SUMMARY FOR BASIS OF APPROVAL

REFERENCE NO. 83-087 DRUG LICENSED NAME: POLIOVIRUS VACCINE INACTIVATED

MANUFACTURER: INSTITUT MERIEUX DRUG TRADE NAME: IPOL

Poliovirus Vaccine Inactivated produced by Institut Merieux is a sterile suspension of three types of poliovirus: Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett). The viruses are grown in microcarrier cultures of VERO cells, a continuous line of monkey kidney cells.

I. INDICATIONS FOR USE

Merieux Poliovirus Vaccine Inactivated (IPV) is indicated for the active immunization of infants, children and adults for the prevention of poliomyelitis. Poliovirus Vaccine Inactivated should be offered to individuals who have refused Poliovirus Vaccine Live Oral Trivalent (OPV) or in whom OPV is contraindicated.

INFANTS, CHILDREN AND ADOLESCENTS: It is recommended that all infants, unimmunized children and adolescents not previously immunized be vaccinated routinely against paralytic poliomyelitis.

The Immunization Practices Advisory Committee (ACIP) recommends OPV as the vaccine of choice for routine immunization of children in the United States, even though both IPV and OPV are effective in preventing poliomyelitis. Parents should be adequately informed of the risks and benefits of both IPV and OPV so that they can make an informed choice.

Children of all ages should have their immunization status reviewed and should be considered for supplemental immunization if they are at increased risk of exposure to poliovirus due to travel to endemic areas or potential contact with recipients of OPV. Previous clinical poliomyelitis (usually due to only a single poliovirus type) or incomplete immunization with OPV are not contraindications to completing the primary series of immunization with IPV.

ADULTS: The current recommendation of the ACIP states that routine primary vaccination of adults (generally those 18 years old or older) residing in the United States is not necessary. Most adults are already immune and have a very small risk of exposure to poliomyelitis in the United States. Immunization is recommended for certain adults who are at greater risk of exposure to wild polioviruses than the general population, including:

- Travelers to regions or countries where poliomyelitis is endemic or epidemic.
- Health care workers in close contact with patients who may be excreting polioviruses.

- Laboratory workers handling specimens that may contain polioviruses.
- Members of communities or specific population groups with disease caused by wild polioviruses.
- Incompletely vaccinated or unvaccinated adults in a household (or other close contacts) with children given OPV provided that the immunization of the child can be assured and not unduly delayed. The adult should be informed of the small OPV related risk to the contact.

IMMUNODEFICIENCY AND ALTERED IMMUNE STATUS: Patients with immunodeficiency are individually at greater risk of developing paralytic poliomyelitis from OPV than persons with a normal immune system. Poliovirus Vaccine Inactivated should be used in all patients with recognized immunodeficiency diseases. This includes patients with asymptomatic human immunodeficiency virus (HIV) infection, AIDS or AIDS Related Complex, combined immunodeficiency, hypoagammaglobulinemia, or agammaglobulinemia, in all patients with altered immune states due to disease such as leukemia, lymphoma, or generalized malignancy, and all patients with an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation. Patients with an altered immune state may or may not develop a protective response against paralytic poliomyelitis after administration of the vaccine. IPV should be given to the young siblings or other members of the household of a patient with diagnosed immunodeficiency.

II. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

The vaccine is packaged in a single dose syringe with needle containing 0.5 ml of product and is intended for subcutaneous injection. It is not to be administered intravenously. Each dose (0.5 ml) of trivalent vaccine is formulated to contain 40 D antigen units of Type 1, 8 D antigen units of Type 2, and 32 D antigen units of Type 3 poliovirus, determined by comparison to a reference preparation.

DOSAGE SCHEDULE

Infants, children and adolescents: The primary series for immunization for infants, children and adolescents of Poliovirus Vaccine Inactivated consists of three 0.5 ml doses administered subcutaneously. The interval between the first two doses should be at least four weeks, but preferably eight weeks. The first two doses are usually integrated with Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP) immunization and are given at two and four months of age. The third dose should follow at least six months but preferably 12 months after the second dose. All children who received a primary series of Poliovirus Vaccine Inactivated, or a combination of IPV and OPV, should be given a booster dose of 0.5 ml of OPV or IPV before entering school, unless the first dose of the primary series was administered on or after the fourth birthday. The need to routinely administer additional doses

is unknown at this time. A final total of four doses is necessary to complete a series of primary and booster doses. Children and adolescents with a previously incomplete series of IPV should receive sufficient additional doses to reach this number.

Adults: For unvaccinated adults at increased risk of exposure to poliovirus, a primary series of Poliovirus Vaccine Inactivated is recommended. The recommended schedule is two 0.5 ml doses given at a 1 to 2 month interval and a third dose of 0.5 ml given 6 to 12 months later. Adults who are at increased risk of exposure and have received an incomplete primary immunization should receive at least a single dose of Poliovirus Vaccine Live Oral or a single 0.5 ml dose of Poliovirus Vaccine Inactivated. Additional doses needed to complete a primary series should be given if time permits.

