

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

Ou-People, Cn-John M. Hyder -S,
0.9.2342,192030301.01.1-2000432462
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

SQUIBB/CONNAUGH

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP

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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.

DIFFICULI.

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

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) \$\pmu\$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.

For active immunization of infants and young children against diphtheria, tetanus and perfussis 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. 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. Anaphylactiol and/or allergic reactions, immunosuppressive therapy, recent gammaglobulin, plasma, or blood transfusions, immunosuppressive therapy, recent gammaglobulin, plasma, or blood transfusions, immunodeficiency disorders, leukemia, lymphoma, or generalized malignancy are also contraindications. 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.

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 consid-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

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.

Neurological complications have been reported. These include cochlear lesion, 6 brachial Neurological complications have been reported. These include cochlear lesion, a brachial plexus neuropathies, a paralysis of the redul nerve, and one reported case of swallowing difficulty. In the differential diagnosis of polyradiculoneuropathies following administration of tetanus toxid, tetanus toxoid should be considered as a possible etiology. 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.

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 Give 0.5 mi 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

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

HOW SUPPLIED Vial, 7.5 ml

STORAGE

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

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 REFERENCES
 Data available from Connaught Laboratories, Inc.
 Active Immunization Procedures. Report of the Committee on Infectious Diseases. American Academy of Pediatrics, Evanston, Illinois, p. 9, 13, 1977
 Pertussis. Report of the Committee on Infectious Diseases. American Academy of Pediatrics, Evanston, Illinois, p. 205, 1977
 Haneberg, B., Matre, R., Winsnes, R., Dalen, A., Vogt, H., Finne, P.H.: Acute hemolytic anemia related to diphtheria-pertussis-tetanus vaccination. Acta Paediatr. Scand. 67:347-350, 1978
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 Harrer, G., Melnizky, U., Wendt, H.: Akkomadationsparese und Schlucklähmung nach Tetanus-Toxoid-Auffrischimpfung. Wen. med. Wschr. 15: 296-297, 1971
 Schlenska, G. K.: Unusual neurological complications following tetanus toxoid administration. J. Neurol. 215: 209-302, 1977
 Active Immunization Procedures. Report of the Committee on Infectious Diseases. American Academy of Pediatrics, Evanston, Illinois, p. 3, 1977
 Advisory Committee on Immunization Practices. Diphtheria and Tetanus Toxoids and Pertussis Vaccine. MMWR 26: 401-402, 1977

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

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CONNAUGHT® is a trademark owned by Connaught Labs

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

Distributed by: E.R. SQUIBB & SONS, Inc.

Princeton, New Jersey 08540

Product information as of July, 1980

Printed in U.S.A. 0779

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IN CONDITIONS WHICH WARE RESUSTENSING OF THE VIGORITY CARE SHOULD BE TAKEN NOT TO STORE THIS PRODUCT NEAR FREEZING SUBFACES. 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.

DESCRIPTIONThis 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) :110,000 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.

IMPLICATIONS

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. Should any symptomatology related to neurological disorders develop following administration, do not attempt further administration 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. Special care should be taken so the injection is not made into a blood vessel.

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

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 module 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 vaccine, and sudden infant death, in particular. Secondary of such plexus neuropathies. 3° paralysis of the radial nerve. 9 paralysis of the recurrent nerve, 9 accommodation paresis, EEG disturbances, and one reported case of swallowing difficulty. In the differential diagnosis of polyradiculoneuropathies following administration of tetanus toxoid, tetanus toxoid should be considered as a possible etiology. 3000

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.

DOSAGESHAKE 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.

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.

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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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
4. Haneberg, B., Matre, R., Winsnes, R., Dalen, A., Vogt, H., Finne, P.H.: Acute hemolytic anemia related to diphtheria-pertussis-tetanus vaccination. Acta Paediatr. Scand. 67:347-350, 1978
5. Follow-up on DTP vaccination and sudden infant deaths-Tennessee. MMWR 28: 134-135, 1979
6. Wirth, G.: Reversible Kochlearisschädigung nach Tetanol-Injektion. Münch. med. Wschr. 107: 379-381, 1965
7. Gersbach, P., Waridel, D.: Paralysis après prévention antitétanique. Schweiz. med. Wschr. 106: 150-153, 1976
8. Tsairis, P., Duck, P.J., Mulder, D. W.: Natural history of brachial plexus neuropathy. Arch. Neurol. 27: 109-117, 1972
9. Blumstein, G.I., Kreithen, H.: Peripheral neuropathy following tetanus toxoid administration. J.A.M.A. 198: 1303-1031, 1966
10. Eicher, W., Neundorfer, B.; Recurrenslahmung 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

Manufactured by: CONNAUGHT LABORATORIES, INC. Swiftwater, Pennsylvania 18370, U.S.A Product information as of July, 1980

Printed in U.S.A. 0700

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.

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 per-tussis 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. **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 gamma-globulin, plasma, or blood transfusions, immunodeficiency disorders, leukemia, lymphoma, or generalized malignancy are also contraindications. **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

Elective immunization of patients over the age <mark>of six months shoul</mark>d be deferred during an outbreak of poliomyelitis.

This product is not recommended for immunizing persons 7 years of age and older. This 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. Should any symptomatology related to neurological disorders develop following administration, do not attempt further administration of pertussis antigen. The development of "excessive screaming syndromer" 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. 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.

Series auscusses have been reported. Systemic reactions include mild to moderate transient fever, chilis, 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.

Neurological complications have been reported. These include cochlear lesion, brachial plexus neuropathies, 11 paralysis of the radial nerve, paralysis of the recurrent nerve, accommodation paresis, EEG disturbances, and one reported case of swallowing difficulty. In the differential diagnosis of polyradiculoneuropathies following administration of tetanus toxoid, should be considered as a possible etiology. Should symptomatology referable to the central nervous system develop following administration, no further immunization with this product should be attempted.

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

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 Immunization13,14

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

Booster Immunization13,14

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

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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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 Advisory Committee on Immunization Practices. Diphtheria and Tetanus Toxoids and Pertussis Vaccine. MMWR 26:401-402, 1977



Mfd. by: CONNAUGHT LABORATORIES, INC Swiftwater, PA 18370 LEDERLE LABORATORIES DIVISION

American Cyanamid Company, Pearl River, N.Y. 10965

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CONNAUGHT



DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP

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DO NOT USE IF RESUSPENSION CANNOT BE ACHIEVED BY VIGOROUS SHAKING

DESCRIPTION

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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 iliness, 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. 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 thormbocytopenia, is a contraindication to further use of this vaccine. Anaphylactoid and/or allergic reactions, immunosuppressive therapy, recent gammagloulin, plasma, or blood transfusions, immunodeficiency disorders, leukemia, lymphoma, or generalized malignancy are also contraindications. 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. Should any symptomatology related to neurological disorders develop following administration, do not attempt further administration pertussis antigen. The development of "excessive screaming syndrome" is an absolute contraindication for any further use of perfussis 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.* Special care should be taken so the injection is not made into a blood vessel.

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. Neurological complications have been reported. These include cochlear lesion, o brachial plexus neuropathies, 7° paralysis of the radial nerve. 9 paralysis of the reacurrent nerve, o accommodation paresis, EEG disturbances, and one reported case of swallowing difficulty. In the differential diagnosis of polyradiculoneuropathies following administration of tetanus toxoid, tetanus toxoid should be considered as a possible etiology.

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

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

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.

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.

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

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

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

REFERENCES

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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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4. Haneberg, B., Matre, R., Winsnes, R., Dalen, A., Vogt, H., Finne, P.H.: Acute hemolytic anemia related to diphtheria-perfussis-tetanus vaccination. Acta Paediatr. Scand. 67:347-350, 1978
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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

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DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP

FOR PEDIATRIC USE

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 1.7
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

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. 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.

0008

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

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, excessives 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

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: 395-367, 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

0008

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 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

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.

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

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 Pertus-

sis 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. 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

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.

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
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. 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!⁶ 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

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.

EFERENCES

Data available from Connaught Laboratories, Inc.
Active Immunization Procedures. Report of the Committee on Infectious Diseases. American Academy of Pediatrics, Evanston, Illinois, p. 3, 1977.
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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. Esterbrook Lane herry Hill, NJ 08034, U.S.A

Printed in U.S.A. 0116

6/19/19

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.*

TABLE 2.* Routine diphtheria, tetanus, and pertussis immunization of - United States, 1985*

Edule summary for children under 7 years

Dese	Age/Interval†	Product
Primary 1 Primary 2 Primary 3 Primary 4	6 weeks old or older 4-8 weeks after first dose§ 4-8 weeks after second dose§ 6-12 months after third dose§	DTP 1 DTP 1 DTP 1 DTP 1
Booster	4-B years old, before entering kindergarten or elementary school (not necessary if touth, primary immunizing dose administered on or after fourth birthday)	DTP 9
Additional	Every 10 years after last dose	Ta

Important details are in the text.

Important details are in the text.

F. 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

- Code of Federal Regulations, 21CFR620.4 (g), 1985.
 Recommendation of the Immunization Practices Advisory Committee. Diphtheria, Tetanus, and Perfussis: Guidelines for vaccine prophylaxis and other preventive measures. MMWR 34: 405-426, 1985.
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- Schlenska, G.K.: Unusual neurological complications following tetanus toxoid administration. J Neurol 215: 299-302, 1977 22





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

DESCRIPTION

Diphtheria and Tetanus Toxolds and Pertussis Vaccine Adsorbed USP, for intramuscular use, combines diphtheria and tetanus toxolds, 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 potassium suifate. 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 LI units of diphtheria toxold and 5 Lf units of tetanus toxold. The total human immunizing dose (the first three 0.5 ml doses given) contains an estimate of 12 units of pertussis vaccine. Each component of the vaccine diphtheria, tetanus and pertussis - meets the required potency standards.

CLINICAL PHARMACOLOGY

Simultaneous immunization against diphtheria, letanus, and perfussis 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.

DUPM MERIA

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 *D. 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 tatal; 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 cultaneous diphtheria reported from a single state. After 1979, cultaneous 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.³

sons 20 years of age or older.*

The current rarity of diphthera 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 Toxolds and Pertussis Vaccine (DTP)) and to an apparent reduction of the circulation of toxolds and order of the circulation 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. *

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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.

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.

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 tox-old 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, ap-proximately 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 im-munication histories are unknown or uncertain.

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. Spores of *C. tetan*) 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 adquate 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.3

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. The role of each of the different components in either the pathogenesis of or the immunity to pertussis is not well understood.

munity to perfussis is not well understood.

General use of standardized perfussis vaccine has resulted in a substantial reduction in cases and deaths from perfussis 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, 2,465 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 8. perfussis - culture and direct-immunofluorescence assay (DFA) - may be unavailable, difficult to perform, or incorrectly interpreted.*

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 1993, 75% were nospitalized; approximately 22% had pneumonia; 2% had one or more selzures; 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.

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 ef-lects and adverse reactions, pertussis immunization is not recommended for children after their seventh birthday.

Evidence of the efficacy of perfussis 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 perfussis cases and 36 deaths between late 1977 and 1980, and 1,440 cases per week reported during the winter of 1981-1982. A similar situation occurred in Japan. 51

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

Product information as of July, 1986

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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 = < x,x,x.

As with any vaccine, vaccination with DTP may not protect 100% of susce,

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 primaty 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 perfussis vaccine is not to be administered. Diphtheria and Tetanus Toxotics Advorbed (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:

- 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
- 5. Convulsion(s) with or without fever occurring within 7 days.
- Encephalopathy occurring within 7 days; this includes severe alterations in consciousness with generalized or local 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.³

Use of this product is also contraindicated II 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.

IT IS ALSO A CONTRAINDICATION TO ADMINISTER OTP 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.*

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 (SEI-ZURES) 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 de cided on an individual basis

The ACIP recommends the following:

- 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 DPV) until further observation and study have clarified the child's neurologic status. In addition, the effect of freatment, 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 is 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.
- 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 perfussis vaccine, even though cause and effect may not be established (see CONTRAINDICATIONS).
- perussis vaccine, even though cause and effect may not be established (see CONTRAINDICATIONS).*
 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 hirther doses of the primary series of DTP, deferral of further doses of DTP or DT four not DPV) 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.
- 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.
- 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).³

natal hypocalcemic tetany or hydrocephalus (following placement of a shunt and without seizures).*

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, it 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. It Diphtheria and Tetanus Toxolds and Pertussis Vaccine Adsorbed USP (DTP) has been administered to persons receiving immunosuppressive therapy, a recent injection of immune globulin or having an immunoselficiancy 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 infarmuscular injection unless the potential benefit clearly outweighs the risk of administration.

The simultaneous administration of DTP, oral polio virus vaccine (DPV), and/or massles-munns-rubella vaccine.

The simultaneous administration of DTP, oral policy 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. *** 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.**

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 pre-vent transmission of hepatitis or other intectious agents from one person to another.

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 latant or shild to be injected.

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

As part of the Infant's or child's immunity accord, informed consent should be obtained and recorded. The lot number and manufacturer of the vaccin instered should be recorded in the event of the occurrence of any symptoms and/or signs of an adverse remainded to the control of 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. "I However, these observations were not noted by Barkin, R.M., et al. "I 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, drowsness, 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). Rash, allergic reactions, and respiratory difficulties, including apnea, have been observed.

Moderate to severe systemic events, such as lever 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.³

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 num-bers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are signifi-cantly less frequent. If local redness of 2.5 cm or greater occurs, the likelihood of recurrence atter another DTP dose increases significantly.

dose increases significantly."

In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England." 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 liliness 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 liliness, 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 vaccine (regardless of outcome) was one in 110,000 doses of DTP, and for a permanel neurologic deflicit, 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.*

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

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

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 ad-ministration, although a causal relationship has not been established.*

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. ** It should be recognized that the first three primary immunizing doses of DTP are usually administered to intants 2-6 months old and that approximately 85% of SIDS cases occur at ages 1-6 months, with the peak incidence occurr-ing at 6 weeks-4 months of age. By chance alone, some SIDS victims can be expected to have recently received vaccine.*

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. "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.

TABLE 1.4 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 Angrexia	1/15 doses
	1/5 doses
More serious systemic	
Persistent, inconsolable crying	7,222,000
(duration ≥ 3 hours) High-pitched, unusual cry	1/100 doses
Fever ≥ 40.5°C (≥ 105°F)	1/900 doses
Collapse (hypotonic-hyporesponsive	1/330 doses
6DISOde)	1/1,750 doses
Convulsions	171,700 00865
(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 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).

The following illnesses have been reported as temporally associated with the vaccine; neurological complications including cochiear lesion; brachial plexus neuropathies, 19-39 paralysis of the radial nerve, 39 paralysis of the radial nerve, 39 paralysis of the recurrent nerve, 49 commodation parests, and EEG disturbances with encephalopathy. 19 In the differential diagnosis of polyradiculoneuropathles following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology. 28

DOSABE AND ADMINISTRATION.

