ZIAGEN Oral Solution: It is a clear to opalescent, yellowish, strawberry-banana-flavored liquid. Each mL of the solution contains abacavir sulfate equivalent to 20 mg of abacavir. It is packaged in plastic bottles as follows:

Bottles of 240 mL (NDC 0173-0664-00) with child-resistant closure. This product does not require reconstitution.

Store at controlled room temperature of 20° to 25°C (68° to 77°F) (see USP). DO NOT FREEZE. May be refrigerated.

ANIMAL TOXICOLOGY

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

GlaxoSmithKline
Research Triangle Park, NC 27709

July 2003 RL-2030

MEDICATION GUIDE

ZIAGEN® (z-EYE-uh-jen) (abacavir sulfate) Tablets and Oral Solution

Generic name: abacavir (uh-BACK-ah-veer) sulfate tablets and oral solution

Read the Medication Guide you get each time you fill your prescription for Ziagen. There may be new information since you filled your last prescription.

What is the most important information I should know about Ziagen?
About 1 in 20 patients (5%) who take Ziagen will have **a serious allergic reaction** (hypersensitivity reaction) **that may cause death if the drug is not stopped right away**.

You may be having this reaction if:

(1) you get a skin rash, or

(2) you get 1 or more symptoms from at least 2 of the following groups:

- **Fever**
- **Nausea, vomiting, diarrhea, abdominal (stomach area) pain**
- **Extreme tiredness, achiness, generally ill feeling**
- **Sore throat, shortness of breath, cough**

If you think you may be having a reaction, **STOP taking Ziagen and call your doctor right away.**

If you stop treatment with Ziagen because of this serious reaction, **NEVER take Ziagen (abacavir) again.** If you take Ziagen again after you have had this serious reaction, **you could die within hours.**

Some patients who have stopped taking Ziagen (abacavir) and who have then started taking Ziagen (abacavir) again have had serious or life-threatening allergic (hypersensitivity) reactions. If you must stop treatment with Ziagen for reasons other than symptoms of hypersensitivity, do not begin taking it again without talking to your health care provider. If your health care provider decides that you may begin taking Ziagen again, you should do so only in a setting with other people to get access to a doctor if needed.

A written list of these symptoms is on the Warning Card your pharmacist gives you. Carry this Warning Card with you.

Ziagen can have other serious side effects. Be sure to read the section below entitled "What are the possible side effects of Ziagen?"

What is Ziagen?
Ziagen is a medication used to treat HIV infection. Ziagen is taken by mouth as a tablet or a strawberry-banana-flavored liquid. Ziagen is a medicine called a nucleoside analogue reverse

transcriptase inhibitor (NRTI). Ziagen is only proven to work when taken in combination with other anti-HIV medications. When used in combination with these other medications, Ziagen helps lower the amount of HIV found in your blood. This helps to keep your immune system as healthy as possible so that it can help fight infection.

Ziagen does not cure HIV infection or AIDS. Ziagen has not been studied long enough to know if it will help you live longer or have fewer of the medical problems that are associated with HIV infection or AIDS. Therefore, you must see your health care provider regularly.

Who should not take Ziagen?
Do not take Ziagen if you have ever had a serious allergic reaction (a hypersensitivity reaction) to abacavir (as Ziagen or Trizivir® [abacavir, lamivudine, and zidovudine] Tablets). If you have had such a reaction, return all of your unused Ziagen to your doctor or pharmacist.

Talk to your doctor if you have liver problems, as some patients with liver disease should not take Ziagen.

How should I take Ziagen?
To help make sure that your anti-HIV therapy is as effective as possible, take your Ziagen exactly as your doctor prescribes it. Do not skip any doses.

The usual dosage for adults (at least 16 years of age) is one 300-mg tablet twice a day. You can take Ziagen with food or on an empty stomach.

Adolescents and children 3 months and older can also take Ziagen. Your doctor will tell you if the oral solution or tablet is best for your child. Also, your child's doctor will decide the right dose based on your child's weight and age. Ziagen has not been studied in children under 3 months of age.

If you miss a dose of Ziagen, take the missed dose right away. Then, take the next dose at the usual scheduled time. Do not let your Ziagen run out. The amount of virus in your blood may increase if your anti-HIV drugs are stopped, even for a short time. Also, the virus in your body may become harder to treat.

What should I avoid while taking Ziagen?
Practice safe sex while using Ziagen. Do not use or share dirty needles. Ziagen does not reduce the risk of passing HIV to others through sexual contact or blood contamination.

Talk to your doctor if you are pregnant or if you become pregnant while taking Ziagen. Ziagen has not been studied in pregnant women. It is not known whether Ziagen will harm the unborn child.

Mothers with HIV should not breastfeed their babies because HIV is passed to the baby in breast milk. Also Ziagen can be passed to babies in breast milk and could cause the child to have side effects.

What are the possible side effects of Ziagen?

Life-threatening allergic reaction. Ziagen has caused some people to have a life-threatening reaction (hypersensitivity reaction) that can cause death. How to recognize a possible reaction, and what to do are discussed in "What is the most important information I should know about Ziagen?" at the beginning of this Medication Guide.

Lactic Acidosis and severe liver problems. Ziagen can cause a serious condition called lactic acidosis and, in some cases, this condition can cause death. Nausea and tiredness that don't get better may be symptoms of lactic acidosis. Women are more likely than men to get this rare but serious side effect.

