WARNINGS

Hypersensitivity Reaction: Fatal hypersensitivity reactions have been associated with therapy with ZIAGEN. Patients developing signs or symptoms of hypersensitivity (which include fever; skin rash; fatigue; gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain; and respiratory symptoms such as pharyngitis, dyspnea, or cough) should discontinue ZIAGEN as soon as a hypersensitivity reaction is first suspected, and should seek medical evaluation immediately. To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, ZIAGEN should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases, gastroenteritis, or reactions to other medications).

ZIAGEN SHOULD NOT be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death.

Severe or fatal hypersensitivity reactions can occur within hours after reintroduction of ZIAGEN in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy.

When therapy with ZIAGEN has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, abacavir should **NOT** be reintroduced. If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Patients should be made aware that a hypersensitivity reaction can occur with reintroduction of abacavir, and that abacavir reintroduction should be undertaken only if medical care can be readily accessed by the patient or others (see ADVERSE REACTIONS).

In clinical trials, hypersensitivity reactions have been reported in approximately 5% of adult and pediatric patients receiving abacavir. Symptoms usually appear within the first 6 weeks of treatment with ZIAGEN although these reactions may occur at any time during therapy (see PRECAUTIONS: Information for Patients and ADVERSE REACTIONS).

Abacavir Hypersensitivity Reaction Registry: To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. Physicians should register patients by calling 1-800-270-0425.

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering ZIAGEN to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with ZIAGEN should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

PRECAUTIONS

General: Abacavir should always be used in combination with other antiretroviral agents. Abacavir should not be added as a single agent when antiretroviral regimens are changed due to

loss of virologic response.

Therapy-Experienced Patients: In clinical trials, patients with prolonged prior nucleoside reverse transcriptase inhibitor (NRTI) exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients (see MICROBIOLOGY: Cross-Resistance).

Fat Redistribution: Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information for Patients: PATIENTS SHOULD BE ADVISED THAT A MEDICATION GUIDE AND WARNING CARD SUMMARIZING THE SYMPTOMS OF ABACAVIR HYPERSENSITIVITY REACTIONS SHOULD BE DISPENSED BY THE PHARMACIST WITH EACH NEW PRESCRIPTION AND REFILL OF ZIAGEN. THE COMPLETE TEXT OF THE MEDICATION GUIDE IS REPRINTED AT THE END OF THIS DOCUMENT. PATIENTS SHOULD BE INSTRUCTED TO CARRY THE WARNING CARD WITH THEM.

Patients should be advised of the possibility of a hypersensitivity reaction to ZIAGEN that may result in death. Patients developing signs or symptoms of hypersensitivity (which include fever; skin rash; fatigue; gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain; and respiratory symptoms such as sore throat, shortness of breath, or cough) should discontinue treatment with ZIAGEN and seek medical evaluation immediately. **ZIAGEN SHOULD NOT be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death.** Patients who have interrupted ZIAGEN for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply) should be made aware that a severe or fatal hypersensitivity reaction can occur with reintroduction of abacavir. Patients should be instructed not to reintroduce abacavir without medical consultation and that reintroduction of abacavir should be undertaken only if medical care can be readily accessed by the patient or others (see ADVERSE REACTIONS and WARNINGS).

ZIAGEN is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using ZIAGEN. Patients should be advised that the use of ZIAGEN has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Patients should be advised that the long-term effects of ZIAGEN are unknown at this time.

ZIAGEN Tablets and Oral Solution are for oral ingestion only.

Patients should be advised of the importance of taking ZIAGEN exactly as it is prescribed.

Drug Interactions: Pharmacokinetic properties of abacavir were not altered by the addition of either lamivudine or zidovudine or the combination of lamivudine and zidovudine. No clinically

significant changes to lamivudine or zidovudine pharmacokinetics were observed following concomitant administration of abacavir.

Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure (see CLINICAL PHARMACOLOGY: Drug Interactions).