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

PIPHTHERIA AND TETANUS **COXOIDS AND PERTUSSIS VACCINE ADSORBED USP** (FOR PEDIATRIC USE)



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

DESCRIPTION

DESCRIPTION
Diphtheria and Tetanus Toxoids and Partussis Vaccine Adsorbed USP, for intramuscular use, combines diphtheria and tetanus loxoids, adsorbed with pertussis vaccine in a sterile isotoric 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 Lt units of diphtheria toxoid and 6 Lt units of Itanus toxoid. The total human immunizing dose the first three 0.5 ml doses given) contains an estimate of 12 units of pertussis vaccine. 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

Corryebacterium 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 statal; 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 (80% 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 reportatory or other mucosal surface) infections and are more commonly recovered from respiratory than from culaneous infections.²

C. diphtheriae can contaminate the skin of certain individuals, usually at the site of a wound. Although a sharply demarcated

C. diphtheriae can contaminate the skin of certain individuals, usually at the site of a wound. Although a sharply demarcated lasion 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

commend only by cuture. Usually other bacterial species can also be solution. Volunteed depinding and additional additional 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 is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by gigstridium tetanı.

gigstridium totani.

Joccurrence of tetanus in the United States has decreased markedly because of the routine use of tetanus toxoid amunization. Nevertheless, the number of reported cases has remained relatively constant in the last decade at an annual average of 90 cases. In 1963, 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 serously 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.⁹ 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 antitioxin 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.

The role of each of the different components in either the pathogenesis of or the immunity to perfussis is not well understood. General use of standardized perfussis vaccine has resulted in a substantial reduction in cases and destrict from perfussis 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 1953, 2,465 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. perfussis* - culture and direct-immunofluorescence assay (DFA) - may be unavailable, difficult to perform, or incorrectly interpreted.? For 1982 and 1983, 53% of reported illnesses from *B. perfussis* 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 perfussis s-related deaths occurred among children less than 1 year old. Perfussis is children less than 1 year old. Perfussis is children to the properties of the prop

children less than 1 year old.²
Perfussis 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 ODC 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 perfussis may not be diagnosed because classic signs, especially the inspiratory whoop, may be absent. Older preschool-aged children and school-aged sibiling who are not fully immunized and develop perfussis 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.³ Controversy regarding use of perfussis 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.^{2,2,4} Because the incidence and severity of perfussis decrease with age and because the vaccine may cause side effects and adverse reactions, perfussis immunization is not recommended for children after their seventh birthday.² Evidence of the efficacy of perfussis vaccine can be provided by the recent British experience, where a reduction in the number of immunized individuals from 79% in 1978, to 31% in 1978 was associated with an epidemic of 102.500 perfussis cases and 36 deaths between tale 1977 and 1980, and 1,440 cases per week reported during the winter of 1981–1982.³ A similar

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

peropriate age for immunization of prematurely born infants is uncertain. Available data indicate that immunization with s 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

"http://mmunization of infants and children to age 7 years against diphtheria, tetanus and pertussis (whooping cough) aneously. 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 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

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

Absolute contraindications: 2

Allergic hypersensitivity to any component of the vaccine.

DTP should not be given! For children with any coagulation disorder that would contraindicate inframuscular injection unless the potential bene 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 state. 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

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.

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

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. If However, these observations were not noted by Barkin, R.M., et al. "Occasionally, a notule 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 DTP are usually self-imited, and need no therapy other than, perhaps, symptomatic treatment (e.g., antipyretics). Plash, allergic reactions, and respiratory difficulties, including apnea, have been observed.

Moderate to severe systemic events, such as fever of 40.5 9.0 (1059 Et ne higher pareignent inconsolable power lasting 2

Moderate to severe systèmic 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. If I local redness of 2.5 cm or greater occurs, the likelihood of recurrence after another DTP dose increases significantly, I linthe National Childhood Encephalopathy Study (NCES), a large, case-control study in England, I4 children 2.3 months of age with serious, acute neurologic disorders, such as encephalopathy or complicated convulsion(s), were more filkely 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 (setimated 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 influence only within 1 days of vaccination (relative risk 4.2, p. 6.001). 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 DP vaccine regardless of outcome) was one in 110,000 doses of DTP, and for a permanent prologic disorder within 7 days after of PP vaccine regardless of vaccine) was one in 110,000 doses of DTP, and for a permanent prologic disorder within 7 days after of provious 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

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

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

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

a datase relationship has not been established.

Sudden Infant death syndrome (SIOS) has occurred in infants following administration of DTP. A large case-control study of SIOS in the United States showed that receipt of DTP was not causally related to SIOS.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 SIOS cases occur at ages 1 - 6 months, with the peak incidence occurring at 6 weeks-4 months of age. By chance alone, some SIOS 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 deficitt	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 ¹⁶ including occhiear lesion, ¹⁶ brachial plexus neuropathies; ^{16,00} paralysis of the radial nerve, ¹⁹ 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 anaphylatic reaction occur due to any component of the vaccine.

- Persisting, inconsolable crying lasting 3 hours or more or an unusual, high-pitched cry occurring within 48 hours.
- Convulsion(s) with or without fever occurring within 7 days.
- Encephalogathy 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 pertusely vaccine, because administration of DTP may coincide with or possibly even aggravate manifestations of the disease. Such disorders include uncontrolled spilepsy, infantile spasms, and progressive encephalopathy;

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

IT IS ALSO A CONTRAINDICATION TO ADMINISTER DTP-TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL. IN MAY CASE, EPINEPHRINE INJECTION (1:100) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

Elective immunization procedures should be deforred during an outbreak of poliomyelitis.9

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

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 DISORDET.

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:

 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 conflusion 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 retainent, 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 perfussis from institutionalization or from attendance at offices 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 femorally associated with DTP. Infants and children who experience
- 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).³
- even though cause and effect may not be established (see CONTRAINDICATIONS).²²
 Incompletely immunized children with neurologic events occurring between doses, Infants and children who have
 raceived 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 DTP) 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 childr'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 oliven.² subsequent dose of DTP is given 2
- a subsequent duse of DIT is given.

 Infants and children with stable neurologic conditions. Infants and children with stable neurologic conditions, including well-controlled setzures, may be vaccinated. The occurrence of single-seizures (temporally unassociated with Including well-controlled setzures, may be vaccinated. The occurrence of single-seizures (temporally unassociated with Including well-controlled setzures can be satisfactorely explained.

 The administration is recommended for infants with
- Children with resolved or corrected neurologic disorders. DTP administration is recommended for inflants 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

nypocalcemic tetany or nyprocephalus (tollowing placement of a shunt and without seizures).² Immunosuppressive interapies, including irradiation, antimetabolities, 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

Hopotheria 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.

to resuspend the contents of the vial.

Inject 0.5 ml intramuscularly. The vastus lateralis (mid-thigh laterally) is the preferred injection site for intants. The gluteus maximus should be avoided due to the potential for damage to the solidic 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 perfussis immunication schedule summary for children under 7 years old. United States. 1985:

Dose	Age/Interval†	Product
Primary 1 Primary 2 Primary 3 Primary 4	6 weeks old or older 4-8 weeks after first dose§ 4-8 weeks after second dose§ 5-12 months after third dose§	DTP ¶ DTP ¶ 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 1
Additional boosters	Every 10 years after last dose	Td

important details are in the text.

Important details are in the text.

Customarily begun at 8 weeks of age, with second and third doses given at 8-week intervals.

Protoriging the interval dose does not require restarting series.

DT, if pertuesis 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

Store between $2^{\circ}-8^{\circ}$ C ($35^{\circ}-46^{\circ}$ F). DO NOT FREEZE. Temperature extremes may adversely affect resuspandability of this vaccine.

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 Code of Federal Regulations, 21CFR620.4 (g), 1985

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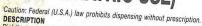
CONNAUGHT LABORATORIES, INC. Swiftwater, Pennsylvania 18070, U.S.A.

Product information as of July, 1986 Printed in U.S.A. 1859





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



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 m gof aluminum added in the form of aluminum potassium whitish in color. Each single dose of 0.5 ml is formulated to contain 6.7 Lf units of diphtheria toxoid and 5.1 funits of tetanus vaccine. In suspension, is a turbid idjuid, toxoid. The total human immunizing dose (the first three 0.5 ml doses given) contains an estimate of 12 units of pertussis classical phabmacol gov.

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 especially a provided by the protein declared from 306 in 1975 to 59 in 1979; most were tin the very young and the elderly, from a single state. After 1979, cutaneous diphtheria was no longer reportable. From 1980 to 1983, only 15 cases of respiratory from a single state. After 1979, cutaneous diphtheria was no longer reportable. From 1980 to 1983, only 15 cases of respiratory from a single state. After 1979, cutaneous diphtheria was no longer reportable. From 1980 to 1983, only 15 cases of respiratory from a single state. After 1979, cutaneous diphtheria reported diphtheria were reported; 11 occurred among persons 20 years of age or older. Promisson of the current rarity of diphtheria in the United States is due primarily to the high level of appropriate immunization among Vaccine (1974) and to an apparent reduction of the circulation of toxigenic strains of C. diphtheriae. Most cases occur among indicate that many adults in the United States are not profected against diphtheria. Sand the results of serosurveys continuing to immunize children more emphasis should be placed on adult immunization programs. If appears that in addition to Both toxigenic and non-toxigenic strains of C. diphtheriae can cause disease, but only strains that produce toxin cause (respiratory or other mucosal surface) infections and are more commonly recovered from respiratory than from cutaneous infections. C. diphtheriae can contaminate the skin of certain individuals, usually at the site of a wound. Although a chearly dependent of the contaminate the skin of certain individuals, usually at the site of a wound.

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 affected indigent adults and certain groups of Native Americans.²
"plete immunization significantly reduces the risk of developing diphtheria, and immunized persons who develop disease "phtheriae" in the pharynx or nose or on the skin.²

TETANUS

Clostridium teta

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 average of 90 cases. In 1983, 91 tetanus cases were reported from 29 states. In recent years, approximately two-thirds of average of 90 cases. In 1983, 91 tetanus cases were reported from 29 states. In recent years, approximately two-thirds of many United States adults are not protected against tetanus. The disease has occurred almost exclusively among persons in 6% of tetanus cases reported during 1982 and 1983, no wound or other condition could be implicated. Non-acute skin Spores of C. tetani are ubiquitous. Serological tests indicate that naturally acquired immunity to tetanus cases.² In the United States. Thus, universal primary immunization, with subsequent maintenance of adequate antitoxin levels by and a completed primary series generally induces protectial age groups. Tetanus toxoid is a highly effective antigen, PERTUSSIS

PERTUSSIS

Pertussis is a disease of the respiratory tract caused by Bordetella pertussis. This gram-negative coccobacillus produces leukceytosis, sensitivity to histamine, changes in glucos and/or insulin levels, neurological effects, and adjuvant activity. General use of standardized pertussis vaccine has resulted in a substantial reduction in cases and dalivant activity. General use of standardized pertussis vaccine has resulted in a substantial reduction in cases and the standardized pertussis vaccine has resulted in a substantial reduction in cases and the standardized pertussis vaccine has resulted in a substantial reduction in cases and the standardized pertussis vaccine has resulted in a substantial reduction in cases and substantial

children less than 1 year old?

Pertussis is highly communicable (attack rates of over 90% have been reported for unimmunized household contacts) and 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. Symptoms of bronchitis or an upper respiratory tract infection, and pertussis may not be diagnosed because classic signs, immunized and develop pertussis can be important sources of infection for young infants, the group at highest risk of disease Controversy regarding use of pertussis vaccine led to a formal reevaluation of the benefits and risks of this vaccine. The

Controversy regarding use of perfussis vaccine led to a formal reevaluation of the benefits and risks of this vaccine. The Recause the incidence and severity of particles depressed 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.

reactions, persussis 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 and 36 deaths between late 1977 and 1980, and 1,440 cases per week reported during the winter of 1981-1982.³ A similar vition occurred in Japan.^{5,6} чето оссиден и заради-этс. Talse 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 coupling illaneously. DTP is recommended for primary immunization of infants and children up to 7 years of age. However, in to be administered, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) should be used. Immunization should CONTRAINDICATIONS

ONTHAINDICATIONS lersons 7 years of age and older must NOT be immunized with Pertussis Vaccine

Absolute contraindications: 2

solute contraindications:
Allergic hypersensitivity to any component of the vaccine
Fever of 40.5°C (105°F) or greater within 48 hours.

Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.

Consulsion(s) with or without fever occurring within 7 days. 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, include uncontrolled epilepsy, infantile spasms, and progressive encephalopathy.

Use of this product is also contraindicated if the child has a personal or family history of a seizure disorder. However, the ACIP vaccination, 2.

Vaccination,²
T IS ALSO A CONTRAINDICATION TO ADMINISTER DTP TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL. IN ANY CASE, FPINEPHRINE 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.

MMUNIZATION 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 ADMINORNTRAINDICATED IF PRODUCT IS AN ABSOLUTE CONTRAINDICATION TO FURTHER USE. USE OF THIS PRODUCT IS ALSO
THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A
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

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

The ACIP recommends the following:

1. Infants as yet unimmunized who are suspected of having underlying neurologic disease. Possible latent central evident as they evolve over time. Because OTP administration may coincide with onset of over manifestations of output disorders and result in confusion about causation it is evident a.

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 administrated separately.²10 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.

In the property of the vaccine of the vaccine of the vaccine of the vaccine 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

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 anothe

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 perfussis antigens. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses. If However, these observations were not noted by Barkin, R.M., et al., 2°Cocasionally, 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 aphea, 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

in Table 1, 213.14

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 monts 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 (setimated 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 PTP vaccine (regardless of outcome) was one in 110,000 doses of DTP, and for a permanent roulogic difficit, one in 310,000 doses. No specific clinical syndrome was identified. Overall, DTP vaccine cancounted 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

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

has ones. Arius 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. 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.

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, ¹⁹ In the differential claignosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology. ²²

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

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

Toustomarily 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.

Tour 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.

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

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



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 contriot pl.; 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 th units of diphtheria toxoid and 5.t 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. Each component of the vaccine - diphtheria, tetanus and pertussis - meets the required potency standards.

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
Corryebacterium 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 or all types declined from 30s in 1975 to 59 in 1979; most were cutaneous diphtheria eported from a single state. After 1979, cutaneous diphtheria was no longer reportable. From 1980 to 1983, only15 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 Toxolds and Pertussis Vaccine (1DTP) 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.?

Both toxigenic and non-toxigenic strains of C. diphtheriae can cause disease, but only strains that produce toxin cause

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 noncutarieous (respiratory or other mucosal surface) infections and are more commonly recovered from respiratory than from cutaneous infections?

