 weeks through 6 years (up to the seventh birthday) ideally beginning when the infant is 6 weeks to 2 months of age.

The primary series consists of four doses. For infants 6 weeks through 12 months of age, administer three 0.5 mL doses intramuscularly at least 4 to 8 weeks apart. The fourth dose is administered 6 to 12 months after the third injection.

BOOSTER IMMUNIZATION

For children between 4 and 6 years of age (preferably at time of kindergarten or elementary school entrance), a booster of 0.5 mL should be administered intramuscularly. Those who receive all four primary immunizing doses before their fourth birthday should receive a single dose of DTP just before entering kindergarten or elementary school. This booster dose is not necessary if the fourth dose in the primary series was administered after the fourth birthday. Thereafter, routine booster immunizations should be with Td, at intervals of 10 years. PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE) (DTP).

TABLE 2[2]

Diphtheria and Tetanus Toxoids Adsorbed USP (For Pediatric Use) (DT) or DTP.

A clinical study was performed in 20 children under one year of age to determine the serological responses and the adverse reactions when Connaught Laboratories, Inc. (CLI) DT was administered as a primary series of three doses. Protective levels of diphtheria and tetanus antitoxins that were equal to or greater than 0.01 I.U./mL were detected in 100% of the children following two doses of the vaccine. However, maternal antibody may have contributed to the total neutralizing antibody in some of these infants. Protective levels of antitoxin were observed in 100% of these infants following three doses of DT. No local or systemic reactions were observed in approximately half of the infants and only mild or moderate reactions were observed in the remainder of the DT study group.[5]

Another clinical study to evaluate serological responses and adverse reactions of CLI DT was performed in 40 children under one year of age. One group of 20 children received 0.5 mL doses of DTP, DT, DTP at two, four and six months of age, respectively. The second group of 20 children received 0.5 mL doses of DTP, DTP, and DT, respectively, at the same ages. The immunologic protection against diphtheria and tetanus as measured by toxin neutralizing antibodies induced by DT was comparable when administered as either a second or third dose.[6] The reaction rates following CLI whole-cell DTP vaccination closely correlated with the rates observed with other commercially available whole-cell DTP vaccines.[7] The incidence of adverse reactions was significantly lower following DT administration ($p < 0.05$). Although the number of vaccinees was small, no persistent screaming episodes or severe neurological reactions such as seizures or encephalopathy were observed with either vaccine in this study.[6]

PERTUSSIS
Disease caused by *Bordetella pertussis* was once a major cause of infant and childhood morbidity and mortality in the United States. Pertussis (whooping cough) became a nationally notifiable disease in 1922, and reports reached a peak of 265,269 cases and 7,518 deaths in 1934. The highest number of reported pertussis deaths (9,269) occurred in 1923. The introduction and widespread use of standardized whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids (DTP) in the late 1940s resulted in a substantial decline in pertussis disease, a decline which continued without interruption for nearly 30 years.[2]

By 1970, the annual reported incidence of pertussis had been reduced by 99%. During the 1970s the annual numbers of reported cases stabilized at an average of approximately 2,300 cases each year. During the 1980s, however, the annual numbers of reported cases gradually increased from 1,730 cases in 1980 to 4,517 cases in 1989. An average of eight pertussis-associated fatalities was reported each year throughout the 1980s.[2]

From 1989 to 1991, 11,446 cases of pertussis were reported for an unadjusted incidence per 100,000 population of 1.7 in 1989, 1.8 in 1990 and 1.1 in 1991. The incidence for 1992 was 1.6 per 100,000. Age specific incidence and hospitalization rates were highest in the first year of life, decreasing with increasing age. Trends of the past years suggest an increase in reported pertussis since 1976, with the peak year being 1990.[8]

