HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZIAGEN safely and effectively. See full prescribing information for ZIAGEN.

ZIAGEN (abacavir) tablets, for oral use
ZIAGEN (abacavir) oral solution
Initial U.S. Approval: 1998

WARNING: HYPERSENSITIVITY REACTIONS
See full prescribing information for complete boxed warning.

- **Serious and sometimes fatal hypersensitivity reactions have occurred with ZIAGEN (abacavir). (5.1)**
- **Hypersensitivity to ZIAGEN is a multi-organ clinical syndrome. (5.1)**
- **Patients who carry the HLA-B*5701 allele are at a higher risk of experiencing a hypersensitivity reaction to abacavir. (5.1)**
- **ZIAGEN is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. (4)**
- **Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)**
- **Following a hypersensitivity reaction to ZIAGEN, NEVER restart ZIAGEN or any other abacavir-containing product. (5.1)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	05/2018
Warnings and Precautions, Lactic Acidosis and Severe Hepatomegaly with Steatosis (5.2)	05/2018
Warnings and Precautions, Fat Redistribution (previous 5.4)	Removed 05/2018
Warnings and Precautions, Myocardial Infarction (5.4)	05/2018

---------- INDICATIONS AND USAGE----------

ZIAGEN, a nucleoside analogue human immunodeficiency virus (HIV-1) reverse transcriptase inhibitor, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

----------DOSAGE AND ADMINISTRATION----------

- Before initiating ZIAGEN, screen for the HLA-B*5701 allele. (2.1)
- Adults: 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily. (2.2)
- Pediatric Patients Aged 3 Months and Older: Administered either once or twice daily. Dose should be calculated on body weight (kg) and should not exceed 600 mg daily. (2.3)
- Patients with Hepatic Impairment: Mild hepatic impairment – 200 mg twice daily. (2.4)

---------- DOSAGE FORMS AND STRENGTHS----------

- Tablets: 300 mg scored (3)
- Oral Solution: 20 mg per mL (3)

---------- CONTRAINDICATIONS ----------

- Presence of HLA-B*5701 allele. (4)
- Prior hypersensitivity reaction to abacavir. (4)
- Moderate or severe hepatic impairment. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.2)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.3)

---------- ADVERSE REACTIONS ----------

- The most commonly reported adverse reactions of at least moderate intensity (incidence greater than or equal to 10%) in adult HIV-1 clinical trials were nausea, headache, malaise and fatigue, nausea and vomiting, and dreams/sleep disorders. (6.1)
- The most commonly reported adverse reactions of at least moderate intensity (incidence greater than or equal to 5%) in pediatric HIV-1 clinical trials were fever and/or chills, nausea and vomiting, skin rashes, and ear/nose/throat infections. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Methadone: An increased methadone dose may be required in a small number of patients. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

- Lactation: Women infected with HIV should be instructed not to breastfeed due to potential for HIV transmission. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HYPERSENSITIVITY REACTIONS

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with ZIAGEN (abacavir).

Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele *[see Warnings and Precautions (5.1)]*.

ZIAGEN is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients *[see Contraindications (4), Warnings and Precautions (5.1)]*. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with ZIAGEN or reinitiation of therapy with ZIAGEN, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue ZIAGEN immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible *[see Contraindications (4), Warnings and Precautions (5.1)]*.

Following a hypersensitivity reaction to ZIAGEN, NEVER restart ZIAGEN or any other abacavir-containing product because more severe symptoms, including death can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

ZIAGEN tablets and oral solution, in combination with other antiretroviral agents, are indicated for the treatment of human immunodeficiency virus (HIV-1) infection.

2 DOSAGE AND ADMINISTRATION

2.1 Screening for HLA-B*5701 Allele prior to Starting ZIAGEN

Screen for the HLA-B*5701 allele prior to initiating therapy with ZIAGEN *[see Boxed Warning, Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage for Adult Patients

The recommended dosage of ZIAGEN for adults is 600 mg daily, administered orally as either 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.