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

***nplete 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 uphtheriae in the pharynx or nose or on the skin.²

TETANUS

stanus 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

who are diffiltratized or inacequately immunized or wnose 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 ubriquitous. 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 fective antign, and a completed primary series generally induces protective levels of serum antitoxin that persist for 10 or more years.² PERTUSSIS

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 dearts 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 Italities 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 and pertussis is children less than 1 year old.²

Pertussis is highly communicable (attack rates of over 90% have been reported for unimmunized heuseshold contracts) and

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 life is recommended.² In older children and adults, including in some instances those previously immunized, infection may 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 shilings 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 perfussis 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 perfussis decrease with age and because the vaccine may cause side effects and adverse reactions, perfussis 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. A similar attention programed in Japan-5 and 1980, and 1,440 cases per week reported during the winter of 1981-1982.

tion occurred in Japan.5,6

*Orc., riate 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

INDICATIONS AND USAGE
For active immunization of infants and children to age 7 years against diphtheria, tetanus and pertussis (whooping cough, iltaneously. DTP is recommended for primary immunization of infants and children up to 7 years of age. However, in see the pertussis vaccine component is contraindicated, or where the physician decides that perfussis vaccine to be administered, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) should be used. Immunization should us 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

Allergic hypersensitivity to any component of the vaccine

Fever of 40.5°C (105°F) or greater within 48 hours.
Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.

Persisting, inconsolable crying lasting 3 hours or more or an unusual, high-pitched cry occurring within 48 hours. Convulsion(s) with or without fever occurring within 7 days.

Encephalopathy occurring within 7 days; this includes severe alterations in consciousness with generalized or focal

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 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

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 REGROUESS 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 nonset 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

Infants and children with neurologic events temporally associated with DTP. Infants and children who experience neizure within 3 days of receipt of DTP or an encephalopathy within 7 days should not receive further pertuss

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 condition including well-controlled seizures, may be vaccinated. The occurrence of single seizures (temporally unassociated w 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. should be vaccinated while still on therapy.2

If Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (DTP) has been administered to persons reveiving 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, it mere is any doubt that a following the simultaneous administration of all vaccines appropriate to the age and previous vaccination status of the recipient, mends the simultaneous administration of DTP, OPV, and MMR to such persons at 15 months of age. This would especially include the simultaneous administration of DTP, OPV, and MMR to such persons at 15 months of age.

PRECAUTIONS

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

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.

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 processing the processin

or child to be injected.

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

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ADVERSE REACTIONS

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

Not all adverse events following administration of providing the second induction with or without tenderness, and everse 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 perfussis antigens. Some data suggest are common after the administration of vaccines containing diphtheria, tetanus, or perfussis antigens. Some data suggest are common after the administration of vaccines who have experienced such responses after prior doses. It however, that febrile reactions were not noted by Barkin, R.M., et al. 12. Occasionally, a nodule may be palpable at the injection site of these observed for officers of the permitten of

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

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Approximate rates for aoverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in Table 1, 215,144. 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., freffulness, 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 the National Childhood Encephalopathy Study (NCES), a large, case-control study in England, 14-didner 2 - 35 months of age with serious, acute neurologic disorders, such as encephalopathy or complicated convulsion(s), where more likely to have received DTP in the 7 days preceding onset than their age, sex., and neighborhood-matched controls. Among children 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 dilines' occurring within the 7-day period of lowing 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 artibutable risk estimates for a serious acute neurologic deficit, 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 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 deficit, one in 310,000 doses. No specific clinical syndrome was ident

nistories. 2.19

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

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 SIDS in the United States showed that receipt of DTP was not causally related to SIDS,16 it should be recognized that the first brief 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 Onset of infantile spasms showed that receipt of DTP or DT was not causally related to infantile spasms. The incidence of onset of with 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.?

TABLE 1.2 Adverse events occurring within 48 hours of DTP impunitations.

BLE 1.2 Adverse events occurring within 48 hours of DTP in Event	Frequency*	
Local Redness Swelling Pain	1/3 doses 2/5 doses 1/2 doses	4
Mild/moderate systemic Fever > 38°C (100.4°F) Drowsiness Fretfulness Vomiting Anorexia	1/2 doses 1/3 doses 1/2 doses 1/15 doses 1/5 doses	
More serious systemic Persistent, inconsolable crying (duration ≥3 hours) High-pitched, unusual cry Fever ≥40.5°C (≥105°F) Collapse (hypotonic-hyporesponsive episode)	1/100 doses 1/900 doses 1/330 doses 1/1,750 doses 1/1,750 doses	140

Acute encephalopathy†
Permanent neurologic deficit† Number of adverse events per total number of doses regardless of dose number in DTP series.

Occurring within 7 days of DTP immunization.

† Occurring within / 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 reported by health-care providers to 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 referral 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 complications¹⁶ including cochier lesion, ¹⁹ brachial plexus neuropathies; ¹⁸20 paralysis of the radial nerve; ²¹ paralysis of the recurrent nerve; ¹⁹ cochier lesion, ¹⁹ brachial plexus neuropathies; ¹⁸20 paralysis of the radial nerve; ²¹ paralysis of the recurrent nerve; ¹⁹ 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. 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 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

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*

iu - Omiteu Otatoe, 1	A Hutomolt	Product
Dose	Age/Interval†	DTD+9
Primary 1 Primary 2 Primary 3 Primary 4 Booster	6 weeks old or older 4-8 weeks after first dose§ 4-8 weeks after second dose§ 6-12 months after third dose§ 4-6 years old, before entering kindergarten or elementary school (not necessary if fourth primary immunizing dose administered on or after fourth brithday)	DTP ¶ DTP ¶ DTP ¶ DTP ¶ DTP ¶
Additional honetors	Every 10 years after last dose	Td

mportant details are in the text.

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.
 Tot, if perfussis vaccine is contraindicated. If the child is 1 year of age or older at the time the primary dose is git 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 $2^{\circ} - 8^{\circ}$ C ($35^{\circ} - 48^{\circ}$ F). DO NOT FREEZE. Temperature extremes may adversely affect resuspendability

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

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

DESCRIPTION

DESCRIPTION
Diphheria and Tetanus Toxolds and Pertussis Vaccine Adsorbed USP, for intramuscular use, combines diphtheria and tetanus toxolds, 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 polassium 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 LI units of diphineria toxold and 5 Lf units of tetanus toxold. 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.

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.

sons 20 years or age or order.*

The current rarily of diphtheria in the United States is due primarily to the high level of appropriate immunization among children (95% of children entering school have received three or more doses of Diphtheria and Tetanus Toxolds 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.*

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 Ar "rans."

Incipe, ie immunization significantly reduces the risk of developing diphtheria, and immunized persons who were 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.

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

elaborated by clostrigium tetani.

The occurrence of tetanus in the United States has decreased markedly because of the routine use of tetanus toxold 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.

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.

Spores of *C. tetani* are ubiquitous. Serological tests indicate that naturally acquired immunity to tetanus tood 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 toxicid is a highly effective antigen, and a completed primary series generally induces protective levels of serum antitoxin that persist for 10 or more years.

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. The role of each of the different components in either the pathogenesis of or the immunity to pertussis is not well understood.

munity 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.

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 is highly computable (attack rates of year 90% have been reported for unimputable disusehold con-

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.³

In older children and adults, including in some instances those previously immunized, infection may result in nonspecific symptoms of bronchilts 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 sc papenged siblings who are not fully immunized and develop pertussis can be important sources of infection for yogap) (Jants, 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.*.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

EV of the efficacy of pertussis vaccine can be provided by the recent British experience, where a reduction in the humber 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. A similar situation occurred in Japan. 3-1

Epinephrine Injection (1:1000) mus. any component of the vaccine

nediately available should an acute anaphylactic reaction occur due to

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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

PRECAUTIONS

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

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, grythema, 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." However, these observations were not noted by Barkin, R.M., et al. 1º 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). 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. "If local redness of 2.5 cm or greater occurs, the likelihood of recurrence after another DTP dose increases significantly."

dose increases significantly."

In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England, "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 lilness 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 lilness, 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 lilness 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."

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 selzures following DTP than those without such histories.^{4, 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.*

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 ad-ministration, although a causal relationship has not been established.*

Sudden infant death syndrome (SIDS) has occurred in infants following administration of DTP. A large case-control study of SIDIS in the United States showed that receipt of DTP was not causally related to SIDS. ** 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 occurr-ing at 6 weeks-4 months of age. By chance alone, some SIDS victims can be expected to have recently received vaccine.*

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. "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.*

TABLE 1.3 Adverse events occurring within 48 hours of DTP immunizations

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

CONTRAINDICATIONS

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

Absolute contraindications:

- 1. Allergic hypersensitivity to any component of the vaccine.
- Fever of 40.5°C (105°F) or greater within 48 hours.
- 3. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- 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.
- 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 anneals of the disease. Such disorders include uncontrolled epilepsy, infantile spasms, and progressive

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

TI IS ALSO A CONTRAINDICATION TO ADMINISTER DTP TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THI-MEROSAL. 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 pollomyelitis.*

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

I'MIS VACCINE MUST DE USED TOF 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 (SEI-THEN USES) 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 THE DESCRIPT OF A SEIZURE DISORDER.

HISTORY OF A SEIZUME DISURDEN.
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 ACTUITY 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:

- 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 immunication with DTP or DT but not DYP) until further observation and study have clarified the child's neurologic munication with DTP or DT should be made no later than the child's first birthday. In making this decision, it spould be recognized that children with severe neurologic disorders may be at enhanced risk of exposure to children may be unimmunized. In addition, because of neurologic handicaps, these children may be in greater leparaty from complications of the disease.
- 2. Infants and children with neurologic events temperally 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).
- perfussis vaccine, even though cause and effect may not be established (see CONTRAINDICATIONS).

 Incompletely Immunized children with neurologic overtis occurring between doses. Intants and children who have received one or more doses of DTP and who experience a neurologic disorder, e.g., a seizure, temporally iem. If the seizure or other disorder occurs before the first birthday and completion of the first three doses of DTP experience of the children series of DTP. Deferral of further doses of DTP or DT (but not DPV) 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 to 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.
- Infants and children with stable neurologic conditions, infants and children with stable neurologic conditions, including well-controlled selzures, may be vaccinated. The occurrence of single selzures (temporally unassociated with DTP) in infants and young children, while necessitating evaluation, need not contraindicate DTP immunization, particularly if the selzures can be satisfactorily explained.
- 5. Children with resolved or corrected neurologic disorders. DTP administration is recommended for intants 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 selzures).*

natal hypocalcemic tetany or hydrocephalus (following placement of a shunt and without seizures).*
mmunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and coricosteroids (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
uppressive therapy will be discontinued shortly, it would be reasonable to defer immunication until the patient
should not be immunication until the patient
should be vaccinated while still on therapy.*

Diphthesis and Tetanus Toyolds and Deffuseis Vaccine Adearthed LISD (DTD) has been administrated to pursons:

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (DTP) has been administered to persons isolating 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 in-amuscular injection unless the potential benefit clearly outwelghs the risk of administration.

amuscular injection unless the potential benefit creatly outweighs the risk of administration.

e simultaneous administration of DTP, oral polio virus vaccine (OPV), and/or measles-mumps-rubella vaccine (MR) has resulted in sercoconversion rates and rates of side effects similar to those observed when the vaccines a administered separately. *I's Therefore, if there is any doubt that a vaccine recipient will return for further vacacines to doses, the ACIP recommends the simultaneous administration of all vaccines appropriate to the age and avious 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.

**Therefore Therefore Therefo

the recurrent nerve, "accommodation paresis, and EEG disturbances with encephalopathy.\(^1\) In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.\(^1\)

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 lateralls (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

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 2.3

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

Dose	Age/Intervalf	Product
Primary 1 Primary 2 Primary 3 Primary 4	6 weeks old or older 4-8 weeks after first dose§ 4-8 weeks after second dose§ 6-12 months after third dose§	OTP† ¶ OTP ¶ OTP ¶ OTP ¶
Booster	4-6 years old, before entering kindergarien 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 doss 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

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.

Product Information as of July, 1986

Printed in U.S.A

1629



PIPHTHERIA AND TETANUS JXOIDS AND PERTUSSIS **VACCINE ADSORBED USP**



(FOR PEDIATRIC USE)

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

Dipthrena and Telanus Toxoids and Pertussis Vaccine Adaorbed USP (For Pediatric Use) combines dipthrena and tetranus (oxoid-adaoched with pertussis vaccine, for intramuscular use, in a starila isotonic sodium chloride solution containing sodium phosphate buffer to control ph. The vaccine, after shaking, is a turbid liquid, whitsh-gray in color. When used to reconstitute Haemophilius b Conjugate Vaccine (Tetanus Toxoid Conjugate), Actilia™ or Omni-HIS™, the combined vaccines appear whitish in color.

Corynelasclerium diphtheriae cultures are grown in a modified Mueller and Miller medium. Costridium letani cultures are grown in a peptone-based medium. Both toxins are detoxilled with formaldehyde. The deloxified materials are separately purified by serial animonium sulfate fractionation and distilization.

armnonium suntate macionation and diamitration.

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 resispended in physiological saline and thimerosal.

The toxolds are assorbed to aluminium potassium sulfate (alum). The adsorbed diphtheria and tetanus toxolds are combined with pertussis vaccine concentrate, and diluted to a final volume using startie phosphale-buffered physiological saline. Each 0.5 mt. dose contains, by assay, not more than 0.17 mg of aluminium and not more than 100 kg (0.02%) of residual formatidityde. Thimerosal (mercury derivative) 110,000 is added as a preservative.

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

autitions per mt. in the guinea pig potency test).

The total human immunizing dose (the first three 0.5 mt. doses administered) contains an estimate of 12 units of pertussis vaccine. (4 protective units per single dose). 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. (CILI) DTP vaccine is used to reconstitute AcHIRI** or OmniHRI**, each single dose of the 0.5 mt. instruct is formulated to contain E.7 Lt of diphtheria toxoid, 5. Lt of of testus toxoid, and an estimate of 4 protective units of pertussis vaccine, 10 up of purified capsular polysacchanide conjugated to 24 up of machyated tetanus toxoid, and 8.5% of sucross.

NOTE: Haemophilus b Conjugate Vaccine (Tatanus Toxoid Conjugate) — Actriliti** is dentical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) — OmniHRI** (distributed by SmithKilne Beecham Pharmaceuticatis); both products are manufactured by Pasteur Ménieux Sérums & Vaccine S.A.

CLINICAL PHARMACOLOGY

DIPHTHERIA

Corynebecterium diphtheriae may cause both localized and generalized disease. Systemic introdication 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.

More than 200 000 cases introduced among some children, were recorded in

neutralizing antibodies to diphtheria toxin.

All one time, diphtheria was common in the Initied States. More than 200,000 cases, primarily among young children, were reported in 1221. Approximately 5% to 10% of cases were fatal; the highest case-fatality ratios were recorded for the very young and the elderfy. Reported cases of diphtheria of all types declined from 306 in 1975 to 58 in 1979, and were cutanous reported from a single state. After 1979, cutanous diphtheria was no longer a notifiable disease. From 1980 to 1999, only 24 cases of respiratory diphtheria were reported; two cases were fatal, and 18 (75%) occurred among persons 20 years of age or older.