During the period 1989 to 1991, of 3,900 reports of hospitalization, 1,115 had developed pneumonia, seizures occurred in 157 cases, encephalopathy was reported for 12, and there were 20 pertussis attributed deaths. These events were more frequently reported in children less than 6 months of age and were generally less frequent with increasing age.[7] Of patients 3 months through 4 years of age, where vaccination status was known, 65% of 4,471 patients had not received the recommended schedule of immunization and 39% had not received any pertussis containing vaccine.[3]

Among older children and adults, including those previously vaccinated, *B. pertussis* infection may result in symptoms of bronchitis or upper-respiratory-tract infection. Pertussis may not be associated with classic signs, especially the inspiratory whoop. Older preschool children and school-age siblings who are not fully vaccinated and who develop pertussis can be important sources of infection for infants <1 year of age. Adults also play an important role in the transmission of pertussis to unvaccinated or incompletely vaccinated infants and young children.[2]

EFFICACY OF PERTUSSIS VACCINE
Although DTP has been evaluated as a control vaccine in a number of clinical trials of "acellular pertussis vaccines," no formal efficacy trial was performed prior to approval. Approval was based on historical and continuing evidence of protection (surveillance) in the population at risk. It was also shown that vaccines with acceptable mouse protection potencies induced protective serum agglutinin antibody titers.[4] The pertussis component of each lot of DTP is tested for potency by a mouse protection test.

In clinical trials, one dose of CLI whole-cell DTP vaccine was used to reconstitute one lyophilized single dose vial of ActHIB™ or OmniHIB™ with no diminution in anti-PRP response or diphtheria, tetanus and pertussis responses.

INDICATIONS AND USAGE
Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) is recommended for active immunization of children up to age 7 years against diphtheria, tetanus, and pertussis (whooping cough) simultaneously. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, DT should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.[2,9]

Persons recovering from confirmed pertussis do not need additional doses of DTP but should receive additional doses of DT to complete the series.[2]

Available data indicate that the appropriate age for institution of immunizations in prematurely born infants is the usual chronological age of 2 months. Vaccine doses should not be reduced for preterm infants.[2,9]

If passive immunization is required, Tetanus Immune Globulin (Human) (TIG) and/or equine Diphtheria Antitoxin are the products of choice for tetanus and diphtheria, respectively (see **DOSAGE AND ADMINISTRATION** section).

When CLI DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, the combined vaccines are indicated for the active immunization of infants and children 2 months through 5 years of age for the prevention of invasive diseases caused by diphtheria, tetanus, pertussis and *H influenzae* type b.[10,11] ***(Refer to ActHIB™ package insert.)***

A single injection containing diphtheria, tetanus, pertussis and Haemophilus b conjugate antigens may be more acceptable to parents and may increase compliance with vaccination programs. Therefore, in those situations where, in the judgment of the physician, it is of benefit to administer a single injection of whole-cell DTP vaccine and Haemophilus b conjugate vaccine concomitantly, ***only CLI whole-cell DTP vaccine may be used for reconstitution of lyophilized ActHIB™ or OmniHIB™.*** Antibody levels associated with protection may not be achieved earlier than two weeks following the last recommended dose. (See **DOSAGE AND ADMINISTRATION** section.)

As with any vaccine, vaccination with DTP or combined vaccines CLI DTP and ActHIB™ or OmniHIB™ may not protect 10J% of susceptible individuals.

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

This vaccine is NOT to be used for the treatment of diphtheria, tetanus, pertussis or H influenzae type b infection.

This vaccine should NOT be used for immunizing persons 7 years of age and older.

CONTRAINDICATIONS
Hypersensitivity to any component of the vaccine, including thimerosal, a mercury derivative, is a contraindication for further use of this vaccine.

It is a contraindication to use this or any other related vaccine after an immediate anaphylactic reaction associated with a previous dose.

It is a contraindication to administer this vaccine in the presence of any evolving neurological condition.

Encephalopathy after a previous dose is a contraindication to further use.