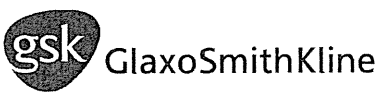
Ziagen can cause other side effects. In studies, the most common side effects with Ziagen were nausea, vomiting, malaise or fatigue, headache, diarrhea, and loss of appetite. Most of these side effects did not cause people to stop taking Ziagen.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

This listing of side effects is not complete. Your doctor or pharmacist can discuss with you a more complete list of side effects with Ziagen.

Ask a health care professional about any concerns about Ziagen. If you want more information, ask your doctor or pharmacist for the labeling for Ziagen that was written for health care professionals.

Do not use Ziagen for a condition for which it was not prescribed. Do not give Ziagen to other persons.



GlaxoSmithKline
Research Triangle Park, NC 27709

July 2003 MG-019

This Medication Guide has been approved by the US Food and Drug Administration.

HUMATIN - paromomycin sulfate capsule
Monarch Pharmaceuticals, Inc.

DESCRIPTION
Humatin is a broad spectrum antibiotic produced by *Streptomyces rimosus* var. *paromomycinus*. It is a white, amorphous, stable, water-soluble product supplied as capsules containing the equivalent of 250 mg paromomycin.
The capsule contains D&C yellow No. 10; FD&C blue No. 1; FD&C red No. 3; FD&C yellow No. 6; gelatin, NF; and titanium dioxide, USP.

ACTION
The *in vitro* and *in vivo* antibacterial action of paromomycin closely parallels that of neomycin. It is poorly absorbed after oral administration, with almost 100% of the drug recoverable in the stool.

INDICATIONS
Humatin is indicated for intestinal amebiasis—acute and chronic (NOTE —It is not effective in extraintestinal amebiasis); management of hepatic coma—as adjunctive therapy.

CONTRAINDICATIONS
Paromomycin sulfate is contraindicated in individuals with a history of previous hypersensitivity reactions to it. It is also contraindicated in intestinal obstruction.

PRECAUTIONS
The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. Constant observation of the patient is essential. If new infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.
The drug should be used with caution in individuals with ulcerative lesions of the bowel to avoid renal toxicity through inadvertent absorption.
Pediatric Use: See **Dosage and Administration** section.

ADVERSE REACTIONS
Nausea, abdominal cramps, and diarrhea have been reported in patients on doses over 3 g daily.

DOSAGE AND ADMINISTRATION
Intestinal amebiasis: Adults and Pediatric Patients: Usual dose—25 to 35 mg/kg body weight daily, administered in three doses with meals, for five to ten days.
Management of hepatic coma: Adults: Usual dose—4 g daily in divided doses, given at regular intervals for five to six days.

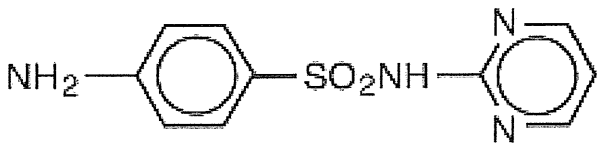
HOW SUPPLIED
Humatin Capsules, each containing paromomycin sulfate equivalent to 250 mg paromomycin, are supplied as follows
NDC 61570-529-10: Bottles of 100
Store at controlled room temperature 15°–30°C (59°–86°F).
Protect from moisture.
Rx only.
Prescribing Information as of November 2001.
Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620
Manufactured by: Caraco Pharmaceutical Laboratories, Ltd., Detroit, MI 48202

SULFADIAZINE - sulfadiazine tablet
Eon Labs, Inc.

Rx only

DESCRIPTION

Sulfadiazine is an oral sulfonamide anti-bacterial agent.
Each tablet, for oral administration, contains 500 mg sulfadiazine. In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, docusate sodium, microcrystalline cellulose, povidone, sodium benzoate, sodium starch glycolate and stearic acid.
Sulfadiazine occurs as a white or slightly yellow powder. It is odorless or nearly so and slowly darkens on exposure to light. It is practically insoluble in water and slightly soluble in alcohol. The chemical name of sulfadiazine is N^1-2-pyrimidinylsulfanilamide. The molecular formula is $C_{10}H_{10}N_4O_2S$. It has a molecular weight of 250.27. The structural formula is shown below:



Most sulfonamides slowly darken on exposure to light.

CLINICAL PHARMACOLOGY

The systemic sulfonamides are bacteriostatic agents having a similar spectrum of activity. Sulfonamides competitively inhibit bacterial synthesis of folic acid (pteroylglutamic acid) from aminobenzoic acid. Resistant strains are capable of utilizing folic acid precursors or preformed folic acid.
Sulfonamides exist in the blood in 3 forms - free, conjugated (acetylated and possibly others) and protein bound. The free form is considered to be the therapeutically active one.
Sulfadiazine given orally is readily absorbed from the gastrointestinal tract. After a single 2 g oral dose, a peak of 6.04 mg/100 mL is reached in 4 hours; of this, 4.65 mg/100 mL is free drug.
When a dose of 100 mg/kg of body weight is given initially and followed by 50 mg/kg every 6 hours, blood levels of free sulfadiazine are about 7 mg/100mL. Protein binding is 38% to 48%. Sulfadiazine diffuses into the cerebrospinal fluid; free drug reaches 32% to 65% of blood levels and total drug 40% to 60%.
Sulfadiazine is excreted largely in the urine, where concentrations are 10 to 25 times greater than serum levels. Approximately 10% of a single oral dose is excreted in the first 6 hours, 50% within 24 hours and 60% to 85% in 48 to 72 hours. Of the amount excreted in the urine, 15% to 40% is in the acetyl form.