Diphtheria is currently a rate disease in the United States primarily because of the high level of appropriate vaccination among children (77% of children entering school have exceived ≥three doses of diphtheria and tetanus toxicids 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 (redequately) immunized persons ²

Both loxigenic and nontoxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce toxin cause myocardits and neutrits. Toxigenic strains are more often associated with severe or fatal illness in noncutaneous (respiratory or other mucesal surface) infections and are more commonly recovered in association with respiratory than from cutaneous infections?

complete vaccination series substantially reduces the risk of developing diphtheria, and vaccinated persons who develop dise milder liferess. Protection lasts at least 10 years. Vaccination does not, however, eliminate carriage at *C. diphtheriae* in nx or nose or on the skin.?

IETANUS:

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

The occurrence of fetanus 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 reposited to the Centers of Disease Centrol and Prevention (CDQ during 1987 and 1988, 88% were ≥50 years of age, while only six were <20 years of age. Whe class-stately rate was 21%. In 1982, 45 cases were reported of which 82% were ≥50 years of age. When the control and Prevention (CDQ during 1987 and 1988, 68% were ≥50 years of age. When the control was prevention (CDQ during 1987 and 1988, 68% were exported of which 82% were ≥50 years of age. When the control was preventionally a prevention of the control was preventionally an exposure of the control was preventionally

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

as users, or medical combines such as a successor were rejudiced in a for facebase.

Spores of C. refair are ubiquitous. Seriologic tests indicate that naturally acquired immunity to tetanus tooin does not occur in the United States. Thus, universal primary vaccination, with subsequent maintenance of adequate antitoxin levels by means of appropriately intend boosters, is necessary to protect persons among all age-groups. Tetanus toxid is a highly effective antigen, and a completed primary series generally induces protective levels of neutralizing antitodies to tetanus toxin that persist for 210 years. 2 The potency of diphtheria and tetanus toxide was determined on the basis of immunogenicity studies with a comparison to a seriological correlate of protection (0.01 LU /mL) established by the Panel on Review of Bacterial Vaccines & Toxoids. 3

EFFICACY OF DIPHTHERIA AND TETANUS TOXOID VACCINES
Circulating protective levels of neutralizing antibodies to diphtheria and tefanus toxins can be induced by the administration of Diphtheria and Tetanus Toxoids Adsorbed USP (For Pediatric Use) (DT) or DTP.

Department and resames council of the processing of the second of the se

sproximately nation me minans and only mind or movarate reactions were overved in the remainder of the DL study group.

Another clinical study to evaluate personage and overvaer reactions of CL DT was performed in 40 children under one year of age. One group of 20 children received 0.5 mt. doses of DTP, DT, DTP at two, four and six months of age, respectively. The second group of 20 children received 0.5 mt. doses of DTP, DT, and DT, respectively, at the same ages. The immunologic protection against diphtheria and tetamus as measured by toxin neutralizing antibodies induced by DT was comparable when administered as uither a second or third dose. The receitor rates following CL whole-ceil DTP vaccination closely correlated with the rates observed with other commercially available whole-ceil DTP vaccination of adverse reactions was significantly lower following DT administration (p < 0.55). Although the number of vaccines was small, no persistent screaming episodes or severe neurological reactions such as seizures or encephalopathy were observed with either vaccine in this study.

PERTUSSIS

PERTUSSIS
Disease caused by *Bordetella pertussis* was once a major cause of infant and childhood morbidity and morbality in the Ilhilled States.
Disease caused by *Bordetella pertussis* was once a major cause of infant and childhood morbidity and morbality in the Ilhilled States.
Perfussis (whooping cough) became a nationally notifiable disease in 1922, and reports reached a peak of 255 269 cases and 7,518
deaths in 1934. The highest number of reported pertussis deaths (9,269) eccurred in 1923. The hirdouction and disease are combined with diphtheria and telanus toxidids (DTP) in the late 1940s resulted in a substantial decline in pertussis disease, a decline winch continued without interruption for hearth 3D years.

9 1 1970. The samular reported incidence of pertussis had been reduced by 99%, foring the 1970s the annual numbers of reported cases stabilized at an average of approximately 2,300 cases saich 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 1990s.²

From 1985 to 1991, 11,446 cases of perhassis 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, will the peak year being 1990.

with the peak year being 1990.⁵

During the period 1989 to 1991, of 3,900 reports of hospitalization, 1,115 had developed pneumoria, 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? Of patients 3 months through 4 years of age, where vaccination status was known, 65% of 4,471 patients had not received the receivement of any entresis containing vaccination. One older children and adults, including those previously vaccinated, 8, pertussis infection may result in symptoms of branchistic or per-respiratory-hard infection. Pertussis may not be associated with classic signs, especially the inspiratory whoop, Older preschool-children and school-sign signs are not fully vaccinated and who develop pertussis can be important sources of infection for infents of vaccinations and sources 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

EFFICACY OF PERTUSSIS VACCINE.
Although DTP lass 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 anceptable mouse profection potencies induced protective serum agglutinin antibody triers. The pertussis component of each lot of DTP is tested for potency by a mouse protection test.

In clinical trials, one does of CLI whole-cell DTP vaccine was used to reconstitute one tyophilized single dose vial of ActHBTM or OmniètBTM with no diminution in anti-PRP response or diphtheria, tofanus and pertussis responses.

en CLI DTP vaccine is used in recursion

Adverse reactions associated with the use of DTP include local redness, warmth, edema, induration with or without tendeness as unicaria and rash. Some data suggest that febrille reactions are more likely to occur in those who have experienced such reafter prior doses,⁵

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to inoderate systemic reactions (e.g., fretrutiness, violating) are significantly less frequent. If local redness 2.5 cm occurs, the likeholood of recurrence after another DTP does increase significantly.

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, hare occurred in infants following the administration of DTP. No association has been shown for hospitalizations due to infectious disease and receipt of DTP. So Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in TABLE 1.2.2

TABLE 12

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	
Vomitting	1/15 doses	
Anorexia	1/5 doses	
Persistent, inconsolable crying	11/2/4====	
(duration ≥3 hours)	1/100 deses	
Fever ≥40.5°C (≥105°F)	1/330 doses	
Nervous System	11,444,484,4	
Collapse (hypotonic-hyporesponsive		
episode)	1/1,750 doses	
Convulsions (with or withou) 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 lever, drowsiness, fretfulness, and anorexia, occur quite trequently. These reactions are significate more common following administration of DTP than following DT, are usually self-limited, and need no therapy other than symptom treatment such as acetaminophen.²

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breating, hypotension, or shock) and death have been reported after receiving preparations containing diphtheria, tetanus, and/or partussis artigens.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 sequelate?

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 to to 10 per million dossę).²

MCROUS SYSTEM
The following neurologic literases have been reported as temporally associated with vaccine containing letanus toxoid: neurological complications^{27,27} including content actions^{28,28} brachial plackus neuropathies 3^{28,28} paralysis of the radial nerve.²⁹ accommodation parasis, and EEG disturbances with encophalogistyly. The report from the IOM suggests that there is a causal relation between Guillain-Barré syndrome (GBS) and vaccines containing tetanus toxoid.²⁹ In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid should be considered as a possible etiology.^{39,29}

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

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

In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England, children 2 to 35 months of age with sections, acute neurologic disorders such as encephalopathy or complicated convolsionts), were more (Rely to have received DTH in the 7 days preceding onset than their age, sex, and relightophrouch methods 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 rologistic receipt of DTP does, compared to children on tereeiving DTP in the 7-day period before enset of their illness, was 3.3 (a < 0.001).³

receipt of DTP dose, compared to children not receiving DTP in the 7-day period petitre 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 (relative risk for illnesses requiring hospitalization attributable to pertussis vaccine are rate. 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 1710,000 doses. In contrast, final analysis of the case-control study lound that the risk of serious neurologic illness following pertussis desease was 1/11,000 pertussis cases. Repeated evaluations have shown that the benefits of vaccine outweigh the risks 4.79.

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 perhassis 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 disable?, However, details are not available to eviolute this study adequately, and the same concerns remain about DTP vaccination or pre-existing reurologic disables.

disorders.*

An IOM report by the Committee to review the adverse consequences of pertussis and rubeila vaccines concluded that evidence is consistent with a causal relation between DTP vaccine and acude encephalopathy, defined in the controlled studies reviewed as encephalopathy, encephalopaths, or encephalopaths. 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 spassms shaked that receipt of DT or DTP was not causally related to infantile spassms. The incidence of oriest of infantile spassms showed that receipt of DT or DTP was not causally related to infantile spassms. The incidence of oriest of infantile spassms showed that receipt of DT or DTP was not causally related to infantile spassms. The incidence of oriest of infantile spassms 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 spassms can be expected to be related by chance alone to event receipt of DTP. In the propriet of the propriet with infantile spassms can be expected to be related by chance alone to event receipt of DTP. It remains to be a second and through the second and through the second and through doses of DTP. It remains to be a second and through the second and through doses of DTP is a second and through the second and through doses of DTP. It remains to be a second and through the second and through the second and through the second and through doses of DTP.

A bulging fontanelle associated with increased intracranal pressure which occurred within 24 hours following DTP immunization has been reported. A causal relationship has not been established 33.33.31

CARDIOVASCULAR SYSTEM
An infant who developed myocarditis several hours after immunization has been reported. 37

RESPIRATORY SYSTEM
Respiratory difficulties, including apriesa, have been observed.

LOCAL

Rash and allergic reactions have been observed.

Sudden forant 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. 3334 to 11 should be recognized that the first three primary immunitying does of DTP are usually administered to Infants 2 to 6 months of age. That approximately 60 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 33345.

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

In general, the rates of minor systemic reactions after DTP was used to reconstitute ActHiB1^{AA} or OmniHIB1^{AA} were comparable to those usually reported after DTP vaccine alone (A.19.38)

When CLI whole-cell DTP was used to reconstitute ActHB™ or Omn#HB™ and administered to infants at Z, 4, and 6 months of age, the systemic adverse experience profile was congurable 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. (4.1) (Refer to ActHB™ 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 (OHHS) 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 toil-free number 1-900-822-7967. [4:17:18]

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.

BIT, P.O. Box 197, Swittwater, PA 18370 or call 1-900-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral drug poducts 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.

wheterest source and contents permit in states contents at 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 inframuscularly. 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 brittiday.

Inject 0.5 mL inframuscularly only. The preferred injection sites are the anteriolateral aspect of the thigh and the delition muscle of the upper sm. The vaccine should not be injected into the gluidad 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 (tractional 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

nded for children 6 weeks through 6 years (up to the seventh birthday) ideally beginning when the infant is This vaccine is recommend 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 inframescularly 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 actuoid entrance), a booster of 0.5 ml

per-respiratory-fract infection. Pertussis may not be associated *B. pertussis* infection may result in symptoms of bronchitis or children and school-age siblings who are not fully vaccinated with classic signs, especially the inspiratory whoop. Older preschool infants of year of age. Adults also play an important role in the transmission of pertussis to unreconstated or incompletely vaccinated in infants and young children.

Infants and young children.

EFFICACY OF PERTIUSSIS 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
antibody titers. The pertussis component of each lot of DTP is tested for potency by a mouse protection potencies induced protection
antibody titers. The pertussis component of each lot of DTP is tested for potency by a mouse protection test.

and the property of the prope

OmniHIEM with no diminution in anti-PRP response or diphtheria, tetanus and pertussis responses.

MICATIONS AND USAGE

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) is recommended for active immunization of the pertusses vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to administered, DT here pertusses vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to administered, DT Persons recovering from confirmed pertussis do not need additional doses of DTP but should receive additional doses of DT to complete the series?

A sailable data indicate that the appropriate age for institution of immunizations in prematurely born infants is the usual chronological gas of 2 months. Vaccine doses should not be reduced for preterm infants 29 for institution of immunizations in prematurely born infants is the usual chronological flagsace immunization is required, Tetanus immune Globulin (Human) (TIG) and/or equine Diphtheria Antitoxin are the products of en CLI DTP vaccine is used to reconstitute Actifilation of months and children 2 months through 5 years of age for the product of influenced type b. (All Refer to Actifilation of a general products of influenced type b.) (All Refer to Actifilation and products of age for the products of invasive diseases caused by diphtheria, tetanus, pertussis A Single injection containing distributions as a reduced and the said of the active immunization.)

J H influenzae type b. 10.31 (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-may be used for reconstitution of lyophilized ActHIB™ or OmniHIB™. Artibody 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.

susceptible innividuals.

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 Merieux Serums & 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 thirmerosal, a mercury derivative, is a contraindication for further use of this

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.

If is a contraindication to administer ruis vaccine in the presence or any evolving neutrogram communi.

Fineephalopathy after a previous dose is a contraindication to further use,
unitzation should be deferred during the course of an acute illness. Vaccination of infants and children with severe, febrile illness
unit generally be deferred until these persons have recovered. However, the presence of minor illnesses such as mild upper
juitatory infections with or without low-grade fever are not contraindications to further use.² ciective 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 perfussis component should be carefully considered. There may be circumstances, such as a high incidence of perfussis, when the perfussis component should be carefully considered. There may be circumstances, such as a high incidence of perfussis, when the THE FOLLOWING EVENTS WERE PREVIOUSLY CONSIDERED CONTRAINDICATIONS AND ARE NOW CONSIDERED WARNINGS.

1. Temperature of 2-40.5°C (105°F) within 48 hours not due to another identifiable cause: Such a temperature is considered a reactions are usually attributed to the perfussis component, accuration with DT should not be discontinued?

2. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours: Althours Albours and usually attributed to the perfussis component.

2. Persistent, inconsolable crying lasting 23 hours, occurring within 48 hours: Follow-up of infants who have cried inconsolable crying lasting 23 hours, occurring within 48 hours: Follow-up of infants who have cried inconsolable crying lasting 24 hours are usually attributed in the perfussion of greater significance, 2 Evidence is insufficient to indicate whether perfussive vaccine-associated with DT should be a consolable crying to requestly following DTP vaccination can be a predictor of increased file/linear-associated protracted, occurs most frequently following the first does and is less frequently reported of recurrence of persistent crying DTP-associated reactions (including high fever, seizures, and hypotonic-hyporensylve global of recurrence of persistent crying DTP-associated reactions (including high fever, seizures, and hypotonic-hyporensylve globalos), suggesting the protoninged crying to represent persistent crying bave had a higher rate of local reactions than children who had other was really a pain reaction.²

Convulsions with or without fever occurring within three days: Short-lived convulsions, with or without fev

OTP-associated reactions (including high fever, seizures, and hypotonic-hyporesponsive episodes), suggesting that prolonged crying was really a pain reaction.