Immunization should be deferred during the course of an acute illness. Vaccination of infants and children with severe, febrile illness should generally be deferred until these persons have recovered. However, the presence of minor illnesses such as mild upper respiratory infections with or without low-grade fever are not contraindications to further use.[2]

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.[12]

WARNINGS
If any of the following events occur in temporal relation to receipt of DTP, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelae.[2]

THE FOLLOWING EVENTS WERE PREVIOUSLY CONSIDERED CONTRAINDICATIONS AND ARE NOW CONSIDERED WARNINGS:[2]

1. **Temperature of ≥40.5°C (105°F) within 48 hours not due to another identifiable cause:** Such a temperature is considered a warning because of the likelihood that fever following a subsequent dose of DTP vaccine also will be high. Because such febrile reactions are usually attributed to the pertussis component, vaccination with DT should not be discontinued.[2]
2. **Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours:** Although these uncommon events have not been recognized to cause death nor to induce permanent neurological sequelae, it is prudent to continue vaccination with DT, omitting the pertussis component.[2]
3. **Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours:** Follow-up of infants who have cried inconsolably following DTP vaccination has indicated that this reaction, though unpleasant, is without long-term sequelae and not associated with other reactions of greater significance.[2] Evidence is insufficient to indicate whether pertussis vaccine-associated protracted, inconsolable, or high-pitched crying or screaming does, or does not, lead to chronic neurologic damage.[13] Inconsolable crying occurs most frequently following the first dose and is less frequently reported following subsequent doses of DTP vaccine. However, crying for >30 minutes following DTP vaccination can be a predictor of increased likelihood of recurrence of persistent crying following subsequent doses. Children with persistent crying have had a higher rate of local reactions than children who had other DTP-associated reactions (including high fever, seizures, and hypotonic-hyporesponsive episodes), suggesting that prolonged crying was really a pain reaction.[2]
4. **Convulsions with or without fever occurring within three days:** Short-lived convulsions, with or without fever, have not been shown to cause permanent sequelae. Furthermore, the occurrence of prolonged febrile seizures (i.e., status epilepticus – any seizure lasting >30 minutes or recurrent seizures lasting a total of 30 minutes without the child fully regaining consciousness), irrespective of their cause, involving an otherwise normal child does not substantially increase the risk for subsequent febrile (brief or prolonged) or afebrile seizures. The risk is significantly increased ($p=0.018$) only among those children who are neurologically abnormal before their episode of status epilepticus.[2] Accordingly, although a convulsion following DTP vaccination has previously been considered a contraindication to further doses, under certain circumstances subsequent doses may be indicated, particularly if the risk of pertussis in the community is high. If a child has a seizure following the first or second dose of DTP, it is desirable to delay subsequent doses until the child's neurologic status is better defined. By the end of the first year of life, the presence of an underlying neurologic disorder has usually been determined, and appropriate treatment instituted. DT vaccine should not be administered before a decision has been made about whether to continue the DTP series. Regardless of which vaccine is given, it is prudent also to administer acetaminophen[2], 15 mg/kg of body weight, at the time of vaccination and every 4 hours subsequently for 24 hours.

Persons who experienced Arthus-type hypersensitivity reactions or a temperature of >103°F (39.4°C) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given even emergency doses of Td more frequently than every 10 years, even if they have a wound that is neither clean nor minor.[2]

DTP should not be given to children with any coagulation disorder, including thrombocytopenia, that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

Recent studies suggest that infants and children with a history of convulsions in first-degree family members (i.e., siblings and parents) have a 3.2-fold increased risk for neurologic events compared with those without such histories.[14] *However, the ACIP has concluded that a family history of convulsions in parents and siblings is not a contraindication to pertussis vaccination and that children with such family histories should receive pertussis vaccine according to the recommended schedule.*[2]

A recent review of all available data by the IOM found evidence is consistent with a causal relation between DTP vaccination and acute encephalopathy, but that there is insufficient evidence to indicate a causal relation between DTP vaccine and permanent neurologic damage.[13]