INDICATIONS AND USAGE

Sulfadiazine tablets are indicated in the following conditions:
Chancroid
Trachoma
Inclusion conjunctivitis
Nocardiosis
Urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) in the absence of obstructive uropathy or foreign bodies, when these infections are caused by susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Staphylococcus aureus*, *Proteus mirabilis* and *P. vulgaris*. Sulfadiazine should be used for urinary tract infections only after use of more soluble sulfonamides has been unsuccessful.
Toxoplasmosis encephalitis in patients with and without acquired immunodeficiency syndrome, as adjunctive therapy with pyrimethamine.
Malaria due to chloroquine-resistant strains of *Plasmodium falciparum*, when used as adjunctive therapy.
Prophylaxis of meningococcal meningitis when sulfonamide-sensitive group A strains are known to prevail in family groups or larger closed populations (the prophylactic usefulness of sulfonamides when group B or C infections are prevalent is not proved and may be harmful in closed population groups).
Meningococcal meningitis, when the organism has been demonstrated to be susceptible.
Acute otitis media due to *Haemophilus influenzae*, when used concomitantly with adequate doses of penicillin.
Prophylaxis against recurrences of rheumatic fever, as an alternative to penicillin.
H. influenzae meningitis, as adjunctive therapy with parental streptomycin.
IMPORTANT NOTES
In vitro sulfonamide susceptibility tests are not always reliable. The test must be carefully coordinated with bacteriologic and clinical response. When the patient is already taking sulfonamides, follow-up cultures should have aminobenzoic acid added to the culture media.

Currently, the increasing frequency of resistant organisms limits the usefulness of antibacterial agents, including the sulfonamides, especially in the treatment of recurrent and complicated urinary tract infections.
Wide variation in blood levels may result with identical doses. Blood levels should be measured in patients receiving sulfonamides for serious infections. Free sulfonamide blood levels of 5 to 15 mg per 100 mL may be considered therapeutically effective for most infections and blood levels of 12 to 15 mg per 100 mL may be considered optimal for serious infections. Twenty mg per 100 mL should be the maximum total sulfonamide level, since adverse reactions occur more frequently above this level.

CONTRAINDICATIONS

Sulfadiazine is contraindicated in the following circumstances: Hypersensitivity to sulfonamides.
In infants less than 2 months of age (except as adjunctive therapy with pyrimethamine in the treatment of congenital toxoplasmosis).
In pregnancy at term and during the nursing period, because sulfonamides cross the placenta and are excreted in breast milk and may cause kernicterus.

WARNINGS

The sulfonamides should not be used for the treatment of group A betahemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent sequelae such as rheumatic fever and glomerulonephritis.
Deaths associated with the administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias.
The presence of such clinical signs as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders.
The frequency of renal complications is considerably lower in patients receiving the more soluble sulfonamides.

PRECAUTIONS

General

Sulfonamides should be given with caution to patients with impaired renal or hepatic function and to those with severe allergy or bronchial asthma.
Hemolysis may occur in individuals deficient in glucose-6-phosphate dehydrogenase. This reaction is dose related.
Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation.

Information for Patients

Patients should be instructed to drink an eight ounce glass of water with each dose of medication and at frequent intervals throughout the day. Caution patients to report promptly the onset of sore throat, fever, pallor, purpura or jaundice when taking this drug, since these may be early indications of serious blood disorders.

Laboratory Tests

Complete blood counts and urinalyses with careful microscopic examinations should be done frequently in patients receiving sulfonamides.

Drug Interactions

Administration of a sulfonamide may increase the effect of oral anticoagulants and methotrexate, probably by displacement of these drugs from binding sites on plasma albumin. Potentiation of the action of sulfonylurea hypoglycemic agents, thiazide diuretics and uricosuric agents may also be noted. This may also be due to displacement of the drugs from albumin or a pharmacodynamic mechanism may play a role. Conversely, agents such as indomethacin, probenecid and salicylates may displace sulfonamides from plasma albumin and increase the concentrations of free drug in plasma.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The sulfonamides bear certain chemical similarities to some goitrogens. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides and long-term administration has produced thyroid malignancies in rats.

Pregnancy

Teratogenic Effects

Pregnancy Category C
The safe use of sulfonamides in pregnancy has not been established. The teratogenic potential of most sulfonamides has not been thoroughly investigated in either animals or humans. However, a significant increase in the incidence of cleft palate and other bony abnormalities in offspring has been observed when certain sulfonamides of the short, intermediate and long acting types were given to pregnant rats and mice in high oral doses (7 to 25 times the human therapeutic dose).

Nursing Mothers
Sulfadiazine is contraindicated for use in nursing mothers because the sulfonamides cross the placenta, are excreted in breast milk and may cause kernicterus.
Because of the potential for serious adverse reactions in nursing infants from sulfadiazine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. See **CONTRAINDICATIONS.**

Pediatric Use
Sulfadiazine is contraindicated in infants less than 2 months of age (except as adjunctive therapy with pyrimethamine in the treatment of congenital toxoplasmosis). See **CONTRAINDICATIONS**and **DOSAGE AND ADMINISTRATION.**

ADVERSE REACTIONS

Blood Dyscrasias
Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia, and methemoglobinemia.

Allergic Reactions
Erythema multiforme (Stevens-Johnson syndrome), generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia, allergic myocarditis, drug fever, and chills.

Gastrointestinal Reactions
Nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis, and stomatitis.

C.N.S. Reactions
Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, and insomnia.

Renal
Crystalluria, stone formation, toxic nephrosis with oliguria and anuria; periarteritis nodosa and lupus erythematosus phenomenon have been noted.