Convulsions with or without fever occurring within three days: Short-lived convulsions, with or without fever, have not been shown to cause permanent soquelae. Furthermore, the occurrence of protonged febrile seizures (i.e., status epilepticus—any seizure asting >30 minutes or recurrent seizures lasting is total of 30 minutes without the child fully regaining consciouses, irrespective or afebrile seizures. The risk is significantly increased (iii) of 18) only among those children who are neurologically abnormal before contraindication to further doses, under certain crumstances subsequent doses may be indicated, particularly if the risk of pertussis until the child's neurologic status is better defined. By the end of the first year of III; the presence of an undergrade and appropriate treatment instituted. DT vaccine should not be administered before a definition and appropriate treatment instituted. The vaccine signed, if proudent also to administer actantinophera? I smyled 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 >132°F. (39 a-40°C) following a prior doses of teams under the provider of the teams of the provider and should not be given even emergency doses of 1d more frequently than every 10 years, even if they have a wound that is neither clean nor minor.

2DT should not be given to children with any coagulation disorder, including thrombocytopenia, that would contraindicate intramuscular

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

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 lamily 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.

18

"fants and children with recognized possible or potential underlying neurologic conditions seem to be at enhanced risk for the searance of manifestations of the underlying neurologic disorder within two or three days following vaccination.² Whether to insider DPI to children with proven or suspected underlying neurologic disorders must be decided on an incividual basis. Important reactions include the current local incidence of perfussis, the near absence of diphtheria in the United States and the wrisk of

Although these events were considered absolute contraindications in previous ACIP recommendations, there may be circumstances such as a high incidence of perfussis, in which the potential benefits outwelgh 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. Controversy regarding the safety of pertussis vaccine during the 1970s let to several studies of the benefits and risks of this vaccination to UTP exists, the vaccine should not be given? during the 1980s. These epidemiologic analyses clearly indicate that the benefits of pertussis vaccination outweigh any risks and have

Dealts 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 ActHB™ or OrmiHB™ 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, hypogarimaglobulinemia, or againmaglobulinemia; attered immune states or diseases such as leukemia, bythough or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolities 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 Sêrums & Vaccins S.A. ECAUTIONS

...NERAL 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

Vaccinie.

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

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

ne 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 1985. ** 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 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 should be lose listed in Their Carlon Vaccine and events should be seen to the U.S. Department of Health and Human Services. Reportable events include those listed in Their Carlon Vaccine and events should be seen to the U.S. Department of Health and Human Services. Reportable events include those listed in Their Arthropy.

DRUG INTERACTIONS

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

In DTP and the or upminera Amutoxin 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.

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. RCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

med to evaluate carcinogenicity, mutagenic potential, or impact on fertility.

PRESNANCY
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 ACHHIB™ OR

OmniHIB™ IN INFANTS BELOW THE AGE OF SIX WEEKS HAVE NOT BEEN ESTABLISHED. (See DOSAGE AND ADMINISTRATION

secuon.)
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 perfussis vaccination exists, or where in the opinion of the physician the perfussis vaccine should not be administered. DT is the appropriate alternative.

If the opinion of the physician he perhassis vaccine should not be administrated, or 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).

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 severith brithday.

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 glutted 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 iffractional dissest is not recommended. The effect of such practices on the frequency of serious adverse

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.

a ended for children 6 weeks through 6 years (up to the seventh birthday) ideally beginning when the infant is

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.

intranuscularly at least 4 to 8 weeks apart. The routin dose is definitionable to be 12 interest and the sum of the 12 interest and 14 to 8 weeks apart. The routin dose is definitionable to 12 interest and 14 to 8 weeks apart. These who receive all four primary immunizing doses before their fourth birthday should be administered intranuscularly. Those who receive all four primary immunizing doses before their fourth birthday should dose in the primary series was administered after the fourth birthday. Thereafter, routine booster immunizations should be with 6, at all the primary series was administered after the fourth birthday. Thereafter, routine booster immunizations should be with 6, at AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE) (0TP).

ROUTINE DIPHTHERIA AND TETANUS. AND PERTUSSIS VACCINES STAND INTERESTITUTE AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE) (0TP).

Dose	Customary Age	TANUS, AND PERTUSSIS VACCINATION SC hildren <7 Years Old - United States, 199 Age/Interval†	
Primary 1	0.11		Product
Primary 2 Primary 3 Primary 4	2 Months 4 Months 6 Months 15 Months	6 weeks old or older 4-8 weeks after first dose* 4-8 weeks after second dose* 6-12 months after third dose*	DTP† DTP† DTP†
Booster	4-6 years old before	entering kindergarten or elementary	DTP†
Autor va	school (not necessary administered after for		DTP†

Every 10 years after last dose 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 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.

There is no need to start the series over again, regardless of the time elapsed between doses.
Diphtheria and Teanus Toxoids and Acellular Portussis Vaccine Adsorbed (DTaP) can be interchangeably used with DTP for the fourth and fifth doses. However Acthird™ cannot be reconstituted with DTaP.

The simultaneous administration of DTP, oral polio virus vaccine (DPV), and measles-mumps-rubella vaccine (MMR) has resulted in sercorouversion rates and rates of side effects similar to those observed when the vaccines are administrated separately. Simultaneous vaccination (at separate sites with separate syringes with DTP, MMR, DPV, or inactivated poliorius vaccine (MCM) altemophius to conjugate vaccine (HbCV) is also acceptable. *The ACIP recommends the simultaneous administration, at separate sites with separate simultaneous administration of 17P, DPV, HbCV, and MMR at ≥15 months of ege.*

If nassive immunization is needed for tetanus. TG is the product of choice. If throughes longer protection than entitivity of scient administration of accident of the product of choice.

If passive immunization is needed for fetanus, 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 The ACIP recommends the use of only adsorbed toxold in this situation.²

The ACIP recommends the use of only adsorbed toxoid in this situation.²

WHEN RECONSTITUTING HAEMOPHILUS & CONJUGATE VACCINE (TETANUS TOXOID CONJUGATE), AcHIB™ or OmniHIB™

NOTE: Haemophilus & Conjugate) — Consilha™ (ifetanus Toxoid Conjugate) — AcHIB™ is identical to Haemophilus & 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 m. dose and inject into the vial of tyophilized 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 toxiol, 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 6.5% of sucrose. (**Meter to Activities**) package insect.)

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.

aspirate to ensure that the needle has not entered a blood vessel.

Each dose of DTP/ActHB™ or OmniHIB™ accines is administered intramuscularly in the outer aspect of the vastus lateralis (midthigh) or defloid. The vaccine should not be injected into the gluteal area or areas where there may be a nerve trunk. During the

When CLI DTP vaccine is used to reconstitute ActHB™ 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 310 RECOMMENDED IMMUNIZATION SCHEDULE

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 be used to reconstitute ActHIRTM/Omeil.	DTP or Applicies Post of the Principle

Acellular Pertussis (DTaP) should NOT be used to reconstitute ActHIB™/DmniHB™. 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.

neuroporus influenzae type b vaccine also should be administered at this time in a separate syninge 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 doeses of a product containing DTP, of the analysis of a product containing DTP or DTP and to the provious the provious terms of the provious

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 of age should receive 1 dose of a product containing *H* influenzae type b conjugate vaccine. A child 15 to 59 months Preterm infants should be vaccinated according to their chronological age from birth.

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 ActhilBTM or OmniHIBTM. There is no need to start the series over again, regardless of the time

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 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
DTP Vial, 7.5 mL – Product No. 49281-280-84

One 7.5 mt. 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 $2^{\circ} - 8^{\circ}$ C ($35^{\circ} - 46^{\circ}$ F). D0 NOT FREEZE.

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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 (Fetanus Toxoid Conjugate), ActiliB™ of monitaliB™, the combined vaccines appear whitish in color and perturbance and the perturbance of the per

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 toxicids are adsorbed to aluminum potassium sulfate (alum). The adsorbed diphtheria and tetanus toxicids are combined with pertussis vaccine concentrate, and diluted to a final volume using sterile phosphate-buffered physiological saline. Each 0.5 m.l. dose contains, by assay, not more than 0.17 m.g of aluminum and not more than 100 µg (0.02%) of residual formative). Thieresaid (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 antitioxin per mL in the guinea plg potency test).

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). 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 AcHIB™ or OmniHBT™, each single dose of the 0.5 ml. mixture is formulated to contain 6.7 Lf of diphtheria toxid, 5. Lf of testaus toxid, an estimate of protective units of pertussis vaccine, 10 μg of purified capsular polysacchanide conjugated to 24 μg of inactivated tetanus toxid, and 8.5% of sucrose.

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxid Conjugate) — AcHIB™ (sistiluted by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccine S.A.

DIPHTHERIA. Corynebacterium diphtheriae may cause both localized and generalized disease. Systemic intoxication is caused by diphtheriae 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 1975, most were cutaneous diphtheriae 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 obses of diphtheria and tetanus toxoids and perfussis vaccina adsorbed [1079] and because of an apparent reduction in the prevalence of toxigenic strains of *C. diphtheriae*. Not cases occur among perfusion is caused to inadequately immunicated persons. 2

inadequately immunized persons.

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.

telani. 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 540 period to the Centers for Disease Control and Prevention (CDC) during 1987 and 1988, 68% were servas of age, while only six were <20 years of age. 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

as users, or instruct ununurums such as auscesses were reported in 14% of cases,.

Spress of C. tetaria rae ubiquitus. Serologic tests indicate that naturally acquired immunity to tetarus toxin does not occur in the United States.

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. Tetarus toxodi is a highly effective antique, and a completed primary series generally induces protective levels of neutralizing antibodies to tetarus toxin that persist for ≥10 years.

2

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

Serological correlate of protection (0.01 tul./ml.) established by the Panel on Review of Bacterial Vaccines & Toxolds.4

EFFICACY OF DIPHTHERIA AND TETANUS TOXOID VACCINES

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 antitions that were equal to or greater than 0.01 tul./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 inflants. Protective levels of antitoxin were observed in 100% of these inflants following three doses of DT. No local or systemic reactions were observed in approximately half of the inflants 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 reactived 0.5 ml. doses of DTP, DTP at two, four and six months of age, responsively. The second group of 20 children reactived 0.5 ml. doses of DTP, DTP at two, four and six months of age, responsively. The second group of 20 children reactived 0.5 ml. doses of DTP, DTP at two, four and six months of age, responsively. The second group of 20 children secured to the 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 was small, no persi

PERTUSSIS
Disease caused by Bordetella pertussis was once a major cause of infant and childhoot morbidity and mortality in the united or 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 toxolas (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

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 1999, 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 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. Tendes of the past years suggest an increases in reported pertussis since 1976, with the peak year being 1990.⁵
During the period 1980 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 perfussis containing vaccine.³
Among older children and adults, including those previously vaccinated, *B. pertussis* infection may result in symptoms of bronchills or upper-respiratory-tract infection. Perfussis may not be associated with classic signs, especially the inspiratory whoop. Older preschool-dider and acknool-age sibilings who are not fully vaccinated and who develop perfussis to unvaccinated or incompletely vaccinated intentals and young children.²
EFFLACY OF PERTUSSIS VACCINE.

infants and young children.²

EFFLCXC OF PERTIJSSIS 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 liters.* 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

or ore is rested for potency by a mouse protection test. In clinical trials, one dose of CLI whole-cell DTP vaccine was used to reconstitute one hyphilized single dose vial of ActHIB™ or OrmaliB™ with no diminution in anti-PRP response or diphtheria, tetanus and pertussis responses.

Ommittee ** with no diminution in anti-their response or diprimental, tetratius and pertussis resputises.

MIDICATIONS AND USAGE

Dipthteria and Tetratus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) is recommended for active immunization of children up to age 7 years against dipthteria, tetratus, 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

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 perfussis do not need additional doses of DTP but should receive additional doses of DT to complete the series.²

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 Actility or promise the combined vaccines are indicated for the active immunization of infants and children? months through 5 years of age for the prevention of invasive diseases caused by diphtheria, tetanus, perfussis and H influence type b.10.11 (Refer to Actility Propackage insert.)

A single injection containing diphtheria, tetanus, perfussis and Hapmonbility is continuate antiques may be made acceptable to parable.

and Hintluenzae type by 10.31 (Refer to ACHIBI** package insert.)

A single injection containing diohtheria, tetanus, pertussis and Haemophilus b conjugate antiqens may be more acceptable to parents and may increase compiliance 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 concentiantly, only CLI whole-cell DTP vaccine may be used for reconstitution of typophilized AcHIBI** on TominiHiBI**. Altibody levels associated with profection 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 menufactured by Pasteur Merieux Serima & Vaccins SA.

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

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

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

WARNINGS

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?

1. Temporature of 240.5°C (10.5°F) within 48 hours not due to another identifiable causes: 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 is should not be discontinued to the pertussis component.

2. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours. Athough these uncommon events have not been recognized to cause death nor to induce permanent neurological sequetae, it is prudent to continue vaccination with DT, omitting the pertussis component.

3. Persistent, inconsolable crying lasting 23 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-priched crying or screaming does, or does not, lead to chronic neurologic damage 3 monosolable crying for>30 minutes following DTP vaccination can be a predictor of increased likelihood of recurrence of persistent crying DTP-associated reactions fincluding high fever, selzures, and hypotonic-hyporeponsive episodes, suggesting the ord persistent crying DTP-associated reactions fincluding high fever, selzures, and hypotonic-hypocoproposive episodes, suggesting the rolloped crying DTP-associated reactions fincluding high fever, selzures, and hypotonic-h

following subsequent doses. Children with persistent crying have had a righter had been been been been checked by the property of the property

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 perfussis 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, 18

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 succination. 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 perfussis, the near absence of diphtheria in the United States and the low risk of

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 the vaccine is 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. ³0 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 AcHIBT™ or OnniHIBTM and administrated to immunosuppressive therapy, the expected artibody responses may not be obtained. This includes patients with severe combined immunodeticnery, hypogammaglobulinemia, or agammaglobulinemia, aftered immunosuppressive the accordance of the accor

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

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 Méneux 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

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.

concerning me use or me 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

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 PARIENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER THE PREVIOUS DOSE (SEE CONTRAINDICATIONS, ADVERSE REACTIONS).

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. The toll-fire 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. 17,16

NUML MITTERACTIONS

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.

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 perfusic vaccine are available, if immunosuppressive therapy will be discontinued shortly, it is reasonable to deler vaccination until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.

for the last period administered to persons receiving immunosuppressive therapy, a recent injection of immunoglobulin or having an immunodeficiency disorder, an adequate immunologic response may not be obtained.

CARCINICENSIS, MUTACRISSIS, 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 ACIHIBTM OR ORMIHIBTM IN INFANTS BELOW THE AGE OF SIX WEEKS HAVE NOT BEEN ESTABLISHED. (See DOSAGE AND ADMINISTRATION

secuon.)
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.

The department can propose a repertussive vaccine strough not be administred, by a some appropriate atternative.