2.3 Recommended Dosage for Pediatric Patients

The recommended dosage of ZIAGEN oral solution in HIV-1-infected pediatric patients aged 3 months and older is 8 mg per kg orally twice daily or 16 mg per kg orally once-daily (up to a maximum of 600 mg daily) in combination with other antiretroviral agents.

ZIAGEN is also available as a scored tablet for HIV-1-infected pediatric patients weighing greater than or equal to 14 kg for whom a solid dosage form is appropriate. Before prescribing ZIAGEN tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow ZIAGEN tablets, the oral solution formulation should be prescribed. The recommended oral dosage of ZIAGEN tablets for HIV-1-infected pediatric patients is presented in Table 1.

Table 1. Dosing Recommendations for ZIAGEN Scored Tablets in Pediatric Patients

Weight(kg)	Once-Daily Dosing Regimen[a]	Twice-Daily Dosing Regimen		
		AM Dose	PM Dose	Total Daily Dose
14 to <20	1 tablet (300 mg)	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
≥20 to <25	1½ tablets (450 mg)	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥25	2 tablets (600 mg)	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

[a] Data regarding the efficacy of once-daily dosing is limited to subjects who transitioned from twice-daily dosing to once-daily dosing after 36 weeks of treatment *[see Clinical Studies (14.2)]*.

2.4 Recommended Dosage for Patients with Hepatic Impairment

The recommended dose of ZIAGEN in patients with mild hepatic impairment (Child-Pugh Class A) 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.

3 DOSAGE FORMS AND STRENGTHS

ZIAGEN tablets contain 300 mg of abacavir as abacavir sulfate. The tablets are yellow, biconvex, scored, capsule-shaped, film-coated, and imprinted with “GX 623” on both sides.

ZIAGEN oral solution contains 20 mg per mL of abacavir as abacavir sulfate. The solution is a clear to opalescent, yellowish, strawberry-banana-flavored liquid, which may turn brown over time.

4 CONTRAINDICATIONS

ZIAGEN is contraindicated in patients:

- who have the HLA-B*5701 allele *[see Warnings and Precautions (5.1)]*.
- with prior hypersensitivity reaction to abacavir *[see Warnings and Precautions (5.1)]*.

- with moderate or severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions have occurred with ZIAGEN (abacavir). These hypersensitivity reactions have included multi-organ failure and anaphylaxis and typically occurred within the first 6 weeks of treatment with ZIAGEN (median time to onset was 9 days); although abacavir hypersensitivity reactions have occurred any time during treatment *[see Adverse Reactions (6.1)]*. Patients who carry the HLA-B*5701 allele are at a higher risk of abacavir hypersensitivity reactions; although, patients who do not carry the HLA-B*5701 allele have developed hypersensitivity reactions. Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with abacavir-containing products where HLA-B*5701 screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when subjects carrying the HLA-B*5701 allele were excluded. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision making.

Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with ZIAGEN:

- All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with ZIAGEN or reinitiation of therapy with ZIAGEN, unless patients have a previously documented HLA-B*5701 allele assessment.
- ZIAGEN is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.
- Before starting ZIAGEN, review medical history for prior exposure to any abacavir-containing product. NEVER restart ZIAGEN or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status.
- To reduce the risk of a life-threatening hypersensitivity reaction, regardless of HLA-B*5701 status, discontinue ZIAGEN immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).
- If a hypersensitivity reaction cannot be ruled out, do not restart ZIAGEN or any other abacavir-containing products because more severe symptoms which may include life-threatening hypotension and death, can occur within hours.
- If a hypersensitivity reaction is ruled out, patients may restart ZIAGEN. Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life-threatening reactions within hours of reinitiating abacavir therapy. Therefore, reintroduction of ZIAGEN or any other abacavir-containing product is

recommended only if medical care can be readily accessed.

- A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

5.2 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including ZIAGEN. A majority of these cases have been in women. Female sex and obesity may be risk factors for the development of lactic acidosis and severe hepatomegaly with steatosis in patients treated with antiretroviral nucleoside analogues. 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.