Miscellaneous Reactions
The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents.

DOSAGE AND ADMINISTRATION
SYSTEMIC SULFONAMIDES ARE CONTRAINDICATED IN INFANTS UNDER 2 MONTHS OF AGE except as adjunctive therapy with pyrimethamine in the treatment of congenital toxoplasmosis.

Usual Dosage for Infants over 2 Months of Age and Children
Initially, one-half the 24-hour dose. Maintenance, 150 mg/kg or 4 g/m2, divided into 4 to 6 doses, every 24 hours, with a maximum of 6 g every 24 hours. Rheumatic fever prophylaxis, under 30 kg (66 pounds), 500 mg every 24 hours; over 30 kg (66 pounds), 1 g every 24 hours.

Usual Adult Dosage
Initially, 2 to 4 g. Maintenance, 2 to 4 g, divided into 3 to 6 doses, every 24 hours.

HOW SUPPLIED
Sulfadiazine 500 mg Tablets are white, unscored, capsule-shaped tablets, imprinted *E* 757 and are available in bottles of 100 and 1000.
Storage: Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container as defined in the USP.
To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
Manufactured for
Sandoz Inc.
Princeton, NJ 08540
Manufactured by
Epic Pharma, LLC
Laurelton, NY 11413
OS7190

Rev. 10/08
MF0757REV10/08
MG #16918

SULFADIAZINE TABLETS USP, 500 MG X 100 TABLETS - LABEL
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SulfADIAZine Tablets USP
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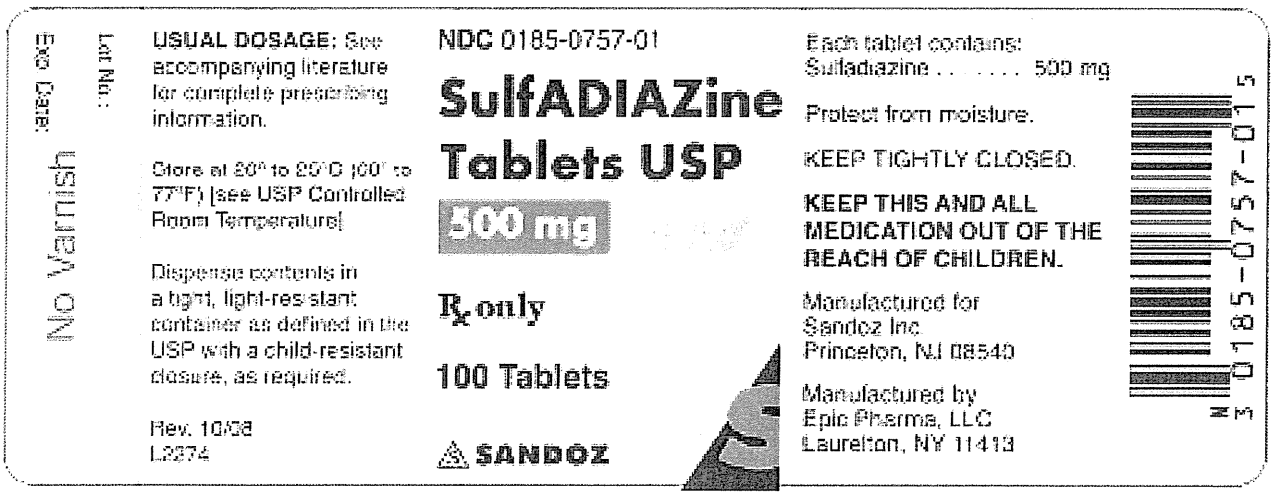

059 94242-0

AHFS Category 80:12

IPV

Poliovirus Vaccine Inactivated

IPOL®

℞ only

DESCRIPTION

IPOL®, Poliovirus Vaccine Inactivated, produced by Sanofi Pasteur SA, is a sterile suspension of three types of poliovirus: Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett). IPOL vaccine is a highly purified, inactivated poliovirus vaccine with enhanced potency. Each of the three strains of poliovirus is individually grown in vero cells, a continuous line of monkey kidney cells cultivated on microcarriers.[1,2] The cells are grown in Eagle MEM modified medium, supplemented with newborn calf serum tested for adventitious agents prior to use, originated from countries free of bovine spongiform encephalopathy. For viral growth the culture medium is replaced by M-199, without calf serum. This culture technique and improvements in purification, concentration and standardization of poliovirus antigen produce a more potent and consistent immunogenic vaccine than the inactivated poliovirus vaccine (IPV) available in the US prior to 1988.[3,4]

After clarification and filtration, viral suspensions are concentrated by ultrafiltration, and purified by three liquid chromatography steps; one column of anion exchanger, one column of gel filtration and again one column of anion exchanger. After re-equilibration of the purified viral suspension, with Medium M-199 and adjustment of the antigen titer, the monovalent viral suspensions are inactivated at +37°C for at least 12 days with 1:4000 formalin.

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. For each lot of IPOL vaccine, D-antigen content is determined *in vitro* using the D-antigen ELISA assay and immunogenicity is determined by *in vivo* testing in animals. IPOL vaccine is produced from vaccine concentrates diluted with M-199 medium. Also present are 0.5% of 2-phenoxyethanol and a maximum of 0.02% of formaldehyde per dose as preservatives. 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 residual calf serum protein is less than 1 ppm in the final vaccine.

The vaccine is clear and colorless and should be administered intramuscularly or subcutaneously.