Infants and children with recognized possible or potential underlying neurologic conditions seem to be at enhanced risk for the appearance of manifestations of the underlying neurologic disorder within two or three days following vaccination.[2] Whether to administer DTP to children with proven or suspected underlying neurologic disorders must be decided on an individual basis. Important considerations include the current local incidence of pertussis, the near absence of diphtheria in the United States and the low risk of infection with *C. tetani*.[2]

Although these events were considered absolute contraindications in previous ACIP recommendations, there may be circumstances, such as a high incidence of pertussis, in which the potential benefits outweigh possible risks, particularly because these events are not associated with permanent sequelae.[2]

The administration of DTP to children with proven or suspected underlying neurologic disorders that are not actively evolving must be decided on an individual basis.

Only full doses (0.5 mL) of DTP vaccine should be given; if a specific contraindication to DTP exists, the vaccine should not be given.[2]

Controversy regarding the safety of pertussis vaccine during the 1970s led to several studies of the benefits and risks of this vaccination during the 1980s. These epidemiologic analyses clearly indicate that the benefits of pertussis vaccination outweigh any risks and have not shown a cause and effect with neurologic illness.[2,9]

Deaths have been reported in temporal association with the administration of DTP vaccine (see **ADVERSE REACTIONS** section).

When CLI DTP vaccine is used alone or to reconstitute ActHIB™ or OmniHIB™ and administered to immunosuppressed persons or persons receiving immunosuppressive therapy, the expected antibody responses may not be obtained. This includes patients with severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation.[15]

Administration of DTP and/or Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) is not contraindicated in individuals with HIV infection.[11]

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

PRECAUTIONS
GENERAL
Care is to be taken by the health-care provider for the safe and effective use of DTP.

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines, previous immunization history, current health status (see **CONTRAINDICATIONS; WARNINGS** sections), and a current knowledge of the literature concerning the use of the vaccine under consideration. Immunosuppressed patients may not respond.

Prior to administration of DTP, health-care personnel should inform the parent or guardian of the patient the benefits and risks of immunization, and also inquire about the recent health status of the patient to be injected.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped and should be properly disposed.

INFORMATION FOR PATIENTS
As part of the child's immunization record, the date, lot number and manufacturer of the vaccine administered MUST be recorded.[16,17,18]

The health-care provider should inform the parent or guardian of the patient about the potential for adverse reactions that have been temporally associated with DTP administration. Parents or guardians should be instructed to report any serious adverse reactions to their health-care provider.

IT IS EXTREMELY IMPORTANT WHEN THE CHILD RETURNS FOR THE NEXT DOSE IN THE SERIES, THAT THE PARENT OR GUARDIAN OF THE PATIENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER THE PREVIOUS DOSE (SEE **CONTRAINDICATIONS; ADVERSE REACTIONS** SECTIONS).

The health-care provider should inform the parent or guardian of the patient the importance of completing the immunization series.

The health-care provider should provide the Vaccine Information Materials (VIMs) which are required to be given with each immunization.

The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986.[16] The toll-free number for VAERS forms and information is 1-800-822-7967.

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records and to report occurrences of certain adverse events to the U.S. Department of Health and Human Services. Reportable events include those listed in the Act for each vaccine and events specified in the package insert as contraindications to further doses of the vaccine.[17,18]

DRUG INTERACTIONS
If DTP and TIG or Diphtheria Antitoxin are administered concurrently, separate syringes and separate sites should be used.

As with other intramuscular injections, use with caution in patients on anticoagulant therapy.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (<2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it is reasonable to defer vaccination until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.[2]

If DTP has been administered to persons receiving immunosuppressive therapy, a recent injection of immunoglobulin or having an immunodeficiency disorder, an adequate immunologic response may not be obtained.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
No studies have been performed to evaluate carcinogenicity, mutagenic potential, or impact on fertility.

PREGNANCY
THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE AND OLDER.