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily) with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Abacavir was administered orally at 3 dosage levels to separate groups of mice (60 females and 60 males per group) and rats (56 females and 56 males in each group) in carcinogenicity studies. Single doses were 55, 110, and 330 mg/kg/day in mice and 30, 120, and 600 mg/kg/day in rats. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose (300 mg twice daily). It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. At systemic exposures approximately 9 times higher than that in humans at the therapeutic dose, abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay.

Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Abacavir had no adverse effects on the mating performance or fertility of male and female rats at doses of up to 500 mg/kg/day, a dose expected to produce exposures approximately 8-fold higher than that in humans at the therapeutic dose based on body surface area comparisons.

Pregnancy: Pregnancy Category C. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Developmental toxicity (depressed fetal body weight and reduced crown-rump length) and increased incidences of fetal anasarca and skeletal malformations were observed when rats were treated with abacavir at doses of 1,000 mg/kg during organogenesis. This dose produced 35 times the human exposure, based on AUC. In a fertility study, evidence of toxicity to the developing embryo and fetuses (increased resorptions, decreased fetal body weights) occurred only at 500 mg/kg/day. The offspring of female rats treated with abacavir at 500 mg/kg/day (beginning at embryo implantation and ending at weaning) showed increased incidence of stillbirth and lower body weights throughout life. In the rabbit, there was no evidence of drug-related developmental toxicity and no increases in fetal malformations at doses up to 700 mg/kg (8.5 times the human exposure at the recommended dose, based on AUC).

There are no adequate and well-controlled studies in pregnant women. ZIAGEN should be used during pregnancy only if the potential benefits outweigh the risk.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to ZIAGEN, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

Although it is not known if abacavir is excreted in human milk, abacavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving ZIAGEN.**

Pediatric Use: The safety and effectiveness of ZIAGEN have been established in pediatric patients aged 3 months to 13 years. Use of ZIAGEN in these age groups is supported by pharmacokinetic studies and evidence from adequate and well-controlled studies of ZIAGEN in adults and pediatric patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics: Special Populations: Pediatric Patients, INDICATIONS AND USAGE: Description of Clinical Studies, WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

Geriatric Use: Clinical studies of ZIAGEN did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Hypersensitivity Reaction: Fatal hypersensitivity reactions have been associated with therapy with ZIAGEN. Therapy with ZIAGEN SHOULD NOT be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death. Patients developing signs or symptoms of hypersensitivity should discontinue treatment as soon as a hypersensitivity reaction is first suspected, and should seek medical evaluation immediately. To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, ZIAGEN should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases, gastroenteritis, or reactions to other medications).

Severe or fatal hypersensitivity reactions can occur within hours after reintroduction of ZIAGEN in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy (see WARNINGS and PRECAUTIONS: Information for Patients).

When therapy with ZIAGEN has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, abacavir should **NOT** be reintroduced. If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of hypersensitivity reaction. Patients should be made aware that a hypersensitivity reaction can occur with reintroduction of abacavir, and that abacavir reintroduction should be undertaken only if medical care can be readily accessed by the patient or others (see WARNINGS).

In clinical studies, approximately 5% of adult and pediatric patients receiving ZIAGEN developed a hypersensitivity reaction. This reaction is characterized by the appearance of symptoms indicating multi-organ/body system involvement. Symptoms usually appear within the first 6 weeks of treatment with ZIAGEN, although these reactions may occur at any time during therapy. Frequently observed signs and symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain. Other signs and symptoms include malaise, lethargy, myalgia, myolysis, arthralgia, edema, pharyngitis, cough, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), dyspnea, headache, and paresthesia. Some patients who experienced a hypersensitivity reaction were initially thought to have acute onset or worsening respiratory disease. The diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of acute onset respiratory diseases, even if alternative respiratory diagnoses (pneumonia, bronchitis, pharyngitis, or flu-like illness) are possible.

Physical findings include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities include elevated liver function tests, increased creatine phosphokinase or creatinine, and lymphopenia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions. Symptoms worsen with continued therapy but often resolve upon discontinuation of ZIAGEN.

Risk factors that may predict the occurrence or severity of hypersensitivity to abacavir have not been identified.

Therapy-Naive Adults: Selected clinical adverse events with a ≥5% frequency during therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with lamivudine 150 mg twice daily and zidovudine 300 mg twice daily from CNAAB3003 are listed in Table 2.