CLINICAL PHARMACOLOGY

Poliomyelitis is caused by poliovirus Types 1, 2, or 3. It is primarily spread by the fecal-oral route of transmission but may also be spread by the pharyngeal route.

Approximately 90% to 95% of poliovirus infections are asymptomatic. Nonspecific illness with low-grade fever and sore throat (minor illness) occurs in 4% to 8% of infections. Aseptic meningitis occurs in 1% to 5% of patients a few days after the minor illness has resolved. Rapid onset of asymmetric acute flaccid paralysis occurs in 0.1% to 2% of infections, and residual paralytic disease involving motor neurons (paralytic poliomyelitis) occurs in approximately 1 per 1,000 infections.[5]

Prior to the introduction of inactivated poliovirus vaccines in 1955, large outbreaks of poliomyelitis occurred each year in the United States (US). The annual incidence of paralytic disease of 11.4 cases/100,000 population declined to 0.5 cases by the time oral poliovirus vaccine (OPV) was introduced in 1961. Incidence continued to decline thereafter to a rate of 0.002 to 0.005 cases per 100,000 population. Of the 127 cases of paralytic poliomyelitis reported in the US between 1980 and 1994, six were imported cases (caused by wild polioviruses), two were "indeterminate" cases, and 119 were vaccine associated paralytic poliomyelitis (VAPP) cases associated with the use of live, attenuated oral poliovirus vaccine (OPV).[6] An all IPV schedule was adopted in 1999, to eliminate VAPP cases.[7]

Poliovirus Vaccine Inactivated induces the production of neutralizing antibodies against each type of virus which are related to protective efficacy. Antibody response in most children were induced after receiving fewer doses[8] of IPV vaccine than the vaccine available in the United States prior to 1988.

Studies in developed[8] and developing[9,10] countries with a similar enhanced IPV manufactured by the same process as IPOL vaccine in primary monkey kidney cells have shown a direct relationship exists between the antigenic content of the vaccine, the frequency of seroconversion, and resulting antibody titer. Approval in the US was based upon demonstration of immunogenicity and safety in US children.[11]

In the US, 219 infants received three doses of a similar enhanced IPV at two, four and eighteen months of age manufactured by the same process as IPOL vaccine except the cell substrate for IPV was using primary monkey kidney cells. Seroconversion to all three types of poliovirus was demonstrated in 99% of these infants after two doses of vaccine given at 2 and 4 months of age. Following the third dose of vaccine at 18 months of age, neutralizing antibodies were present at a level of ≥1:10 in 99.1% of children to Type 1 and 100% of children to Types 2 and 3 polioviruses.[3]

IPOL vaccine was administered to more than 700 infants between 2 to 18 months of age during three clinical studies conducted in the US using IPV only schedules and sequential IPV-OPV schedules.[12,13] Seroprevalence rates for detectable serum neutralizing antibody (DA) at a ≥1:4 dilution were 95% to 100% (Type 1); 97% to 100% (Type 2) and 96% to 100% (Type 3) after two doses of IPOL vaccine depending on studies.

TABLE 1 US STUDIES WITH IPOL VACCINE ADMINISTERED USING IPV ONLY OR SEQUENTIAL IPV-OPV SCHEDULES

Age (months) for				Post Dose 2				Post Dose 3				Pre Booster				Post Booster			
2	4	6	12 to 18		Type 1	Type 2	Type 3		Type 1	Type 2	Type 3		Type 1	Type 2	Type 3		Type 1	Type 2	Type 3
Dose 1	Dose 2	Dose 3	Booster	N*	%DA**	%DA	%DA	N*	%DA	%DA	%DA	N*	%DA	%DA	%DA	N*	%DA	%DA	%DA
STUDY 1[11¶]																			
I(s)	I(s)	NA†	I(s)	56	97	100	97		–	–	–	53	91	97	93	53	97	100	100
O	O	NA	O	22	100	100	100		–	–	–	22	78	91	78	20	100	100	100
I(s)	O	NA	O	17	95	100	95		–	–	–	17	95	100	95	17	100	100	100
I(s)	I(s)	NA	O	17	100	100	100		–	–	–	16	100	100	94	16	100	100	100
STUDY 2[10§]																			
I(c)	I(c)	NA	I(s)	94	98	97	96		–	–	–	100	92	95	88	97	100	100	100
I(s)	I(s)	NA	I(s)	68	99	100	99		–	–	–	72	100	100	94	75	100	100	100
I(c)	I(c)	NA	O	75	95	99	96		–	–	–	77	86	97	82	78	100	100	97
I(s)	I(s)	NA	O	101	99	99	95		–	–	–	103	99	97	89	107	100	100	100
STUDY 3[10§]																			
I(c)	I(c)	I(c)	O	91	98	99	100	91	100	100	100	41	100	100	100	40	100	100	100
I(c)	I(c)	O	O	96	100	98	99	94	100	100	99	47	100	100	100	45	100	100	100
I(c)	I(c)	I(c) + O	O	91	96	97	100	85	100	100	100	47	100	100	100	46	100	100	100

* N = Number of children from whom serum was available
** Detectable antibody (neutralizing titer ≥1:4)
† NA – No poliovirus vaccine administered
¶ IPOL vaccine given subcutaneously
§ IPOL vaccine given intramuscularly
I IPOL vaccine given either separately in association with DTP in two sites (s) or combined (c) with DTP in a dual chambered syringe
O OPV

In one study,[13] the persistence of DA in infants receiving two doses of IPOL vaccine at 2 and 4 months of age was 91% to 100% (Type 1), 97% to 100% (Type 2), and 93% to 94% (Type 3) at twelve months of age. In another study,[12] 86% to 100% (Type 1), 95% to 100% (Type 2), and 82% to 94% (Type 3) of infants still had DA at 18 months of age.