PEDIATRIC USE
SAFETY AND EFFECTIVENESS OF DTP VACCINE OR AT THE TIME WHEN DTP VACCINE IS USED TO RECONSTITUTE ActHIB™ OR OmniHIB™ IN INFANTS BELOW THE AGE OF SIX WEEKS HAVE NOT BEEN ESTABLISHED. (See **DOSAGE AND ADMINISTRATION** section.)

This vaccine is recommended for immunizing children 6 weeks of age through 6 years of age (up to the seventh birthday). DTP is the preferred vaccine in this age group, but in those situations where an *absolute contraindication* to pertussis vaccination exists, or where in the opinion of the physician the pertussis vaccine should not be administered, DT is the appropriate alternative.

Full protection is achieved upon completion of primary immunization with either four doses of DTP, or three doses of DTP followed by a dose of an approved acellular DTP. A fifth dose of DTP or an approved acellular DTP is required.

THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE AND OLDER. For persons 7 years of age and older, the recommended vaccine is Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td).

An infant who developed myocarditis several hours after immunization has been reported.[32]

RESPIRATORY SYSTEM
Respiratory difficulties, including apnea, have been observed.

LOCAL
Rash and allergic reactions have been observed.

Sudden Infant Death Syndrome (SIDS) has temporally occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS.[33,34,35] It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2 to 6 months of age and that approximately 85% of SIDS cases occur at ages 1 to 6 months, with the peak incidence occurring at 6 weeks to 4 months of age. By chance alone, some SIDS victims can be expected to have recently received DTP.[33,34,35]

When CLI whole-cell DTP was administered concomitantly (at separate sites with separate syringes) with ActHIB™ or OmniHIB™, the systemic adverse experience profile was not different from that seen when CLI whole-cell DTP vaccine was administered alone.[10,11] ***(Refer to ActHIB™ package insert.)***

In general, the rates of minor systemic reactions after DTP was used to reconstitute ActHIB™ or OmniHIB™ were comparable to those usually reported after DTP vaccine alone.[6,19,36]

When CLI whole-cell DTP was used to reconstitute ActHIB™ or OmniHIB™ and administered to infants at 2, 4, and 6 months of age, the systemic adverse experience profile was comparable to that observed when the two vaccines were given separately. An increase in the rate of local reactions was observed in some instances within the 24-hour period after immunization.[10,11] ***(Refer to ActHIB™ package insert.)***

Reporting of Adverse Events
Reporting by parents or guardians of all adverse events occurring after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by health-care providers to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.[16,17,18]

Health-care providers also should report these events to the Director of Medical Affairs, Connaught Laboratories, Inc., Route 611, P.O. Box 187, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION
Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, the vaccine should not be administered.

SHAKE VIAL WELL *before withdrawing each dose. Vaccine contains a bacterial suspension. Vigorous agitation is required to resuspend the contents of the vial.* Discard if vaccine cannot be resuspended.

For Administration of DTP Vaccine Only:
The primary series for children less than 7 years of age is four doses of 0.5 mL each given intramuscularly. The customary age for the first dose is 2 months of age but may be given as young as 6 weeks of age and up to the seventh birthday.

Inject 0.5 mL intramuscularly only. The preferred injection sites are the anterolateral aspect of the thigh and the deltoid muscle of the upper arm. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk. During the course of primary immunizations, injections should not be made more than once at the same site.

The use of reduced volume (fractional doses) is not recommended. The effect of such practices on the frequency of serious adverse events and on protection against disease has not been determined.

Do NOT administer this product subcutaneously.

Special care should be taken to ensure that the injection does not enter a blood vessel.

PRIMARY IMMUNIZATION
This vaccine is recommended for children 6 weeks through 6 years (up to the seventh birthday) ideally beginning when the infant is 6 weeks to 2 months of age.