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 aceilular DTP. A fifth dose of DTP or an approved aceilular DTP is required.

todes to an approved actinual DIF. A mini dose or DIF or all approved actinual DIF is required.

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

ADVERSE REACTIONS

Adversa-reactions associated with the use of DTP include local redness, warmth, edema, induration with or without tender less, as well as utilicaria 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., fretfuiness, vomiting) are significantly less frequent.

If local redness 2.5 cm occurs, the likelihood of recurrence after another DTP dose increases significantly.

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, 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

ADVERSE EVENTS OCCURRING WITHIN 48 HOUR	Frequency*	
Event		
Local	1/3 doses	
Redness	2/5 doses	
Swelling	1/2 doses	
Pain	We detail	
Systemic	1/2 doses	
Fever ≥38°C (100.4°F)	1/3 doses	
Drowsiness	1/2 doses	
Fretfulness	1/15 doses	
Vomiting	1/5 doses	
Anorexia	W. = 70000	
Persistent, inconsolable crying	1/100 doses	
(duration ≥3 hours)	1/330 doses	
Fever ≥40.5°C (≥105°F)	WARE COLUM	
Nervous System		
Collapse (hypotonic-hyporesponsive	1/1.750 doses	
episode)	1/1,750 doses	
Convulsions (with or without fever)	11 11/100 00000	

*Rate per total nu

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
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

treatment such as acetamnopnen.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
reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.²
reported after receiving preparations, characterized by severe local reactions (generally starting 2 to 8 hours after an injection), may follow receipt of tetanus toxoid.²

Notion receipt or retainus toxolo.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 appliable 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

Injection have been reported (6 to 10 per million doses).²

NERVOUS SYSTEM

NERVOUS SYSTEM

The following neurologic illnesses have been reported as temporally associated with vaccine containing tetanus toxoid: neurologic complications^{21,22} including cochiear lesion ²² brachial plexus neuropathies.^{22,24} paralysis of the radial nerve.²² paralysis of the complications^{21,22} including cochiear lesion ²³ brachial plexus neuropathies.^{22,24} paralysis of the radial nerve.²² paralysis of the country of the report from the IOM suggests that the recurrent nerve.²² accommodation paresis, and EEG disturbances with encephalopathy.¹⁹ The report from the IOM suggests that there recurrent nerve.²³ accommodation paresis, and EEG disturbances with encephalopathy.¹⁹ The report from the IOM suggests that there recurrent nerve.²³ accommodation paresis and ac

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

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 in the National Childhood Encephalopathy or complicated convolusions), were more likely to have received DTP in the serious, acute neurologic disorders such as encephalopathy or complicated convolusions), were more likely to have received DTP in the serious, acute neurologic disorders such as encephalopathy or complicated convolusions), were more likely to have received DTP in the role of the receiver of the relative risk (estimated by odds ratio) of a neurologic illness security within the role of the receiver of the receive

An IOM report by the Committee to review the adverse consequences of perfussis 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, encephalopathils, or encephalomyelits. 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 soasms has occurred in infants who have recently received DTP or DT. As a total of the property of

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. 38 The incidence of onset of with infantile spasms increases at 3 to 9 months of age, the time period in which the second and third doess 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. A bulging fortnenelle associated with increased intracranial pressure which occurred within 24 hours following DTP immunization has been reported. A causal relationship has not been established. 93,931

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.

hash 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, 33-34-51 it should be recognized that the first three SIDS in the United States showed that receipt of DTP was not causally related to SIDS, 33-34-51 it should be recognized that the first three SIDS in the United States showed that receipt and the state of the SIDS and the SIDS and the state of SIDS and the SIDS 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, 33,34,55.

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. (0.11) (Refer to ActHIB™ package insert.)

In general, the rates of minor systemic reactions after DTP was used to reconstitute ActHIBTM or OmniHIBTM were comparable to those usually reported after DTP vaccine atone. At 12.5 minor of the property of 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. (Refer to ActHiBTM package insert.)

Reporting of Adverse Events
Reporting by parents or guardians of all adverse events occurring after vaccine administration should be encouraged. Adverse events
Reporting by parents or guardians of all adverse events occurring after vaccine administration with vaccine should be reported by health-care providers to the U.S. Department of Health and Human Services
following immunication with vaccine should be reported by health-care providers to the U.S. Department of Health and Human Services
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Health-care providers also should report these events to the Director of Medical Affairs, Connaught Laboratories, Inc., Route 611, P.D. 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 VAL 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.

the contents of the vial. Discard i vaccine dannot 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 tripian 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.

Specials are around on the control of the property of the seventh birthday) ideally beginning when the infant is FINIMARY MINUNIZATION 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.

to weerks to 4 timenus or ages.

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.

Intramuscularly at least 4 to weeks apair. The load most account of the BOOSTERI MININIZATION

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

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

BOOSTER IMMUNICATION
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 or birthday, Thereafter, routine booster munications should be with fig. at intervals of 10 years. PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DIPHTHERIA AND TETANUS TOXOIDS AND PERTURSIS AUCCINE ADSORDED USP (FOR PEDIATRIO USE) (DTP).

Dose	Customary Age	Age/Interval†	Product
Primary 1 Primary 2 Primary 3 Primary 4	2 Months 4 Months 6 Months 15 Months	6 weeks old or older 4-8 weeks after first dose* 4-8 weeks after second dose* 6-12 months after third dose*	DTP† DTP† DTP† DTP†
Booster		entering kindergarten or elementary y if fourth primary vaccinating dose urth birthday)	DTP†
Additional Boosters		Every 10 years after last dose	Td

Additional Boosters

* 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

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 (ØPV), and measles-mumps-rubella vaccine (MMR) has resulted in serconversion rates and rates of side effects similar to those observed when the vaccines are administred separately. Simultaneous vaccination (at separate sites with separate syringes) with DTP, MMR, DPV, or inactivated poliovirus vaccine (IPV), and Haemophilus b conjugate vaccine HibVO) is also acceptable.² The ACIP recommends the simultaneous administration, at separates 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, DPV, HbCV, and MMR at ≥15 months of age.²

If ossisvie immunization is needed for tetanus. Ti6 is the product of choice, it provides longer protection than antitoxin of animal origin

simultaneous administration of DTP, DVP, HbCV, and MMR at 21 smorths of age.
If passive immunization is needed for letanus, 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 HAEMOPHILLIS & CONJUGATE VACCINE (TETANUS TOXOID CONJUGATE), ActHIB™ or OmniHIB™ NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate). — ActHIB™ of actHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate). — OmniHIB™ (distributed by SmithNiline Beecham Pharmaceuticals), both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

CI. Jubblescell DTP vaccine size on an bused for expenditivition of ActHIB™ or Conpilition. Cleanes both the DTC and ActHIB™ or

CLI whole-cell DTP vaccine also can be used for reconstitution of AcIHIB™ or OmniHIB™. Cleanse both the DTP and AcIHIB™ or OmniHIB™ vaccine val rubber barries 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 Nyophilized AcIHIB™ or OmniHIB™. After reconstitution and thorough agitation, AcIHIB™ or OmniHIB™ will appear whitish in color. Using a new syringe, administer 0.5 mL dose of DTP/AcIHIB™ or OmniHIB™ waccines.

When CLI whole-cell DTP vaccine is used to reconstitute ActHIBTM or OmniHIBTM, 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 success. *Reflect to Actificial Reflect* (actification for the contained of the conta

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.

aspirate to ensure that the needed has not entered a blood vessel. Each dose of DPFAcHIB™ on OmniHIB™ vaccines is administered intramuscularly in the outer aspect of the vastus lateralis (mid-thigh) or detoid. 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 AcHIB™ or OrmHIB™, 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

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 by the Vaccine assistance as administrative to this time in a separate syringe at a uniterial 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 prefussis-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 AcHIB™ or OmniHB™. 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 Haemophilius b Conjugate Vaccine (Tetanus Toxoid Conjugate) (10 x 1 Dose vials per package) — Product No. 4228-1549-10

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

e 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 Toxolds and Pertussis vaccine between 2° - 8°C (35° - 46°F). DO NOT PREEZE.

Store between 2" – 8"C (35" – 46"F). DO NOT FREEZE. Temperature extremes may adversely affect resuspendability of this vecicine. Store lyophility de 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 as of November 1993

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

Printed in U.S.A. 2512



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 Perfussis Vaccine Adsorbed USP (For Pediatric Use) combines diphtheria and tetanus toxoids adsorbed with perfussis vaccine, for intramuscular use, in a sterile isotonic sodium chloride solution containing sodium phosphate buffer to control pH. The vaccine, after shaking, is a turiful 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 Conjudate Vaccine appear whitish in color confidence of the perfusion of the perfusi

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 thinnerosal and resuspended in physiological saline and thinnerosal. The toxolds are adsorbed to aluminum potassium sulfate (alum). The adsorbed diphtheria and tetanus toxolds are combined with pertussis vaccine concentrate, and diluted to a final volume using sterile phosphate-buffered physiological saline. Each 0.5 mL dose (onecruy derivative):110,000 is added as a preservative.

Each 0.5 mL dose is formulated to contain 6.7 tL of diphtheria toxold and 5 tL of tetanus toxold (both toxolds induce at least 2 units of antitioxin per mL in the guinea pig potency test).

antition per intension goines and powers y usay.

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.

(4 protective units per single cose).² The potency or me pertussis component of each for of DTP is tested in a mouse protection test. At the time when Connaught Laboratories, Inc. (CLI) DTP vaccine is uses for perconstitute ActHiB™ or OmniHB™, each single dose of the 0.5 mL mixture is formulated to contain 6.7 Li of diphtheria toxoid, 5 Li of tof testuaus toxoid, an estimate of 4 protective units of pertussis vaccine, 10 μg of purified capsular polysacchanide conjugated to 24 μg of inactivated tetanus toxoid, and 8.5% of sucrose.

NOTE: Haemophilus b Conjugate) — OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccine SA.

CLINICAL PHARMACOLOGY

DPHTHERIA

Comprehenciarium 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 At one time, diphtheria was rommon 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 diphtheriar propried from a diphtheria was no longer a notifiable disease. From 1990 to 1989, only 24 cases of respiratory diphtheria report dip two cases were fatal, and 18 (75%) occurred among persons 20 years of age or older?

Diohtheria is currently a rare disease in the United States originarily because of the high level of accomplisher among children.

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

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

tetam.

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 ≥50 years of age, while cases 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

Snores of C. Intani are uniquitious. Seriolonic tests indicate that naturally accounted immunity to tetanus twin does not consult to the property of the pro

as ucers, or medical conditions such as abscesses were reported in 14% of cases.²
Spores of C. tatani 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 toxiod is a highly effective antigen, and a completed primary series generally induces protective levels of neutralizing antibodies to tetanus toxin that persist for 210 years.²
The potency of diphtheria and tetanus toxiods was determined on the basis of immunogenicity studies with a comparison to a serological correlate of protection (0.01 1.0/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 antitioxins that were equal to or greater than 0.01 t.U./mt. were detected in 100% of the children following two doses of the vaccine. However, maternal artibody 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 conserved in approximately half of the infants and only mild or moderate reactions were observed in the remainder of the DT study group.⁵

approximately half of the infants and only mild or moderate reactions were observed in the remainder of the DT study group.§
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 mt. doses of DTP, DTP at two, four and six months of age, respectively. The second group of 20 children received 0.5 mt. doses of DTP, DTP, and DT, respectively, at the same ages. The immunologic protection against diphtheria and tetanus as measured by toxin neutralizing antibindes induced by DT was comparable when administered as either a second or third dose.§ The reaction rates following CLI whole-cell DTP vaccination closely correlated with the rates observed with other commercially available whole-cell DTP vaccine 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 setzures or encephalopathy were observed with either vaccine in this study.§

PERTUSSIS
Disease caused by Bordetelfa 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 oblightheria and tetanus toxolis (DTP) in the late 1940s resulted in a
substantial decline in pertussis disease, a decline which continued without interruption for nearly 30 years.

9 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 and 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

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 with the peak year being 1990.

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? Of patients 3 months through 4 years of age, where vacchation status was known, 65% of 4,471 petients had not received the recommended schedule of immunization and 39% had not received any pertussis containing vaccine.

Among older children and adults, including those previously vaccinated, *B. pertussis* infection may result in symptoms of bronchills or upper-respiratory-tract infection. Pertussis may not be associated with classic signs, especially the inspiratory whoop. Older preschool children and school-age sbillings who are not fully vaccinated and who develop pertussis can be important sources of infection for infants -d 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 In clinical trials, and the protection protection test.

In pertussis component of each tot of DTP is tested for potency by a mouse protection test. antitiony treas. The pertussis component of both is reacted for potenty by a mode procedure tool.

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.

OmniHIB™ with no diminution in anti-PHP response or ulprimetric, letterus and personals responses.

NotaTion And DisAGE

Diphtheria and Tetarus Toxidis and Perfussis Vaccine Adsorbed USP (For Pediatric Use) is recommended for active immunization of children up to age 7 years against diphtheria, tetarus, and perfussis (whooping cough) simultaneously. However, in instances where the perfussis vaccine component is contraindicated, or where the physician decides that perfussis 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 severath birthday.43

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 himtenzae type 1.00. Hefer to ActHIR™ mackage inject.

Adverse reactions associated with the use of DTP include local redness, warmth, edema, induration with or without tenderness, as well as utricaria 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., freffulness, vomiting) are significantly less frequent. In If local redness 2.5 cm occurs, the ilkelihood of recurrence after another DTP does increases significantly.

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in

Event	Frequency*		
Local			_
Redness		1/3 doses	
Swelling			
Pain		2/5 doses	
Systemic		1/2 doses	
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		1/5 doses	
(duration ≥3 hours)		2000	
Fever ≥40.5°C (≥105°F)		1/100 doses	
Vervous System		1/330 doses	
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 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.^{21,24} paralysis of the radial nerve.²⁵ paralysis of the recurrent nerve.²⁵ 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 difficial diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid should be considered as a possible

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

Short-lived convuisions (usually recrule), 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 senous, acute neurologic disorders such as encephalopathy or complicated convulsion(s), were more likely to have received DTP in the 7 days periodig onset than their age, sex., and neighbornood 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 tollowing receipt of DTP does, compared to children on treceiving DTP in the 7-day period before onset of their illness, was 3.0 p<0.001). Which this 7-day period, the risk was significantly increased for immunized children only within 3 days of vaccination (relative risk 4.2, hospitalization attributable risk of such linesses occurring 4 to 7 days after vaccination was 2.1 (p<0.01). Serious neurologic illnesses requiring attributable risk of such linesses is accine are rare. Final analysis of a comprehensive case-control study has certified that the interest of the case-control study loss and the risk of such liness following pertussis disease was 1/11,000 doess. In contrast, final analysis of the case-control study loss of the case-control study loss neurologic illness following pertussis disease was 1/11,000 of the case-control study loss of the risk of serious neurologic illness following pertussis disease was 1/11,000 of the case-control study loss of the risk of serious neurologic illness following permanent neurologic damage. Preliminary data from a 10-year follow-up study of some of the children studied in th

disorders.e.