In trials and field studies conducted outside the US, IPOL vaccine, or a combination vaccine containing IPOL vaccine and DTP, was administered to more than 3,000 infants between 2 to 18 months of age using IPV only schedules and immunogenicity data are available from 1,485 infants. After two doses of vaccine given during the first year of life, seroprevalence rates for detectable serum neutralizing antibody (neutralizing titer ≥1:4) were 88% to 100% (Type 1); 84% to 100% (Type 2) and 94% to 100% (Type 3) of infants, depending on studies. When three doses were given during the first year of life, post-dose 3 DA ranged between 93% to 100% (Type 1); 89% to 100% (Type 2) and 97% to 100% (Type 3) and reached 100% for Types 1, 2, and 3 after the fourth dose given during the second year of life (12 to 18 months of age).[14]

In infants immunized with three doses of an unlicensed combination vaccine containing IPOL vaccine and DTP given during the first year of life, and a fourth dose given during the second year of life, the persistence of detectable neutralizing antibodies was 96%, 96% and 97% against poliovirus Types 1, 2, and 3, respectively, at six years of age. DA reached 100% for all types after a booster dose of IPOL vaccine combined with DTP vaccine.[11] A survey of Swedish children and young adults given a Swedish IPV only schedule demonstrated persistence of detectable serum neutralizing antibody for at least 10 years to all three types of poliovirus.[15]

IPV is able to induce secretory antibody (IgA) produced in the pharynx and gut and reduces pharyngeal excretion of poliovirus Type 1 from 75% in children with neutralizing antibodies at levels less than 1:8 to 25% in children with neutralizing antibodies at levels more than 1:64.[4,14,16-22] There is also evidence of induction of herd immunity with IPV,[15,23-26] and that this herd immunity is sufficiently maintained in a population vaccinated only with IPV.[26]

VAPP has not been reported in association with administration of IPOL vaccine.[27] It is expected that an IPV only schedule will eliminate the risk of VAPP in both recipients and contacts compared to a schedule that included OPV.[7]

INDICATIONS AND USAGE

IPOL vaccine is indicated for active immunization of infants (as young as 6 weeks of age), children and adults for the prevention of poliomyelitis caused by poliovirus Types 1, 2, and 3.[28]

INFANTS, CHILDREN AND ADOLESCENTS

General Recommendations

It is recommended that all infants (as young as 6 weeks of age), unimmunized children and adolescents not previously immunized be vaccinated routinely against paralytic poliomyelitis.[29] Following the eradication of poliomyelitis caused by wild poliovirus from the Western Hemisphere (including North and South America).[30] An IPV-only schedule was recommended to eliminate VAPP.[7]

All children should receive four doses of IPV at ages 2, 4, 6 to 18 months and 4 to 6 years. OPV is no longer available in the US and is not recommended for routine immunization.[7] OPV is only recommended for special circumstances including the control of outbreaks.

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 IPOL vaccine.

Children Incompletely Immunized

Children of all ages should have their immunization status reviewed and be considered for supplemental immunization as follows for adults. Time intervals between doses longer than those recommended for routine primary immunization do not necessitate additional doses as long as a final total of four doses is reached (see **DOSAGE AND ADMINISTRATION** section).

ADULTS

General Recommendations

Routine primary poliovirus vaccination of adults (generally those 18 years of age or older) residing in the US is not recommended. Unimmunized adults who are potentially exposed to wild poliovirus and have not been adequately immunized should receive polio vaccination in accordance with the schedule given in the **DOSAGE AND ADMINISTRATION** section.[28]

Persons with previous wild poliovirus disease who are incompletely immunized or unimmunized should be given additional doses of IPOL vaccine if they fall into one or more categories listed previously.

The following categories of adults are at an increased risk of exposure to wild polioviruses:[28,31]

- 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.

IMMUNODEFICIENCY AND ALTERED IMMUNE STATUS

IPOL vaccine should be used in all patients with immunodeficiency diseases and members of such patients' households when vaccination of such persons is indicated. This includes patients with asymptomatic HIV infection, AIDS or AIDS-Related Complex, severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation. Immunogenicity of IPOL vaccine in individuals receiving immunoglobulin could be impaired and patients with an altered immune state may or may not develop a protective response against paralytic poliomyelitis after administration of IPV.[32]

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

Use with other vaccines: refer to **DOSAGE AND ADMINISTRATION** section for this information.

CONTRAINDICATIONS

IPOL vaccine is contraindicated in persons with a history of hypersensitivity to any component of the vaccine, including 2-phenoxyethanol, formaldehyde, neomycin, streptomycin and polymyxin B.

No further doses should be given if anaphylaxis or anaphylactic shock occurs within 24 hours of administration of one dose of vaccine.

Vaccination of persons with an acute, febrile illness should be deferred until after recovery; however, minor illness, such as mild upper respiratory infection, with or without low grade fever, are not reasons for postponing vaccine administration.

WARNINGS

Neomycin, streptomycin, polymyxin B, 2-phenoxyethanol, and formaldehyde are used in the production of this vaccine. Although purification procedures eliminate measurable amounts of these substances, traces may be present (see **DESCRIPTION** section) and allergic reactions may occur in persons sensitive to these substances (see **CONTRAINDICATIONS** section).

Systemic adverse reactions reported in infants receiving IPV concomitantly at separate sites or combined with DTP have been similar to those associated with administration of DTP alone.[11] Local reactions are usually mild and transient in nature.

