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

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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21年度　総括・分担研究報告書

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