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including ZIAGEN. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

5.4 Myocardial Infarction

Several prospective, observational, epidemiological studies have reported an association with the use of abacavir and the risk of myocardial infarction (MI). Meta-analyses of randomized, controlled, clinical trials have observed no excess risk of MI in abacavir-treated subjects as compared with control subjects. To date, there is no established biological mechanism to explain a potential increase in risk. In totality, the available data from the observational studies and from controlled clinical trials show inconsistency; therefore, evidence for a causal relationship between abacavir treatment and the risk of MI is inconclusive.

As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking).

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Serious and sometimes fatal hypersensitivity reactions *[see Boxed Warning, Warnings and*

Precautions (5.1)].

- Lactic acidosis and severe hepatomegaly with steatosis *[see Warnings and Precautions (5.2)]*.
- Immune reconstitution syndrome *[see Warnings and Precautions (5.3)]*.
- Myocardial infarction *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials Experience in Adult Subjects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Serious and Fatal Abacavir-Associated Hypersensitivity Reactions

In clinical trials, serious and sometimes fatal hypersensitivity reactions have occurred with abacavir *[see Boxed Warning, Warnings and Precautions (5.1)]*. These reactions have been characterized by 2 or more of the following signs or symptoms: (1) fever; (2) rash; (3) gastrointestinal symptoms (including nausea, vomiting, diarrhea, or abdominal pain); (4) constitutional symptoms (including generalized malaise, fatigue, or achiness); (5) respiratory symptoms (including dyspnea, cough, or pharyngitis). Almost all abacavir hypersensitivity reactions include fever and/or rash as part of the syndrome.

Other signs and symptoms have included lethargy, headache, myalgia, edema, arthralgia, and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, myolysis, and death have occurred in association with these hypersensitivity reactions. Physical findings have included lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and maculopapular or urticarial rash (although some patients had other types of rashes and others did not have a rash). There were reports of erythema multiforme. Laboratory abnormalities included elevated liver chemistries, elevated creatine phosphokinase, elevated creatinine, and lymphopenia, and abnormal chest x-ray findings (predominantly infiltrates, which were localized).

Additional Adverse Reactions with Use of ZIAGEN

Therapy-Naive Adults: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or equal to 5% frequency during therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily from CNA30024 are listed in Table 2.

Table 2. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, Greater than or Equal to 5% Frequency) in Therapy-Naive Adults (CNA30024[a]) through 48 Weeks of Treatment

Adverse Reaction	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Dreams/sleep disorders	10%	10%
Drug hypersensitivity	9%	<1%[b]
Headaches/migraine	7%	11%
Nausea	7%	11%
Fatigue/malaise	7%	10%
Diarrhea	7%	6%
Rashes	6%	12%
Abdominal pain/gastritis/ gastrointestinal signs and symptoms	6%	8%
Depressive disorders	6%	6%
Dizziness	6%	6%
Musculoskeletal pain	6%	5%
Bronchitis	4%	5%
Vomiting	2%	9%

[a] This trial used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the trial, suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 subjects in the abacavir group and 3% of 325 subjects in the zidovudine group.

[b] Ten (3%) cases of suspected drug hypersensitivity were reclassified as not being due to abacavir following unblinding.

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or equal to 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 CNA3005 are listed in Table 3.

14 CLINICAL STUDIES

14.1 Adult Trials

Therapy-Naive Adults

CNA30024 was a multicenter, double-blind, controlled trial in which 649 HIV-1-infected, therapy-naive adults were randomized and received either ZIAGEN (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily); or zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily). The duration of double-blind treatment was at least 48 weeks. Trial participants were male (81%), white (51%), black (21%), and Hispanic (26%). The median age was 35 years; the median pretreatment CD4+ cell count was 264 cells per mm^3, and median plasma HIV-1 RNA was 4.79 log_{10} copies per mL. The outcomes of randomized treatment are provided in Table 7.