III. MANUFACTURING AND CONTROLS

Manufacturing and Controls

Poliovirus Vaccine Inactivated produced by Institut Merieux is a sterile suspension of three types of poliovirus: Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett). The viruses are grown in a culture of VERO cells, a continuous line of African Green (Cercopithecus) monkey kidney cells, by the microcarrier technique. The viruses are concentrated, purified, and made noninfectious by inactivation with formaldehyde. Each 0.5 ml dose of trivalent vaccine is formulated to contain 40 D antigen units of Type 1, 8 D antigen units of Type 2, and 32 D antigen units of Type 3 poliovirus, 0.5% phenoxyethanol and a maximum of 0.02% formaldehyde. Neomycin, streptomycin and polymyxin B are used in vaccine production, and although purification procedures eliminate measurable amounts, less than 5 ng neomycin, 200 ng streptomycin and 25 ng polymyxin B per dose may still be present.

The vaccine is clear and colorless. The [redacted] final product are tested for sterility, general safety, physicochemical assays and potency.

Stability Studies

On September 5, 1989, Institut Merieux submitted stability data on 9 lots of vaccine stored at 2° to 8° C. These lots were tested by in vitro potency tests and physicochemical tests for [redacted] An expiration date of 36 months from the date of manufacture when stored at 2° to 8° C is based on real time stability data. [redacted]

Validation

All key items of equipment used in manufacturing and filling of the vaccine have been validated. Air systems are HEPA-filtered

and water systems are periodically tested to ensure compliance with specifications. Appropriate specifications have been established for monitoring of environmental conditions for each critical area.

Labeling

The labeling, including the package insert, has been reviewed and is in compliance with applicable regulations for biological products. The package insert (copy attached) contains appropriate statements concerning indications, dosage, warnings, precautions etc.

Establishment Inspection

Prelicense inspections of Institut Merieux facilities in Marcy l'Etoile, France were performed on September 18-20, 1989 and April 24-26, 1990. The facilities, manufacturing procedures, quality controls, storage facilities and conditions, records and other aspects of manufacturing of this vaccine are considered satisfactory and in compliance with applicable regulations.

Environmental Impact Analysis Report

An appropriate review and statement assessing environmental impact was filed by the manufacturer and accepted by the licensing committee. A finding of no significant impact is attached.

IV. PHARMACOLOGY

Poliovirus Vaccine Inactivated is a purified, inactivated poliovirus vaccine produced by microcarrier culture. This culture technique and improvements in purification, concentration and standardization of poliovirus antigen have resulted in a more potent and more consistently immunogenic vaccine than the inactivated polio vaccine licensed in the United States prior to 1987. Fewer doses of IPV produced by this technique are needed to satisfactorily immunize children. Studies in developed and developing countries have shown a direct relationship between the antigenic content of this vaccine and the frequency of seroconversion and resulting antibody titer.

The transmission of wild poliovirus in the U.S. and most European countries with good hygienic conditions is mainly through the oral-oral route. Inactivated polio vaccine reduces pharyngeal excretion of poliovirus in vaccinees with high antibody titers.

V. MEDICAL

Background Clinical Studies:

A clinical trial was carried out at Johns Hopkins University using a

Poliovirus Vaccine Inactivated manufactured by Institut Merieux. This vaccine was manufactured using the same process as the current vaccine except the cell substrate was primary monkey kidney cells. After receiving doses at 2 and 4 months of age approximately 99% of the children had neutralizing antibodies to all three types of poliovirus. A significant increase in titers occurred after a third dose given at 18 months of age. There were 331 infants enrolled in the trial of whom 219 received three doses of inactivated poliovirus vaccine.

Clinical trials demonstrating Immunogenicity and Safety:

Clinical trials with the vaccine made in Vero cells were carried out in infants at the State University of New York/Children's Hospital, Buffalo, New York by clinical investigators Drs. H. Faden and P. Ogra and at Johns Hopkins University, Baltimore, Maryland by Drs. M. McBean and J. Modlin. In addition 30 adults were studied at the Buffalo study site.

These trials compared different combinations or schedules in infants using the Merieux Poliovirus Vaccine Inactivated and OPV. The schedules using IPV were a)IPV-IPV-IPV, b)IPV-OPV-OPV, c)IPV-IPV-OPV with doses given at 2, 4 and 12 months of age. Blood samples for antibody determinations were collected just prior to administration of each dose of vaccine and one month after the second and third doses of vaccine. A detectable serum neutralizing antibody titer was considered [redacted]

For the adults, one dose was administered to the entire group and one half of the group also received a second dose. Serum antibody titers were done prior to immunization and 1 month after each dose.