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 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 does 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.²⁸

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

n infant who developed myocarditis several hours after immunization has been RESPIRATORY SYSTEM Respiratory difficulties, including apnea, have been observed.

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 18-48-81 is should be receipt of DTP was not causally related to SIDs 38-34-38 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 60 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 33-33-35.

When CLI whole-cell DTP was administered concomitantly (at separate sites with separate syringes) with AcHIB™ or OmniHiB™, the systemic adverse experience profile was not different from that seen when CLI whole-cell DTP vaccine was administered alone.

"Bit (Refer to AcHIB™ plackage insert.)

In general, the rates of minor systemic reactions after DTP was used to reconstitute ActHIB™ or OmniHIB™ were comparable to those

When CLI whole-cell DTP was used to reconstitute AcHIBTM or OmniHIBTM 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. **Increase** **Inc

Reporting of Adverse Events
Reporting by parents or guardians of all adverse events occurring after vaccine administration should be encouraged. Adverse events
following immunication with vaccine should be reported by health-care providers to the U.S. Department of Health and Human Services
(DHKS) 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 VAL 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 brithday.

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 insurant immunication.

This vaccine is recommended for children 6 weeks through 6 years (up to the seventh birthday) ideally beginning when the infant is 3 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. Inframuscuarry at least 4 to weeks apair. The found lose is dominated and in the Month of the Mo

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

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 0.1 LI./mt. were detected in 100% of the children following two doses of the contributions that were equal to or greater than 0.1 LI./mt. were detected in 100% of the children following two doses of the of antitoxin were observed in 100% of these infants tollowing three doses of 10. No local or systemic reactions were observed in sproximately half of the infants and only mild or moderate reactions were observed in the remainder of the DT study group.§ age. One group of 20 children ecological responses and adverse reactions of CLI DT was performed in 40 children group of 20 children received 0.5 mt. doses of DTP, DTP, and DT, respectively, at the same ages. The immunologic protection adjainst second or third dose.§ The reaction risk of the converse of the commerciality available whole-cell DTP vaccination closely correlated with the rates observed with other administration (p. <0.05). Although the number of vaccinese was small, no persistent seconds or severe neurological PERISSISS.

PERTUSSIS
Disease caused by *Bordetella pertussis* was once a major cause of infant and childhood morbidity and mortality in the United States. Pertussis (whopping cough) became a nationally notifiable disease in 1922, and reports reached a peak of 265,269 cases and 7,518 ceaths in 1934. The highest number of reported pertussis deaths (9,289) occurred in 1923. The introduction and widespread use of standardized whole-cell pertussis vaccines combined with diphtheria and telamus toxolis (DTP) in the late 1940's resulted in a substantial decline in pertussis disease, a decline which continued without interruption for nearly 30 years.

By 1970, the annual reported incidence of pertussis had been reduced by 99%. During the 1970s the annual numbers of reported cases a 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-nociated 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 with the peak year being 1990. But the per 100,000 reports of the per 100,000 and population of 1.7 in 1989,1.8 in with the peak year being 1990. But 1991, or 1,500 reports of the peat years suggest an increase in reported pertussis since 1976, burring the period 1989 to 1991, of 3,900 reports of hospitalization, 1,115 had developed pneumonia, seizures occurred in 157 cases, children less than 6 months of age and were generally less frequent with increasing age. 70 patients 3 months through 4 years of age, 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 o upper-respiratory-tract infection. Pertussis may not be associated with classic signs, especially the inspiratory whoop. Older preschoc infants < | year of age. Adults also play an important role in the transmission of pertussis can be important socies of infection for infants and young children.² EFFICACY OF PERTUSSIS VACCINE
Although DTP has been evaluated as a control vaccine in a number of clinical trails of "assillation".

EFFICACY OF PERTUSSIS VACCINE
Although OTP has been evaluated as a control vaccine in a number of clinical trials of "acellular pertussis vaccines," no formal efficacy
population at risk. It was also shown that vaccines with acceptable mouse protection potencies induced protective serum agglutinin
antibody titres. The pertussis component of each lot of DTP is tested for potency by a mouse protection test.

animony wers. The perfussis component of each for or DTF is asset to perfusely by a modes profession for the following 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 perfussis responses.

MINIORATIONS AND USAGE

Inhibitaria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) is recommended for active immunization of children of the 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 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

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}

age 07.2 months. Vaccine goes should not be reduced for preterm infants.2.8

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, perfussis and H influenzae type b.10.11 (Refer to ActHIB™ package Insert.)

A single injection containing diphtheria, tetause, 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 cell DTP vaccine and programs and Haemophilus b conjugate vaccine concomitantly, only CLI whole-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 Actitle™ or OmniHill®™ Almay 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

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

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 liness. 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 tow-grade fever are not contraindications to further use.²

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

Should generatly be deserted with mose procession are excellented to the second generatly be deserted with the second generative to without low-grade fever are not contraindications to further use.² Elective immunization procedures should be deterred during an outbreak of poliomyelitis.¹²

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

THE FOLLOWING EVENTS WERE PREVIOUSLY CONSIDERED CONTRANDICATIONS AND ARE NOW CONSIDERED WARNINGS.²

1. Temperature of >40.5°C (105°P) within 48 hours and due to another identifiable causer. Such a temperature is considered a warning because of the likelihood that fever following a subsequent dose of DTP vaccine also will be high exactions are usually attributed to the perturbs component, according to the discontinued.²

2. Collapse or shock-like state (hypotonic-hyporesponsive epicando) within 48 hours. Although these uncommon events have not been recognized to cause death not or induce permanent neurological sequelae. It is prodent to continue vaccination with DT, omitting the perturbsis component.²

2. Persistent, inconsolable crying lasting >3 hours, occurring within 48 hours. Follow-up of Infants who have credit 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 perturbsis vaccines associated protracted, inconsolable, or high-pitched crying or screaming does, or does not, lead to chronic neurologic damage. ³ Inconsolable crying occurs most frequently following the first does and is less requently reported following subsequent doses of

Persons who experienced Arthus-type hypersositivity reactions or a temperature of 1736° (39.4°C) following a prior dose of tetanus toxold usually have high serum tetanus antitoxin levels and should not be given even emergency doses of Td more frequently than every DIP should not be given even emergency doses of Td more frequently than every DIP should not be given be children with any coagulation disorder, including thrombocytopenia, that would contraindicate inframuscular 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 perfussis vaccination and that children with such family histories should receive perfussis vaccine according to the recommended schedule.

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

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 perfussis, the near absence of diphtheria in the United States and the low risk of infection with C. Identil.² Although these events were considered absolute contraindications in previous ACIP recommendations, there may be circumstances, such as a high incidence of perfussis, 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.

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.²⁸ 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 ActHBTM or OmniHBTM and administered to immunosystems before persons receiving immunosuppressive therapy, the expected antibody responses may not be obtained. This includes patients with severe combined immunodicinency, phyogramingolbulinemia, or agammaglobulinemia; aftered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolities or radiation. ¹⁵

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

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 Pastern Menerus Sérumas & Vaccins Sx.

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.

vactorie.

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 gua 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. NOTES intercools agents from person, or person, receives shown 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

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 AFIER 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

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 1986.18 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 Accine Injury Compensation Program, established by the National Childhood Vaccine Injury Accine Injury Accine Injury Accine Injury Compensation Program, established by the National Childhood Vaccine Injury Accine Injury Compensation Program, established by the National Childhood Vaccine Injury Accine Injury Compensation Program, established by the National Childhood Vaccine Injury Compensation Program, established by the National Childhood Childhood

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, cytoxic drugs, and corticosteroids (used in great 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.

CARCINGOERISS, MUTAGERSISS, IMPARAEMT 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.

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

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 perfussis vaccination exists, or where in the opinion of the physician the perfussis 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).

CANDULVASCULAR 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-334-368 it should be recognized that the first three organized manufactured to the state of the s 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, 16.11 (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 5.19,36

When CLI whole-cell DTP was used to reconstitute ActHB™ or OmniHiB™ and administered to infants at 2, 4, and 6 months of age, in the systemic adverse experience profile was comparable to that observed when the two vaccines were given separately. An increase nackage insert.)

Refer to ActHB™

**Ref

package insert.)

Reporting of Adverse Events

Reporting of 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 (OHHS) 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 toil-free number 1-800-822-7967. [617:18]

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 conteints of the vial. Discard if vaccine cannot be resuspended.

The vaccine should not be injected into the justage are the anticological and the delibid 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.

Course of primary minimizations, 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.

of 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.

Intramiscularly at least 4 to 8 weeks apart. The louril loose is adminiscretion of the finding and the substance of the subst

ROUTINE DIPHTHERIA, TETANUS, AND PERTUSSIS VACCINATION SCHEDULE

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

Use DT if perfussis vaccine is contraindicated. If the child is ≥1 year of age at the time that primary dose three is due, a third dose for 12 months after the second dose completes primary vaccination with DT.
 Prolonging the interval dose not require restarting series.

Preterm infants should be vaccinated according to their chronological age from birth. 2.9

Preterm infants should be vaccinated according to their chronological age from birth z.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 clapsed 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 AcHIB™ cannot be reconstituted with DTaP.

The simultaneous administration of DTP, orapio low inus vaccine (PPN), and measles-mumps-rubella vaccine (MMR) has resulted in serconversion rates and rates of side effects similar to those observed when the vaccines are administered separate lists with separate syrings, and in the separate sizes with separate cyrings with separate syrings, and vaccines are administration, at separate sizes with separate syrings, of all vaccines appropriate to the age and previous vaccination status of the recipients including the special circumstance of simultaneous administration, at separate sizes with separate of the product of the product of choice. It provides longer protection than antitiox of a comparate of the service of the product of choice. It provides longer protection than antitiox of a contract of the product of choice. It provides longer protection than antitiox of a contract of the product of choice. It provides longer protection than antitiox of a contract of the product of choice. It provides longer protection than antitiox of a contract of the product of the provides longer protection than antitiox of a contract of the product of the provides longer protection than antitiox of a contract of the provides longer protection than antitiox of a contract of the provides longer protection than antitiox of a contract of the provides longer protection than antitiox of a contract of the provides and the provides and the provides longer protection than antitiox of a contract of the provides longer protection than

CLI whole-cell DTV vaccine also can be used for reconstitution of ActHB™ or DmiHBI™. Cleanse both the DTP and ActHBI™ or DmiHBI™ accine vial rubber barriers with a suitable germicide prior to reconstitution. Thoroughly agitate the vial of CLI whole-cell DTV vaccine, then withdraw a O.6 mt. does and niject into the vial of lyophitized ActHBI™ or OmniHBI™. After reconstitution and thorough agitation, AcHBIR™ or OmniHBI™ will appear whitish in color. Using a new syringe, administer 0.6 mt. does of DTPActHBI™ or OmniHBI™ acrenas. When CLI whole-cell DTP vaccine is used to reconstitute ActHB™ 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 telanus toxoid, an estimate of 4 protective units of perfussis vaccine, 10 µg of purified capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid, and 8.5% of sucrose. (Refer to ActiviBM* package insect.)

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. aspirate to ensure that the needle has not entered a blood vessel.

Each dose of DP/ActHIB™ or OmniHIB™ vaccines is administered intramuscularly in the outer aspect of the vastus lateralis (midthigh) 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™ of monithie™, 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 310 RECOMMENDED IMMUNIZATION SCHEDULE

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™ o Acellular Pertussis (DTaP)
Fifth	4 to 6 years	DTP or Acellular Pertussis (DTaP)

Accilibit Perfussis (DTaP) should NOT be used to reconstitute ActHIBTM/OmniHIBT^M. 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 assumed an administered at this time in a separate syringe at a different site. 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 flowth of a product containing DTP or DTaP approximately 12 months later and a fitth dose of a product containing DTP or DTaP at 4 to 6 years of a ground the dose of a product containing DTP or DTaP at 4 to 6 years of the dose of a product containing DTP or DTaP at 4 to 6 years of the dose of a product containing DTP or DTaP at 4 to 6 years of the dose of a product containing on the dose of a product containing DTP or DTaP at 4 to 6 years of the dose of a product containing on the dose of a product containing DTP or DTaP at 4 to 6 years of the dose of a product containing DTP or DTAP at 4 to 6 years of the dose of a product containing the dose of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to 6 years of a product containing DTP or DTAP at 4 to

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. A child 15 to 59 months Preterm infants should be vaccinated according to their chronological age from birth.9 Interruption of the recommended schedule with a delay between classes should not interfere with the final immunity achieved when CLI DTP vaccine is used to reconstitute ActHi8™ 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 0mmiHIB™ are the same vaccine, these may be used interchangeably.

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

DO NOT INJECT INTRAVENOUSLY.

One 7.5 mL vial of Connaught Laboratories, Inc. Diphtheria and Tetanus Toxoids and Pertussis Vaccine as Diluent packaged with Vial. 1 Dose lyobhilized 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.

10RAGE tore 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.

(35° – 46°F). D0 NOT FREEZE.

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Manufactured by: CONNAUGHT LABORATORIES, INC.



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, whitisti-gay in color. When used to reconstitute Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), ActHIB™ or OrmiNHB™, the combined vaccines appear whitish in color.

Corynebacterium diphtheriae cultures are grown in a modified ulleler and Miller medium! Costridium tetani cultures are grown in a peptine-based medium. Both toxins are detoxified with formaldehyde. The detoxified materials are separately purified by serial ammonium sulfate fractionation and diafilitration.

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 telanus toxoids are adsorbed to aluminum potassium sulfate (alum). The adsorbed diphtheria and telanus toxoids are combined with contains, by assay, not more than 0.17 mg of aluminum and not more than 10.0 μg (0.02%) of residual formaldehyde. Thimerosal Each 0.5 mL dose (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 Connaight Laboratories, Inc. (CLI) DTP vaccine is used to reconstitute Actility no formulated to contain 6.7 Lf of dipitheria toxoid, 5.Lf of tetanus toxoid, an estimate of 4 protective units of the 0.5 mL mixture is formulated to contain 6.7 Lf of dipitheria toxoid, 5.Lf of tetanus toxoid, an estimate of 4 protective units of perfussis vaccine, 10 μg of purified capsular polysaccharide conjugated to 24 μg of inactivated tetanus toxoid, and 8.5% of succrose.

NOTE: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) — Actiliti™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) — Actiliti™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) — Conmittel™ (distributed by SmithKline Beecham Pharmaceuticals); both products are

CLINICAL PHARMACOLOGY

DIPHTHENA Conynebacterium 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.

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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 toxolds 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; AC 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 pharyrx or nose or on the skin. F

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

tetani.