Table 7. Outcomes of Randomized Treatment through Week 48 (CNA30024)

Outcome	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Responder[a]	69% (73%)	69% (71%)
Virologic failures[b]	6%	4%
Discontinued due to adverse reactions	14%	16%
Discontinued due to other reasons[c]	10%	11%

[a] Subjects achieved and maintained confirmed HIV-1 RNA less than or equal to 50 copies per mL (less than 400 copies per mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR standard test 1.0 PCR).

[b] Includes viral rebound, insufficient viral response according to the investigator, and failure to achieve confirmed less than or equal to 50 copies per mL by Week 48.

[c] Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 209 cells per mm^3 in the group receiving ZIAGEN and 155 cells per mm^3 in the zidovudine group. Through Week 48, 8 subjects (2%) in the group receiving ZIAGEN (5 CDC classification C events and 3 deaths) and 5 subjects (2%) on the zidovudine arm (3 CDC classification C events and 2 deaths) experienced clinical disease progression.

CNA3005 was a multicenter, double-blind, controlled trial in which 562 HIV-1-infected, therapy-naive adults were randomized to receive either ZIAGEN (300 mg twice daily) plus COMBIVIR (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times a day) plus COMBIVIR twice daily. The trial was stratified at randomization by pre-entry plasma HIV-1 RNA 10,000 to 100,000 copies per mL and plasma HIV-1 RNA greater than

100,000 copies per mL. Trial participants were male (87%), white (73%), black (15%), and Hispanic (9%). At baseline the median age was 36 years; the median baseline CD4+ cell count was 360 cells per mm^3, and median baseline plasma HIV-1 RNA was 4.8 log_{10} copies per mL. Proportions of subjects with plasma HIV-1 RNA less than 400 copies per mL (using Roche AMPLICOR HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Table 8.

Table 8. Outcomes of Randomized Treatment through Week 48 (CNA3005)

Outcome	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 265)
Responder[a]	49%	50%
Virologic failure[b]	31%	28%
Discontinued due to adverse reactions	10%	12%
Discontinued due to other reasons[c]	11%	10%

[a] Subjects achieved and maintained confirmed HIV-1 RNA less than 400 copies per mL.

[b] Includes viral rebound and failure to achieve confirmed less than 400 copies per mL by Week 48.

[c] Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

Treatment response by plasma HIV-1 RNA strata is shown in Table 9.

Table 9. Proportions of Responders through Week 48 by Screening Plasma HIV-1 RNA Levels (CNA3005)

Screening HIV-1 RNA (copies/mL)	ZIAGEN plus Lamivudine/Zidovudine (n = 262)		Indinavir plus Lamivudine/Zidovudine (n = 265)	
	<400 copies/mL	n	<400 copies/mL	n
≥10,000 - ≤100,000	50%	166	48%	165
>100,000	48%	96	52%	100

In subjects with baseline viral load greater than 100,000 copies per mL, percentages of subjects with HIV-1 RNA levels less than 50 copies per mL were 31% in the group receiving abacavir versus 45% in the group receiving indinavir.

Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells per mm^3 was observed in both treatment arms. Through Week 48, 9 subjects (3.4%) in the group receiving abacavir (6 CDC classification C events and 3 deaths) and 3 subjects (1.5%) in the group receiving indinavir (2 CDC classification C events and 1 death) experienced clinical disease progression.

CNA30021 was an international, multicenter, double-blind, controlled trial in which 770 HIV-1-infected, therapy-naive adults were randomized and received either abacavir 600 mg

once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least 48 weeks. Trial participants had a mean age of 37 years; were male (81%), white (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells per mm^3 (range: 21 to 918 cells per mm^3) and the median baseline plasma HIV-1 RNA was 4.89 log_{10} copies per mL (range: 2.60 to 6.99 log_{10} copies per mL).

The outcomes of randomized treatment are provided in Table 10.