The primary series consists of four doses. For infants 6 weeks through 12 months of age, administer three 0.5 mL doses intramuscularly at least 4 to 8 weeks apart. The fourth dose is administered 6 to 12 months after the third injection.

BOOSTER IMMUNIZATION
For children between 4 and 6 years of age (preferably at time of kindergarten or elementary school entrance), a booster of 0.5 mL should be administered intramuscularly. Those who receive all four primary immunizing doses before their fourth birthday should receive a single dose of DTP just before entering kindergarten or elementary school. This booster dose is not necessary if the fourth dose in the primary series was administered after the fourth birthday. Thereafter, routine booster immunizations should be with Td, at intervals of 10 years. PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE) (DTP).

TABLE 2[2] **ROUTINE DIPHTHERIA, TETANUS, AND PERTUSSIS VACCINATION SCHEDULE**
Summary For Children <7 Years Old – United States, 1991

Dose	Customary Age	Age/Interval†	Product
Primary 1	2 Months	6 weeks old or older	DTP†
Primary 2	4 Months	4-8 weeks after first dose*	DTP†
Primary 3	6 Months	4-8 weeks after second dose*	DTP†
Primary 4	15 Months	6-12 months after third dose*	DTP†
Booster	4-6 years old, before entering kindergarten or elementary school (not necessary if fourth primary vaccinating dose administered after fourth birthday)		DTP†
Additional Boosters		Every 10 years after last dose	Td

* Use DT if pertussis vaccine is contraindicated. If the child is ≥1 year of age at the time that primary dose three is due, a third dose 6 to 12 months after the second dose completes primary vaccination with DT.
† Prolonging the interval does not require restarting series.

Preterm infants should be vaccinated according to their chronological age from birth.[2,9]

Interruption of the recommended schedule with a delay between doses does not interfere with the final immunity achieved with DTP. There is no need to start the series over again, regardless of the time elapsed between doses.

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) can be interchangeably used with DTP for the fourth and fifth doses. However ActHIB™ cannot be reconstituted with DTaP.

The simultaneous administration of DTP, oral poliovirus vaccine (OPV), and measles-mumps-rubella vaccine (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately. Simultaneous vaccination (at separate sites with separate syringes) with DTP, MMR, OPV, or inactivated poliovirus vaccine (IPV), and Haemophilus b conjugate vaccine (HbCV) is also acceptable.[2] The ACIP recommends the simultaneous administration, at separate sites with separate syringes, of all vaccines appropriate to the age and previous vaccination status of the recipients including the special circumstance of simultaneous administration of DTP, OPV, HbCV, and MMR at ≥15 months of age.[2]

If passive immunization is needed for tetanus, TIG is the product of choice. It provides longer protection than antitoxin of animal origin and causes few adverse reactions. The currently recommended prophylactic dose of TIG for wounds of average severity is 250 units intramuscularly. When tetanus toxoid and TIG are administered concurrently, separate syringes and separate sites should be used. The ACIP recommends the use of only adsorbed toxoid in this situation.[2]

WHEN RECONSTITUTING HAEMOPHILUS b CONJUGATE VACCINE (TETANUS TOXOID CONJUGATE), ActHIB™ or OmniHIB™
NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

CLI whole-cell DTP vaccine also can be used for reconstitution of ActHIB™ or OmniHIB™. Cleanse both the DTP and ActHIB™ or OmniHIB™ vaccine vial rubber barriers with a suitable germicide prior to reconstitution. Thoroughly agitate the vial of CLI whole-cell DTP vaccine, then withdraw a 0.6 mL dose and inject into the vial of lyophilized ActHIB™ or OmniHIB™. After reconstitution and thorough agitation, ActHIB™ or OmniHIB™ will appear whitish in color. Withdraw and administer 0.5 mL dose of DTP/ActHIB™ or OmniHIB™ vaccines.