The occurrence of tetanus in the United States has decreased dramatically from 560 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, 86% were ≥50 years of age, while only six were ≥20 years of age, while only six were ≥20 years of age, while one of age, 3 The disease continues to occur almost exclusively among persons who are unvaccinated of which 82% were ≥50 years of age, and 1988, and 1989, and are unvaccinated or inadequately vaccinated or inadequately accinated or 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.3 Thus, universal primary vaccination, with subsequent maintenance of adequate antitoxin levels by means of appropriately limited boosters, is necessary to protect persons among all age-groups. Tetanus toxodi is a nighty effective artigen, and a completed primary series generally induces protective levels of neutralizing antibodies to tetanus toxin that persist for >10 years.2

Complete primary series generally insulates procedure review or insulating amounts to remains until that persist to any peals."
The potency of diphtheria and tetanus toxicids was determined on the basis of immunogenities studies with a comparison to a serological correlate of protection (0.01 LU./ml.) established by the Panel on Review of Bacterial Vaccines & Toxoxids.⁴

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.

Diphtheria and Tetanus Toxords Assorbed USP (For Prediatric USP) (UT) or IP.

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. (CL) DT was administered as a primary series of three doses. Protective levels of diphtheria and tetanus antitioxins 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 antitioxin 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

PERTUSSIS

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 details 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 toxolis (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 1889 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. During the period 1993 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. 70 flatinist 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 dary pertussis containing vaccine.

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 inection 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?

infants and young children.s

EFFICACY OF PERTILOSIS 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 it of 010° 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 tyophilized single dose vial of ActHIB™ or OmniHIB™ with no diminution in anti-PRP response or diphtheria, tetanus and pertussis responses.

INDICATIONS AND USAGE

INDICATIONS AND USAGE
Diphtheria and Telanus 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 couph) simultaneously. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not pad 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 urticars and rash. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses.⁶

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after prior doses.⁵
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. ¹⁸ If local fedness 2.5 cm cocurs, the likelihood of recurrence after another DTP dose increases significantly, ¹⁸
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. ¹⁹
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 12

Event	Frequency*
ocal	
Redness	4.00
Swelling	1/3 doses
Pain	2/5 doses
vstemic	1/2 doses
Fever ≥38°C (100.4°F)	
Drowsiness	1/2 doses
Fretfulness	1/3 doses
Vomiting	1/2 doses
	1/15 doses
Anorexia	1/5 doses
Persistent, inconsolable crying	1, 6,51035
(duration ≥3 hours)	1/100 doses
Fever ≥40.5°C (≥105°F)	1/330 doses
ervous System	17000 00303
Collapse (hypotonic-hyporesponsive	
episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,/30 00868

*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 hyporesnsitivity reactions, characterized by severe local reactions (generally starting 2 to 8 hours after an injection), may follow receipt of tetanus toxolid.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

NERVOUS SYSTEM
The following neurologic illnesses have been reported as temporally associated with vaccine containing tetanus toxoid: neurological complications? 1.22 including co-chiear lesion, 72 brachial piexus neuropathies, 79.24 paralysis of the radial nerve, 75 paralysis of the recurrent nerve, 73 continuodation paresis, and EEG disturbances with encephalopathy 19. The report from the IOM suggests that there is a causal relation between Guilain-Barrie syndrome (GBS) and vaccines containing tetanus toxoid. 8 In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid should be considered as a possible cology, 19.27.

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

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 for known to be neurologic ornal period to the process of their age-, sex-, and neighborhood-matched controls. Among children known to be neight your preceipt of DTP does, compared to children on treceiving DTP in the 7-day period to children on the 7-day period to living more preceipt of DTP does, compared to children on the 7-day period tollowing process of their liness, was 3.3 (p. co.0.01). Within this 7-day period, the risk was significantly increased for immunized children only within 3 days of vaccination (relative risk 4.2, p. co.0.01). The relative risk for litheases occurring 4 to 7 days after vaccination was 2.1 (p. co.1). Serious neurologic illnesses requiring attributable risk of such illnesses is 1 in 140,000 doses administered. An earlier analysis had estimated this risk at 17110,000 doses in contrast, final analysis of the case-control subty has control subty has estimated that the risk of such illness following period to consider a subty found that the risk of serious neurologic illness following period selection subject to enough uncertainty to preclude drawing valid conclusions about whether a causal relation exists between pertussis vaccine and permanent neurologic disability. However, details are not available to evaluate this study adequately, and the same concerns remain about DTP vaccination in the original National in the original Nations to love one of the children studied in the or

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: OJ 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, is

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 does 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 in been reported. A causal relationship has not been established: 29,30,31

CARDIOVASCULAR SYSTEM

hin infant who developed myocarditis several hours after immunization has been reported.32 RESPIRATORY SYSTEM

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 necept of DTP was not causally related to SIDS.33.43 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 occurring at 6 weeks to 4 months of age and that approximately 85% of SIDS cases can be expected to have recently received DTP. 33.43 at 6 when the 4 months of age. By chance alone SIDS victims when CLI whole-cell DTP was administered concomitantly (at separate sites with separate syringes) with ActHIB™ or OmniHIB™ the systemic adverse systemic profile was not different from that seen when CLI whole-cell DTP vaccine was administered alone. 19.11 (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

DUSING AND AUMINISTRATION

Parentreal forg 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 administrated.

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. instructs as a mortis of age our may be given as young as o weers or age and up to the seventh brinday.

Inject 0.5 m Lintramsucularly 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.

Special care should be arread as a second process. Special care should be specially specially specially specially specially beginning when the infant is a vaccine is recommended for children 6 weeks through 6 years (up to the seventh birthday) ideally beginning when the infant is

6 Weeks through 12 months of age, administer three 0.5 mL doses inframuscularly at least 4 to 8 weeks apart. The fourth dose is administered 6 to 12 months after the third injection,

Inframuscularly at least 4 to 8 weeks apart. The fourth upon to administrate 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 recessary 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. PERSONA 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE) (DTP).

Respiratory difficulties, including apnea, have been observed.

Rash and allergic reactions have been observed

PERTIUSSIS
Disease caused by Bordetella pertussis was once a major cause of infant and childhood morbidity and morbility in the United States
Pertussis (whooping cough) became a nationally notifiable disease in 1922, and reports reached a peak of 265,269 cases and 7,514
deaths in 1934. The highest number of reported pertussis deaths (9,269) occurred in 1923. The introduction and widespread use o
standardized whole-cell pertussis vaccines combined with hightheria and testarus toxicids (0TP) in the 1976 Most resulted in substantial decline in pertussis disease, a decline which continued without interruption for nearly 30 years, the 1876 Most resulted in substantial decline in pertussis disease, a decline which continued without interruption for nearly 30 years, the 1876 Most resulted in substantial decline in pertussis disease, a decline which continued without interruption for nearly 30 years, the 1876 Most resulted in 1876 Most resu

by 1970, the annual reported incidence of perturbsish had been reduced by 99%. Outrigh 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.

with the peak year being 1990.⁸
During the period 1989 to 1991, of 3,900 reports of hospitalization, 1,115 had developed pneumonia, selzures occurred in 157 cases, encephalopathy was reported for 12, and there were 20 perfussis attributed deaths. These events were more frequently reported in children less than 6 months of age and were generally less frequent with increasing age.²⁷ 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 perfussis containing vaccine.²
Among older children and adults, including those previously vaccinated. *B. perfussis* infection may result in symptoms of bronchitis or upper-respiratory-tract infection. Perfussis 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 perfussis can be important sources of infection for infants
I year of age. Adults also play an important role in the transmission of perfussis to unvaccinated or incompletely vaccinated infants and young children.²
EFEICACY OF PERTILISIS VACCINE

EFFICACY OF PERTUSSIS VACCINE EFFICACY OF PERIUSSIS 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 rise. It was also shown that vaccines with acceptable mouse protection opencies induced protective serum agglutinin antibody titers. If 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.

MilholicaTions 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 contrainficated, 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 (39).

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}

age of 2 months. Vaccine doses should not be reduced or preterm intants.²⁹ If passive immunization is required, Tetanus Immune Globulin (Human) (TiG) and/or equine Diphtheria Antitoxin are the products of choice for retanus and diphtheria, respectively (see **DOSAGE AND ADMINISTRATION** section).

When CLI DTP vaccine is used to reconstitute ActHiBTM of OmniHIBTM 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 ActHiBTM 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 Actilities of minihila and the special content of the program of th 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 Toxold Conjugate) — ActHIB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxold Conjugate) — OmniHIB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pastern Merieus Sérumas & 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

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

The submanification to administer in section in the presence or any evolving neutrograd continuor.

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 ever are not contraindications to further use?

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

potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelea.

THE FOLLOWING EVENTS WERE PREVIOUSLY CONSIDERED CONTRAINOCATIONS AND ARE NOW CONSIDERED WARNINGS.

THE FOLLOWING EVENTS WERE PREVIOUSLY CONSIDERED CONTRAINOCATIONS AND ARE NOW CONSIDERED WARNINGS.

Temperature of 240.5°C (10°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, accination with DT should not be discontinued.

2. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours: Although these uncommon events have not been reconjized to cause death nor to induce permanent neurological sequelae, it is prudent to continue vaccination with DT, omitting the pertussis component.

2. 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. ≥ Cividence is insufficient to indicate whether pertussis vaccine-asted 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. Children with 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 than children who had other DTP-associated reactions than children with on had other DTP-associated reactions than children with on had other DTP-associated reactions.

hollowing subsequent ages. Cellular will persistent crying mare rate a righter rate of note reached and manufacture and a company of the property of the prope

DTP should not be given to children with any coagulation disorder, including thrombocytopenia, that would contraindicate intraminjection 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 contrainficiation to perfussis vaccination and that children with such family histories should receive perfussis vaccine according to the recommended schedule.

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. ²² 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. Intensit. ²²

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 OTP 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 filness. ^{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 AcIHIBTM or OmniHIBTM and administered to immunosuppressed persons persons receiving immunosuppressive therapy, the expected antibody responses may not be obtained. This includes patients severe combined immunodeficiency, hypogammaglobulinemia, or aganmaglobulinemia, aftered immune states due to diseases si as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylat drugs, antimetabolities 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) – ActHlB™ is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) – OmniHlB™ (distributed by SmithKline Beecham Pharmaceuticals); both products are manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

PRECAUTIONS

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

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 si immunization history, current health status (see CONTRAMIDICATIONS; MARAINIOS Sections), and a current knooneering 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

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-ser 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

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 Folimbood Vaccine injury Act of 1986. ** The total-free number for VAERS forms and information is 1-800-922-7967.

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

Immunosuppressive therapies, including irradiation, antimetabolites, allylating agents, cytoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (<2 weeks) corticosteroid therapy or interarticular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with perturbusive vaccine are available, if immunosuppressive therapy will be discontinued shortly, it is reasonable to deter 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.

CARCINGCENESSIS, MUTACENESSIS, IMPARIMENT 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

SIGUSE. AND EFFECTIVENESS OF DTP VACCINE OR AT THE TIME WHEN DTP VACCINE IS USED TO RECONSTITUTE ACHIB™ OR B™ IN INFANTS BFLOW THE AGE OF SIX WEFKS HAVE NOT BEFN ESTABLISHED. (See DOSAGE AND ADMINISTRATION

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 pertusive vaccination exists, or where in the opinion of the physician the pertussis vaccine should not be administered, 17 is the appropriate atternative.

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).

RESPIRATORY SYSTEM Respiratory difficulties, including apnea, have been observed.

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-3x3-38 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 6 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 3x3-3x5.

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 ActMIP™ 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, 5.19,3.6

When CLI whole-cell DTP was used to reconstitute ActHB™ or OmniHB™ 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} (Retar to ActHB™ package insert.)

package insert.)

Reporting of Adverse Events

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 (OHHS) 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 1-800-822-7957. 1817.18

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 DAMINISTRATION
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.

instructs is a muniture to a great in any entering as a version age and up to the seventir binding.

The preferred inject 0.5 mL intramuscularly only. The preferred injection sites are the anterotateral aspect of the thigh and the delitoid 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 Tribusaction 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 kindergarter 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 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, routhe 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 TETAMUS TOXDIDS AND PERTUSSIS VACCINE ADSORBED USP (FOR PEDIATRIC USE) (ITTP).

ROUTINE DIPHTHERIA, TETANUS, AND PERTUSSIS VACCINATION SCHEDULE
Summary For Children -77 Years Old - United States, 1991

Dose	Customary Age	Age/Interval†	Product	
Primary 1 Primary 2 Primary 3	2 Months 4 Months 6 Months	6 weeks old or older 4-8 weeks after first dose* 4-8 weeks after second dose*	DTP† DTP† DTP†	
Primary 4 Booster		6-12 months after third dose* entering kindergarten or elementary if fourth primary vaccinating dose	DTP†	
Additional Boosters	administered after for		Td	

* Use DT if perfussis 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 dose 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 Toxola and Acellular Pertussis Vaccine Adsorbed (DTaP) can be interchangeably used with DTP for the fourth and fifth doses. However ActHIBTM cannot be reconstituted with DTaP.

and fifth doses. However ActHB™ cannot be reconstituted with D1aP.

The simultaneous administration of DTP, oral polivoirus vaccine (oPV), and measles-mumps-rubella vaccine (MMR) has resulted in scroonversion rates and rates of side effects similar to those observed when the vaccines are administered separately. Simultaneous vaccination (at separate sites with separate sirgings) with DTP, MMR, oPV, or incachated polivoirus vaccine (PV) at latenophilus b conjugate vaccine (HbO/) is also acceptable. 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, HbO/, and MMR at ≥ 5 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 toxorid and TIG are administered concurrently, separate syringes and separate sites should be used. The AGIP 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.

International by Pasteur Merieux Serums & 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™ waccine 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.

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

After reconstitution, each 0.5 mt. 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 DTI/ACHHIS™ or OrminiliB™ vaccines is administered intramuscularly in the outer aspect of the vastus lateralis (mid-thigh) or detend. 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 ActHIBTM or OmniHIBTM, 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

RECOMMENDED IMMUNIZATION SCHEDULE

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 ActHIBTM/OmniHIBTM. 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.

heamopnius immenzae type o vaccine also should be administered at this time in a separate syninge at a direrent site.

For Previously Unwaccinated Children
Immunization schedules should be considered on an individual basis for children not vaccinated according to the recommended schedule. Three doeses of a product containing DTP, given at approximately 2-month intervals, are required followed by a fourth does of a product containing DTP or DTaP at 4 to 6 years of a product containing DTP or DTaP at 4 to 6 years of age. If the fourth does 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 ActHB™ or OmniHB™. 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 m. Lind Connaught Laboratories, inc. Diphtheria and Tetanus Toxoids and Pertussis Vaccine as Diluent packaged with Vial. 1 Dose (vophilized 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 $2^{\circ} - 8^{\circ}$ C ($35^{\circ} - 46^{\circ}$ 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 $2^{\circ} - 8^{\circ}$ C ($35^{\circ} - 46^{\circ}$ F). DO NOT FREEZE.

(35° – 40° T). Untul TRELEC.

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