Table 10. Outcomes of Randomized Treatment through Week 48 (CNA30021)

Outcome	ZIAGEN 600 mg q.d. plus EPIVIR plus Efavirenz (n = 384)	ZIAGEN 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386)
Responder[a]	64% (71%)	65% (72%)
Virologic failure[b]	11% (5%)	11% (5%)
Discontinued due to adverse reactions	13%	11%
Discontinued due to other reasons[c]	11%	13%

[a] Subjects achieved and maintained confirmed HIV-1 RNA less than 50 copies per mL (less than 400 copies per mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR standard test version 1.0).

[b] Includes viral rebound, failure to achieve confirmed less than 50 copies per mL (less than 400 copies per mL) by Week 48, and insufficient viral load response.

[c] Includes consent withdrawn, lost to follow up, protocol violations, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 188 cells per mm^3 in the group receiving abacavir 600 mg once daily and 200 cells per mm^3 in the group receiving abacavir 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group receiving ZIAGEN 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%) in the group receiving ZIAGEN 300 mg twice daily (7 CDC classification C events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed to trial medications.

14.2 Pediatric Trials

Therapy-Experienced Pediatric Subjects

CNA3006 was a randomized, double-blind trial comparing ZIAGEN 8 mg per kg twice daily plus lamivudine 4 mg per kg twice daily plus zidovudine 180 mg per m^2 twice daily versus lamivudine 4 mg per kg twice daily plus zidovudine 180 mg per m^2 twice daily. Two hundred and five therapy-experienced pediatric subjects were enrolled: female (56%), white (17%), black (50%), Hispanic (30%), median age of 5.4 years, baseline CD4+ cell percent greater than 15% (median = 27%), and median baseline plasma HIV-1 RNA of 4.6 log_{10} copies per mL. Eighty

percent and 55% of subjects had prior therapy with zidovudine and lamivudine, respectively, most often in combination. The median duration of prior nucleoside analogue therapy was 2 years. At 16 weeks, the proportion of subjects responding based on plasma HIV-1 RNA less than or equal to 400 copies per mL was significantly higher in subjects receiving ZIAGEN plus lamivudine plus zidovudine compared with subjects receiving lamivudine plus zidovudine, 13% versus 2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 $\log_{10}$ copies per mL in the group receiving ZIAGEN plus lamivudine plus zidovudine compared with -0.21 $\log_{10}$ copies per mL in the group receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were 69 cells per mm^3 in the group receiving ZIAGEN plus lamivudine plus zidovudine and 9 cells per mm^3 in the group receiving lamivudine plus zidovudine.

Once-Daily Dosing

ARROW (COL105677) was a 5-year randomized, multicenter trial which evaluated multiple aspects of clinical management of HIV-1 infection in pediatric subjects. HIV-1–infected, treatment-naive subjects aged 3 months to 17 years were enrolled and treated with a first-line regimen containing ZIAGEN and lamivudine, dosed twice daily according to World Health Organization recommendations. After a minimum of 36 weeks of treatment, subjects were given the option to participate in Randomization 3 of the ARROW trial, comparing the safety and efficacy of once-daily dosing with twice-daily dosing of ZIAGEN and lamivudine, in combination with a third antiretroviral drug, for an additional 96 weeks. Of the 1,206 original ARROW subjects, 669 participated in Randomization 3. Virologic suppression was not a requirement for participation at baseline for Randomization 3 (following a minimum of 36 weeks of twice-daily treatment), 75% of subjects in the twice-daily cohort were virologically suppressed compared with 71% of subjects in the once-daily cohort.

The proportions of subjects with HIV-1 RNA less than 80 copies per mL through 96 weeks are shown in Table 11. The differences between virologic responses in the two treatment arms were comparable across baseline characteristics for gender and age.