Although no causal relationship between IPOL vaccine and Guillain-Barré Syndrome (GBS) has been established,[28] GBS has been temporally related to administration of another inactivated poliovirus vaccine. Deaths have been reported in temporal association with the administration of IPV (see **ADVERSE REACTIONS** section).

PRECAUTIONS

GENERAL

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 to the vaccine or similar vaccines.

Health-care providers should question the patient, parent or guardian about reactions to a previous dose of this product, or similar product.

Epinephrine Injection (1:1000) and other appropriate agents should be available to control immediate allergic reactions.

Health-care providers should obtain the previous immunization history of the vaccinee, and inquire about the current health status of the vaccinee.

Immunodeficient patients or patients under immunosuppressive therapy may not develop a protective immune response against paralytic poliomyelitis after administration of IPV.

Administration of IPOL vaccine is not contraindicated in individuals infected with HIV.[33,34,35]

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

INFORMATION FOR PATIENTS

Patients, parents, or guardians should be instructed to report any serious adverse reactions to their health-care provider.

The health-care provider should inform the patient, parent, or guardian of the benefits and risks of the vaccine.

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

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

DRUG INTERACTIONS

There are no known interactions of IPOL vaccine with drugs or foods. Concomitant administration, of other parenteral vaccines, with separate syringes at separate sites, is not contraindicated. The first two doses of IPOL vaccine may be administered at separate sites using separate syringes concomitantly with DTaP, acellular pertussis, *Haemophilus influenzae* type b (Hib), and hepatitis B vaccines. From historical data on the antibody responses to diphtheria, tetanus, acellular pertussis, Hib, or hepatitis B vaccines used concomitantly or in combination with IPOL vaccine, no interferences have been observed on the immunological end points accepted for clinical protection.[11,16,36] (See **DOSAGE AND ADMINISTRATION** section.)

If IPOL vaccine has been administered to persons receiving immunosuppressive therapy, an adequate immunologic response may not be obtained. (See **PRECAUTIONS** – GENERAL section.)

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate carcinogenic potential or impairment of fertility have not been conducted.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with IPOL vaccine. It is also not known whether IPOL vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. IPOL vaccine should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether IPOL vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when IPOL vaccine is administered to a nursing woman.

PEDIATRIC USE

SAFETY AND EFFECTIVENESS OF IPOL VACCINE IN INFANTS BELOW SIX WEEKS OF AGE HAVE NOT BEEN ESTABLISHED.[12,20] (See **DOSAGE AND ADMINISTRATION** section.)

In the US, infants receiving two doses of IPV at 2 and 4 months of age, the seroprevalence to all three types of poliovirus was demonstrated in 95% to 100% of these infants after two doses of vaccine.[12,13]

ADVERSE REACTIONS

BODY SYSTEM AS A WHOLE

In earlier studies with the vaccine grown in primary monkey kidney cells, transient local reactions at the site of injection were observed.[3] Erythema, induration and pain occurred in 3.2%, 1% and 13%, respectively, of vaccinees within 48 hours post-vaccination. Temperatures of ≥39°C (≥102°F) were reported in 38% of vaccinees. Other symptoms included irritability, sleepiness, fussiness, and crying. Because IPV was given in a different site but concurrently with Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP), these systemic reactions could not be attributed to a specific vaccine. However, these systemic reactions were comparable in frequency and severity to that reported for DTP given alone without IPV.[12] Although no causal relationship has been established, deaths have occurred in temporal association after vaccination of infants with IPV.[37]

Four additional US studies using IPOL vaccine in more than 1,300 infants,[12] between 2 to 18 months of age administered with DTP at the same time at separate sites or combined have demonstrated that local and systemic reactions were similar when DTP was given alone.

TABLE 2[12] PERCENTAGE OF INFANTS PRESENTING WITH LOCAL OR SYSTEMIC REACTIONS AT 6, 24, AND 48 HOURS OF IMMUNIZATION WITH IPOL VACCINE ADMINISTERED INTRAMUSCULARLY CONCOMITANTLY AT SEPARATE SITES WITH SANOFI¶ WHOLE-CELL DTP VACCINE AT 2 AND 4 MONTHS OF AGE AND WITH SANOFI ACELLULAR PERTUSSIS VACCINE (TRIPEDIA®) AT 18 MONTHS OF AGE

REACTION	AGE AT IMMUNIZATION								
	2 Months (n=211)			4 Months (n=206)			18 Months† (n=74)		
	6 Hrs.	24 Hrs.	48 Hrs.	6 Hrs.	24 Hrs.	48 Hrs.	6 Hrs.	24 Hrs.	48 Hrs.
Local, IPOL vaccine alone§									
Erythema >1"	0.5%	0.5%	0.5%	1.0%	0.0%	0.0%	1.4%	0.0%	0.0%
Swelling	11.4%	5.7%	0.9%	11.2%	4.9%	1.9%	2.7%	0.0%	0.0%
Tenderness	29.4%	8.5%	2.8%	22.8%	4.4%	1.0%	13.5%	4.1%	0.0%
Systemic*									
Fever >102.2°F	1.0%	0.5%	0.5%	2.0%	0.5%	0.0%	0.0%	0.0%	4.2%
Irritability	64.5%	24.6%	17.5%	49.5%	25.7%	11.7%	14.7%	6.7%	8.0%
Tiredness	60.7%	31.8%	7.1%	38.8%	18.4%	6.3%	9.3%	5.3%	4.0%
Anorexia	16.6%	8.1%	4.3%	6.3%	4.4%	2.4%	2.7%	1.3%	2.7%
Vomiting	1.9%	2.8%	2.8%	1.9%	1.5%	1.0%	1.3%	1.3%	0.0%
Persistent Crying	Percentage of infants within 72 hours after immunization was 0.0% after dose one, 1.4% after dose two, and 0.0% after dose three.								