Table 2. Selected Clinical Adverse Events Grades 1-4 (≥5% Frequency) in Therapy-Naive Adults (CNAAB3003) Through 16 Weeks of Treatment

Adverse Event	ZIAGEN/Lamivudine/Zidovudine (n = 83)	Lamivudine/Zidovudine (n = 81)
Nausea	47%	41%
Nausea and vomiting	16%	11%
Diarrhea	12%	11%
Loss of appetite/anorexia	11%	10%
Insomnia and other sleep disorders	7%	5%

Selected clinical adverse events with a ≥5% frequency during therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from CNAAB3005 are listed in Table 3.

Table 3. Selected Clinical Adverse Events Grades 1-4 (≥5% Frequency) in Therapy-Naive Adults (CNAAB3005) Through 48 Weeks of Treatment

Adverse Event	ZIAGEN/Lamivudine/Zidovudine (n = 262)	Indinavir/Lamivudine/Zidovudine (n = 264)
Nausea	60%	61%
Nausea and vomiting	30%	27%
Diarrhea	26%	27%
Loss of appetite/anorexia	15%	11%
Insomnia and other sleep disorders	13%	12%
Fever and/or chills	20%	13%
Headache	28%	25%
Malaise and/or fatigue	44%	41%

Five subjects in the abacavir arm of study CNAAB3005 experienced worsening of pre-existing depression compared to none in the indinavir arm. The background rates of pre-existing depression were similar in the 2 treatment arms.

Pediatric Patients: Selected clinical adverse events with a ≥5% frequency during therapy with ZIAGEN 8 mg/kg twice daily, lamivudine 4 mg/kg twice daily, and zidovudine 180 mg/m^2 twice daily compared with lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m^2 twice daily from CNAA3006 are listed in Table 4.

Table 4. Selected Clinical Adverse Events Grades 1-4 (≥5% Frequency) in Therapy-Experienced Pediatric Patients (CNAA3006) Through 16 Weeks of Treatment

Adverse Event	ZIAGEN/Lamivudine/Zidovudine (n = 102)	Lamivudine/Zidovudine (n = 103)
Nausea and vomiting	38%	18%
Fever	19%	12%
Headache	16%	12%
Diarrhea	16%	15%
Skin rashes	11%	8%
Loss of appetite/anorexia	9%	2%

Laboratory Abnormalities: Laboratory abnormalities (anemia, neutropenia, liver function test abnormalities, and CPK elevations) were observed with similar frequencies in the 2 treatment groups in studies CNAAB3003 and CNAA3006. Mild elevations of blood glucose were more frequent in subjects receiving abacavir. In study CNAAB3003, triglyceride elevations (all grades) were more common on the abacavir arm (25%) than on the placebo arm (11%). In study CNAAB3005, hyperglycemia and disorders of lipid metabolism occurred with similar frequency in the abacavir and indinavir treatment arms.

Other Adverse Events: In addition to adverse events in Tables 2, 3, and 4, other adverse events observed in the expanded access program were pancreatitis and increased GGT.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during use of abacavir in clinical practice.

Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to abacavir, or a combination of these factors.

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).

Skin: Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

There have also been reports of erythema multiforme with abacavir use.

OVERDOSAGE

There is no known antidote for ZIAGEN. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION

A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill. To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. Physicians should register patients by calling 1-800-270-0425.

ZIAGEN may be taken with or without food.

Adults: The recommended oral dose of ZIAGEN for adults is 300 mg twice daily in combination with other antiretroviral agents.

Adolescents and Pediatric Patients: The recommended oral dose of ZIAGEN for adolescents and pediatric patients 3 months to up to 16 years of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents.

Dose Adjustment in Hepatic Impairment: The recommended dose of ZIAGEN in patients with mild hepatic impairment (Child-Pugh score 5 to 6) is 200 mg twice daily. To enable dose reduction, ZIAGEN Oral Solution (10 mL twice daily) should be used for the treatment of these patients. The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate to severe hepatic impairment, therefore ZIAGEN is contraindicated in these patients.