When CLI whole-cell DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, administer **intramuscularly only. Vaccine should be used immediately (i.e. within 30 minutes) after reconstitution.**

After reconstitution, each 0.5 mL dose is formulated to contain 6.7 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, an estimate of 4 protective units of pertussis vaccine, 10 µg of purified capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid, and 8.5% of sucrose. ***(Refer to ActHIB™ package insert.)***

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

Each dose of DTP/ActHIB™ or OmniHIB™ vaccines is administered intramuscularly in the outer aspect of the vastus lateralis (mid-thigh) or deltoid. The vaccine should not be injected into the gluteal area or areas where there may be a nerve trunk. During the course of primary immunizations, injections should not be made more than once at the same site.

When CLI DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™, the combined vaccines are indicated for infants and children 2 months through 5 years of age for intramuscular administration in accordance with the schedule indicated in Table 3.[10]

TABLE 3[10] **RECOMMENDED IMMUNIZATION SCHEDULE**
For Previously Unvaccinated Children

DOSE	AGE	IMMUNIZATION
First, Second and Third	At 2, 4 and 6 months	DTP or DTP/ActHIB™ or DTP/OmniHIB™
Fourth	At 15 to 18 months	DTP or DTP/ActHIB™ or DTP/OmniHIB™ or Acellular Pertussis (DTaP)*
Fifth	At 4 to 6 years	DTP or Acellular Pertussis (DTaP)*

* Acellular Pertussis (DTaP) should NOT be used to reconstitute ActHIB™/OmniHIB™. When administering DTaP for the fourth dose, *Haemophilus influenzae* type b vaccine also should be administered at this time in a separate syringe at a different site.

For Previously Unvaccinated Children
Immunization schedules should be considered on an individual basis for children not vaccinated according to the recommended schedule. Three doses of a product containing DTP, given at approximately 2-month intervals, are required followed by a fourth dose of a product containing DTP or DTaP approximately 12 months later and a fifth dose of a product containing DTP or DTaP at 4 to 6 years of age. If the fourth dose of a pertussis-containing vaccine is not given until after the fourth birthday, no further doses of a pertussis-containing vaccine are necessary.

The number of doses of a product containing *H influenzae* type b conjugate vaccine indicated depends on the age that immunization is begun. A child 7 to 11 months of age should receive 3 doses of a product containing *H influenzae* type b conjugate vaccine. A child 12 to 14 months of age should receive 2 doses of a product containing *H influenzae* type b conjugate vaccine. A child 15 to 59 months of age should receive 1 dose of a product containing *H influenzae* type b conjugate vaccine.

Preterm infants should be vaccinated according to their chronological age from birth.[9]

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved when CLI DTP vaccine is used to reconstitute ActHIB™ or OmniHIB™. There is no need to start the series over again, regardless of the time elapsed between doses.

It is recommended that the same conjugate vaccine be used throughout each immunization schedule, consistent with the data supporting approval and licensure of the vaccine. Since ActHIB™ and OmniHIB™ are the same vaccine, these may be used interchangeably.

DO NOT INJECT INTRAVENOUSLY.

HOW SUPPLIED
DTP Vial, 2.5 mL – Product No. 49281-280-05
DTP Vial, 5 mL – Product No. 49281-280-10
DTP Vial, 7.5 mL – Product No. 49281-280-84

One 7.5 mL vial of Connaught Laboratories, Inc. Diphtheria and Tetanus Toxoids and Pertussis Vaccine as Diluent packaged with Vial, 1 Dose lyophilized Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) (10 x 1 Dose vials per package) – Product No. 49281-549-10

Administer vaccine immediately (i.e. within 30 minutes) after reconstitution.

STORAGE
Store between 2° – 8°C (35° – 46°F). DO NOT FREEZE. Temperature extremes may adversely affect resuspendability of this vaccine.

Store lyophilized vaccine packaged with vial containing Diphtheria and Tetanus Toxoids and Pertussis vaccine between 2° – 8°C (35° – 46°F). DO NOT FREEZE.

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Product information
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