¶ Sanofi Pasteur Inc. formerly known as Aventis Pasteur Inc.
§ Data are from the IPOL vaccine administration site, given intramuscularly.
* The adverse reaction profile includes the concomitant use of Sanofi whole-cell DTP vaccine or Tripedia vaccine with IPOL vaccine. Rates are comparable in frequency and severity to that reported for whole-cell DTP given alone.
† Children who have been vaccinated with Tripedia vaccine.

DIGESTIVE SYSTEM
Anorexia and vomiting occurred with frequencies not significantly different as reported when DTP was given alone without IPV or OPV.[12]

NERVOUS SYSTEM
Although no causal relationship between IPOL vaccine and GBS has been established,[28] GBS has been temporally related to administration of another inactivated poliovirus vaccine.

Reporting of Adverse Events
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 US 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 that vaccine.[38,39,40]

Reporting by parents or guardians of all adverse events after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by health-care providers to the US 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.[38,39,40]

Health-care providers also should report these events to the Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION
Before administration, parenteral drug products should be checked visually for any deviation from normal appearance including container integrity. The syringe or vial and its packaging should be inspected prior to use for evidence of leakage, premature activation of the plunger, or a faulty tip seal. If evidence of such defects are observed, the syringe should not be used.

After preparation of the injection site, immediately administer IPOL vaccine intramuscularly or subcutaneously. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. In older children and adults IPOL vaccine should be administered intramuscularly or subcutaneously in the deltoid area.

The syringe is intended for single use only, must not be reused, and must be disposed of properly and promptly following its use.

To help avoid HIV (AIDS), HBV (Hepatitis), and other infectious diseases due to accidental needlesticks, contaminated needles should not be recapped or removed, unless there is no alternative or that such action is required by a specific medical procedure.

Care should be taken to avoid administering the injection into or near blood vessels and nerves. If blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedures using a new dose of vaccine administered at a different site.

DO NOT ADMINISTER VACCINE INTRAVENOUSLY.

Children
The primary series of IPOL vaccine consists of three 0.5 mL doses administered intramuscularly or subcutaneously, preferably eight or more weeks apart and usually at ages 2, 4, and 6 to 18 months. Under no circumstances should the vaccine be given more frequently than four weeks apart. The first immunization may be administered as early as six weeks of age. For this series, a booster dose of IPOL vaccine is administered at 4 to 6 years of age.[41]

Use with Other Vaccines
From historical data on the antibody responses to diphtheria, tetanus, whole-cell or acellular pertussis, Hib, or hepatitis B vaccines used concomitantly with IPOL vaccine, no interferences have been observed on the immunological end points accepted for clinical protection.[11,16,36] (See DRUG INTERACTIONS section.)

If the third dose of IPOL vaccine is given between 12 to 18 months of age, it may be desirable to administer this dose with Measles, Mumps, and Rubella (MMR) vaccine and/or other vaccines using separate syringes at separate sites,[28] but no data on the immunological interference between IPOL vaccine and these vaccines exist.

Use in Previously Vaccinated Children
Children and adolescents with a previously incomplete series of polio vaccine should receive sufficient additional doses of IPOL vaccine to complete the series. OPV is no longer recommended for routine immunization and is recommended only in special circumstances[7] (see **General Recommendations** section).

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

The need to routinely administer additional doses is unknown at this time.[28]

Adults
Unvaccinated Adults
A primary series of IPOL vaccine is recommended for unvaccinated adults at increased risk of exposure to poliovirus. While the responses of adults to primary series have not been studied, the recommended schedule for adults is two doses given at a 1 to 2 month interval and a third dose given 6 to 12 months later. If less than 3 months but more than 2 months are available before protection is needed, three doses of IPOL vaccine should be given at least 1 month apart. Likewise, if only 1 or 2 months are available, two doses of IPOL vaccine should be given at least 1 month apart. If less than 1 month is available, a single dose of IPOL vaccine is recommended.[28]

Incompletely Vaccinated Adults
Adults who are at an increased risk of exposure to poliovirus and who have had at least one dose of OPV, fewer than three doses of conventional IPV or a combination of conventional IPV or OPV totaling fewer than three doses should receive at least one dose of IPOL vaccine. Additional doses needed to complete a primary series should be given if time permits.[28]

Completely Vaccinated Adults
Adults who are at an increased risk of exposure to poliovirus and who have previously completed a primary series with one or a combination of polio vaccines can be given a dose of IPOL vaccine.

The preferred injection site of IPOL vaccine for adults is in the deltoid area.

HOW SUPPLIED
Syringe, without needle, 0.5 mL (10 per package).
Product No. 49281-860-55

Vial, 10 Dose – Product No. 49281-860-10

CPT® Code: 90713

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STORAGE
The vaccine is stable if stored in the refrigerator at 2°C to 8°C (35°F to 46°F). The vaccine must not be frozen.

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創薬基盤推進研究事業：政策創薬総合研究事業

厚生労働省　エイズ治療薬研究班

国内未承認エイズ治療薬等を用いたＨＩＶ感染症治療薬及びＨＩＶ感染症至適治療法の開発に係る応用研究

平成２３年度　総括・分担研究報告書

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