Table 11. Virologic Outcome of Randomized Treatment at Week 96[a] (ARROW Randomization 3)

Outcome	ZIAGEN plus Lamivudine Twice-Daily Dosing (n = 333)	ZIAGEN plus Lamivudine Once-Daily Dosing (n = 336)
HIV-1 RNA <80 copies/mL[b]	70%	67%
HIV-1 RNA ≥80 copies/mL[c]	28%	31%
No virologic data		
Discontinued due to adverse event or death	1%	<1%
Discontinued study for other reasons[d]	0%	<1%
Missing data during window but on study	1%	1%

[a] Analyses were based on the last observed viral load data within the Week 96 window.

[b] Predicted difference (95% CI) of response rate is -4.5% (-11% to 2%) at Week 96.

[c] Includes subjects who discontinued due to lack or loss of efficacy or for reasons other than an adverse event or death, and had a viral load value of greater than or equal to 80 copies per mL, or subjects who had a switch in background regimen that was not permitted by the protocol.

[d] Other includes reasons such as withdrew consent, loss to follow-up, etc. and the last available HIV-1 RNA less than 80 copies per mL (or missing).

16 HOW SUPPLIED/STORAGE AND HANDLING

ZIAGEN tablets, containing abacavir sulfate equivalent to 300 mg abacavir are yellow, biconvex, scored, capsule-shaped, film-coated, and imprinted with “GX 623” on both sides. They are packaged as follows:

Bottles of 60 tablets (NDC 49702-221-18).

Unit dose blister packs of 60 tablets (NDC 49702-221-44). 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 is a clear to opalescent, yellowish, strawberry-banana-flavored liquid, which may turn brown over time. 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 49702-222-48) 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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Hypersensitivity Reactions

Inform patients:

- that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of ZIAGEN, and instruct the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about ZIAGEN. The complete text of the Medication Guide is reprinted at the end of this document.
- to carry the Warning Card with them.
- how to identify a hypersensitivity reaction *[see Warnings and Precautions (5.1), Medication Guide]*.
- that if they develop symptoms consistent with a hypersensitivity reaction they should call their healthcare provider right away to determine if they should stop taking ZIAGEN.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if ZIAGEN is not immediately discontinued.
- to not restart ZIAGEN or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.
- that if they have a hypersensitivity reaction, they should dispose of any unused ZIAGEN to avoid restarting abacavir.
- that a hypersensitivity reaction is usually reversible if it is detected promptly and ZIAGEN is stopped right away.
- that if they have interrupted ZIAGEN for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- to not restart ZIAGEN or any other abacavir-containing product without medical consultation and only if medical care can be readily accessed by the patient or others.

Lactic Acidosis/Hepatomegaly with Steatosis

Advise patients that lactic acidosis and severe hepatomegaly with steatosis have been reported with use of nucleoside analogues and other antiretrovirals. Advise patients to stop taking ZIAGEN if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.2)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when ZIAGEN is started *[see Warnings and Precautions (5.3)]*.

Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ZIAGEN during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

Missed Dose

Instruct patients that if they miss a dose of ZIAGEN, to take it as soon as they remember. Advise patients not to double their next dose or take more than the prescribed dose *[see Dosage and Administration (2)]*.

Availability of Medication Guide

Instruct patients to read the Medication Guide before starting ZIAGEN and to re-read it each time the prescription is renewed. Instruct patients to inform their physician or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

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Manufactured for:

ViiV Healthcare
Research Triangle Park, NC 27709

by:

GlaxoSmithKline
Research Triangle Park, NC 27709

ZGN:xxPI

MEDICATION GUIDE

ZIAGEN (ZY-uh-jen) **(abacavir)** **tablets**	**ZIAGEN (ZY-uh-jen)** **(abacavir)** **oral solution**

What is the most important information I should know about ZIAGEN?

ZIAGEN can cause serious side effects, including:

- **Serious allergic reactions (hypersensitivity reaction)** that can cause death have happened with ZIAGEN and other abacavir-containing products. Your risk of this allergic reaction is much higher if you have a gene variation called HLA-B*5701. Your healthcare provider can determine with a blood test if you have this gene variation.