HOW SUPPLIED

ZIAGEN is available as tablets and oral solution.

ZIAGEN Tablets: Each tablet contains abacavir sulfate equivalent to 300 mg abacavir. The tablets are yellow, biconvex, capsule-shaped, film-coated, and imprinted with "GX 623" on one side with no marking on the reverse side. They are packaged as follows:

Bottles of 60 tablets (NDC 0173-0661-01).

Unit dose blister packs of 60 tablets (NDC 0173-0661-00). Each pack contains 6 blister cards of 10 tablets each.

Store at controlled room temperature of 20° to 25°C (68° to 77°F) (see USP).

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.

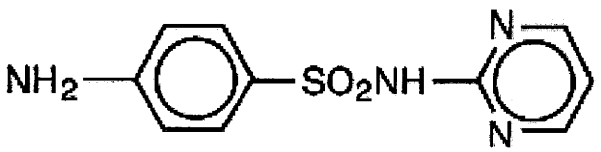
HOW SUPPLIED
Humatin Capsules, each containing paromomycin sulfate equivalent to 250 mg paromomycin, are supplied as follows
NDC 61570-529-10: Bottles of 100
Store at controlled room temperature 15°–30°C (59°–86°F).
Protect from moisture.
Rx only.
Prescribing Information as of November 2001.
Distributed 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
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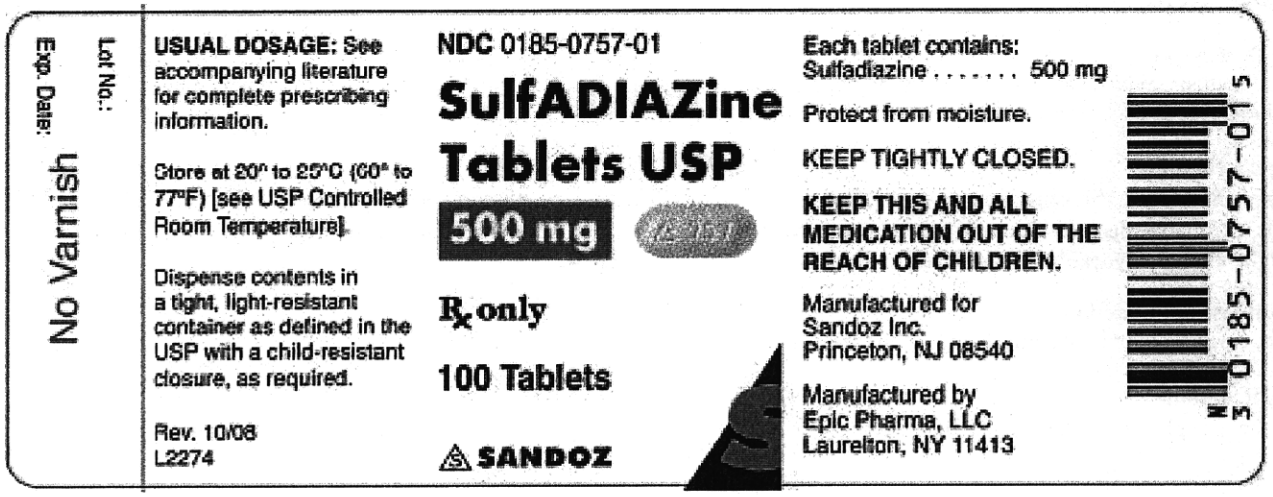

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Poliovirus Vaccine Inactivated

IPOL®

IPV

℞ 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 2 Dose 1	4 Dose 2	6 Dose 3	12 to 18 Booster	Post Dose 2 N*	Post Dose 2 Type 1 %DA**	Post Dose 2 Type 2 %DA	Post Dose 2 Type 3 %DA	Post Dose 3 N*	Post Dose 3 Type 1 %DA	Post Dose 3 Type 2 %DA	Post Dose 3 Type 3 %DA	Pre Booster N*	Pre Booster Type 1 %DA	Pre Booster Type 2 %DA	Pre Booster Type 3 %DA	Post Booster N*	Post Booster Type 1 %DA	Post Booster Type 2 %DA	Post Booster Type 3 %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.