Of the infants immunized, 120 were evaluable for serum antibody titers after 2 doses of IPV. These included children from both the IPV-IPV-IPV and IPV-IPV-OPV groups. Detectable neutralizing antibodies were induced in 98.3% (Type 1), 100% (Type 2), and 97.5% (Type 3) of children. There were 83 infants in the IPV-IPV-IPV group who were evaluable for serum antibody titers at completion of the immunizing schedule. In this group detectable serum neutralizing antibodies were found in 97.6% (Type 1) and 100% (Types 2 and 3) of subjects after 3 doses. Table 1 shows the results for each group in which more than one dose of IPV was given after receiving 1, 2 or 3 doses of IPV.

The geometric mean titers (GMTs) rose at least 10-fold after 2 doses of IPV and at least 100-fold after 3 doses of IPV for virus Types 1, 2 and 3. Table 2 shows the GMTs for the groups in which at least 2 doses of IPV were given.

Of the 30 adults studied, nearly all had detectable neutralizing antibodies at the time of entry into the study. Of the 15 adults receiving one or two doses the increase in GMT was at least 17, 34 and 57-fold for Types 1, 2 and 3 respectively.

These results compared well with those obtained in 1984/1985 with

enhanced potency IPV produced in primary monkey kidney cells by both Institut Merieux and Connaught Laboratories Limited and tested in 900 children in parallel with OPV by Johns Hopkins School of Public Health and Hygiene.

In the Buffalo and Baltimore study, Merieux IPV induced comparable responses in premature and full term infants. Single and two dose boosters in adults produced high anamnestic responses and showed a second booster dose is unnecessary.

A total of approximately 400 doses of IPV were given in these studies. Safety was assessed in the Johns Hopkins study by a follow-up telephone call with subjects at 24 hours and 2 and 3 days after each immunization to inquire about adverse experiences. Surveillance at Buffalo was limited to an interview during each immunization visit. No serious adverse experiences were reported at either study site. One adult complained of redness at the injection site.

There were no significant local or systemic reactions following injection of IPV. In the Johns Hopkins study, there were 7% (6/86), 12% (8/65) and 4% (2/45) of children with temperatures over 100.6° F, following the first, second and third doses respectively. Most of the children received DTP at the same time as IPV and therefore it was not possible to attribute reactions to a particular vaccine; however, such reactions were not significantly different than when DTP is given alone.

VI. ADVISORY PANEL CONSIDERATION

The Vaccines and Related Biological Products Advisory Committee discussed the pending product license application on July 31, 1989 and recommended approval.

VII. APPROVED PACKAGE INSERT

A copy of the approved package insert is attached.

Paul Albrecht, M.D.
Chairman

Ronald Lundquist, Ph.D.

Table 1

Percent Serum Neutralizing Antibodies After IPV[1]

	Type 1			
Months	IPV-IPV-IPV		IPV-IPV-OPV	
2	92/116	(79.3)	29/34	(85.3)
4	68/93	(73.1)	27/29	(93.1)
5	89/91	(97.8)	29/29	(100.0)
12	78/85	(91.8)	*[2]	
13	81/83	(97.6)	*	

	Type 2			
Months	IPV-IPV-IPV		IPV-IPV-OPV	
2	100/116	(86.2)	32/34	(94.1)
4	89/93	(95.7)	29/29	(100.0)
5	91/91	(100.0)	29/29	(100.0)
12	79/85	(92.9)	*	
13	83/83	(100.0)	*	

	Type 3			
Months	IPV-IPV-IPV		IPV-IPV-OPV	
2	87/116	(75.0)	26/34	(76.5)
4	78/93	(83.9)	23/29	(79.3)
5	88/91	(96.7)	29/29	(100.0)
12	77/85	(90.6)	*	
13	83/83	(100.0)	*	

[1]Number with titers [redacted] (percent)

[2]No further doses of IPV given

Table 2

Geometric Mean Titers (GMTs) of Infants Receiving at Least 2 doses of IPV

Type 1

Months	IPV-IPV-IPV		IPV-IPV-OPV	
	n	GMT	n	GMT
2	116	20.97	34	30.07
4	93	12.16	29	22.90
5	91	208.84	29	354.70
12	85	74.19	*[1]	
13	83	2101.29	*	

Type 2

Months	IPV-IPV-IPV		IPV-IPV-OPV	
	n	GMT	n	GMT
2	116	36.24	34	56.54
4	93	41.52	29	51.17
5	91	552.15	29	709.40
12	85	128.45	*	
13	83	5120.00	*	

Type 3

Months	IPV-IPV-IPV		IPV-IPV-OPV	
	n	GMT	n	GMT
2	116	15.40	34	15.05
4	93	21.15	29	15.89
5	91	605.15	29	1200.22
12	85	84.99	*	
13	83	4332.44	*	

[1]No further doses of IPV given