  If you get a symptom from 2 or more of the following groups while taking ZIAGEN, call your healthcare provider right away to find out if you should stop taking ZIAGEN.

	Symptom(s)
Group 1	**Fever**
Group 2	**Rash**
Group 3	**Nausea, vomiting, diarrhea, abdominal (stomach area) pain**
Group 4	**Generally ill feeling, extreme tiredness, or achiness**
Group 5	**Shortness of breath, cough, sore throat**

  A list of these symptoms is on the Warning Card your pharmacist gives you. **Carry this Warning Card with you at all times.**

  If you stop ZIAGEN because of an allergic reaction, never take ZIAGEN (abacavir) or any other abacavir-containing medicine (EPZICOM, TRIUMEQ, or TRIZIVIR) again.
  - If you have an allergic reaction, dispose of any unused ZIAGEN. Ask your pharmacist how to properly dispose of medicines.
  - If you take ZIAGEN or any other abacavir-containing medicine again after you have had an allergic reaction, **within hours** you may get **life-threatening symptoms** that may include **very low blood pressure or death.**
  - If you stop ZIAGEN for any other reason, even for a few days, and you are not allergic to ZIAGEN, talk with your healthcare provider before taking it again. Taking ZIAGEN again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before.

If your healthcare provider tells you that you can take ZIAGEN again, start taking it when you are around medical help or people who can call a healthcare provider if you need one.

What is ZIAGEN?

ZIAGEN is a prescription HIV-1 (Human Immunodeficiency Virus type 1) medicine used with other antiretroviral medicines to treat HIV-1 infection. HIV-1 is the virus that causes Acquired Immune

Deficiency Syndrome (AIDS).

The safety and effectiveness of ZIAGEN has not been established in children under 3 months of age.

When used with other antiretroviral medicines to treat HIV-1 infection, ZIAGEN may help:

- reduce the amount of HIV-1 in your blood. This is called “viral load”.
- increase the number of CD4+ (T) cells in your blood, that help fight off other infections.

Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

ZIAGEN does not cure HIV-1 infection or AIDS. You must keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illnesses.

Who should not take ZIAGEN?

Do not take ZIAGEN if you:

- have a certain type of gene variation called the HLA-B*5701 allele. Your healthcare provider will test you for this before prescribing treatment with ZIAGEN.
- are allergic to abacavir or any of the ingredients in ZIAGEN. See the end of this Medication Guide for a complete list of ingredients in ZIAGEN.
- have liver problems.

What should I tell my healthcare provider before taking ZIAGEN?

Before you take ZIAGEN, tell your healthcare provider if you:

- have been tested and know whether or not you have a particular gene variation called HLA-B*5701.
- have or have had liver problems, including hepatitis B or C virus infection.
- have heart problems, smoke, or have diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.
- drink alcohol or take medicines that contain alcohol.
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
  Pregnancy Registry. There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take ZIAGEN.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-

counter medicines, vitamins, and herbal supplements.

Some medicines interact with ZIAGEN. **Keep a list of your medicines to show your healthcare provider and pharmacist.** You can ask your healthcare provider or pharmacist for a list of medicines that interact with ZIAGEN. **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take ZIAGEN with other medicines.

Tell your healthcare provider if you take:

- any other medicine to treat HIV-1
- methadone

How should I take ZIAGEN?

- **Take ZIAGEN exactly as your healthcare provider tells you.**
- Do not change your dose or stop taking ZIAGEN without talking with your healthcare provider. If you miss a dose of ZIAGEN, take it as soon as you remember. Do not take 2 doses at the same time. If you are not sure about your dosing, call your healthcare provider.
- Stay under the care of a healthcare provider while taking ZIAGEN.
- ZIAGEN may be taken with or without food.
- For children aged 3 months and older, your healthcare provider will prescribe a dose of ZIAGEN based on your child's body weight.
- Tell your healthcare provider if you or your child has trouble swallowing tablets. ZIAGEN comes as a tablet or as a liquid (oral solution).
- Do not run out of ZIAGEN. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run out, get more from your healthcare provider or pharmacy.
- If you take too much ZIAGEN, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of ZIAGEN?

- **ZIAGEN can cause serious side effects including:**
- **See "What is the most important information I should know about ZIAGEN?"**
- **Build-up of acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take ZIAGEN. Lactic acidosis is a serious medical emergency that can cause death. **Call your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:**
  - feel very weak or tired
  - unusual (not normal) muscle pain
  - trouble breathing
  - stomach pain with nausea and vomiting
  - feel cold, especially in your arms and legs
  - feel dizzy or light-headed
  - have a fast or irregular heartbeat

- **Serious liver problems** can happen in people who take ZIAGEN. In some cases, these serious liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis) when you take ZIAGEN. **Call your healthcare provider right away if you have any of the following signs of liver problems:**
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea-colored" urine
  - light-colored stools (bowel movements)
  - loss of appetite for several days or longer
  - nausea
  - pain, aching, or tenderness on the right side of your stomach area

You may be more likely to get lactic acidosis or serious liver problems if you are female or very overweight (obese).

- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after you start taking ZIAGEN.
- **Heart attack (myocardial infarction).** Some HIV-1 medicines including ZIAGEN may increase your risk of heart attack.

The most common side effects of ZIAGEN in adults include:

- nausea
- headache
- generally not feeling well
- tiredness
- vomiting
- bad dreams or sleep problems

The most common side effects of ZIAGEN in children include:

- fever and chills
- nausea
- vomiting
- rash
- ear, nose, or throat infections

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ZIAGEN. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZIAGEN?

- Store ZIAGEN at room temperature, between 68°F to 77°F (20°C to 25°C).
- Do not freeze ZIAGEN oral solution. You may store ZIAGEN oral solution in a refrigerator.

Keep ZIAGEN and all medicines out of the reach of children.

General information for safe and effective use of ZIAGEN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not

use ZIAGEN for a condition for which it was not prescribed. Do not give ZIAGEN to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for the information about ZIAGEN that is written for health professionals.

For more information go to www.ZIAGEN.com or call 1-877-844-8872.

What are the ingredients in ZIAGEN?

Active ingredient: abacavir

Inactive ingredients:

Tablets:

Colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

Tablet film-coating contains: hypromellose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.

Oral Solution:

Artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), sorbitol solution, and water.

Manufactured for:

ViiV Healthcare

Research Triangle Park, NC 27709

by:

GlaxoSmithKline

Research Triangle Park, NC 27709

ZGN:xMG

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 05/2018

(Front of card)

WARNING CARD
ZIAGEN® (abacavir) tablets and oral solution

Patients taking ZIAGEN may have a serious allergic reaction (hypersensitivity reaction) that can cause death. If you get a symptom from 2 or more of the following groups while taking ZIAGEN, call your healthcare provider right away to find out if you should stop taking this medicine.

	Symptom(s)
Group 1	**Fever**
Group 2	**Rash**
Group 3	**Nausea, vomiting, diarrhea, or abdominal (stomach area) pain**
Group 4	**Generally ill feeling, extreme tiredness, or achiness**
Group 5	**Shortness of breath, cough, or sore throat**

Always carry this Warning Card with you to help recognize symptoms of this allergic reaction.

(Back of Card)

WARNING CARD

ZIAGEN® (abacavir) tablets and oral solution

If you must stop treatment with ZIAGEN because you have had an allergic reaction to abacavir, **NEVER** take ZIAGEN or another abacavir-containing medicine (EPZICOM®, TRIUMEQ®, or TRIZIVIR®) again. If you have an allergic reaction, dispose of any unused ZIAGEN. Ask your pharmacist how to properly dispose of medicines. If you take ZIAGEN or another abacavir-containing medicine again after you have had an allergic reaction, **WITHIN HOURS** you may get **life-threatening symptoms** that may include **very low blood pressure** or **death**.

Please read the Medication Guide for additional information on ZIAGEN.

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