AUSTRALIAN PRODUCT INFORMATION

TRIZIVIR (abacavir, lamivudine and zidovudine) film-coated tablets

Abacavir, a component of TRIZIVIR tablets, is associated with hypersensitivity reactions, which can be life-threatening, and in rare cases fatal. TRIZIVIR, or any other medicinal product containing abacavir (KIVEXA, ZIAGEN and TRIUMEQ), MUST NEVER be restarted following a hypersensitivity reaction (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

1 NAME OF THE MEDICINE

Abacavir (as sulfate), lamivudine and zidovudine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TRIZIVIR tablets are a fixed combination product containing abacavir (as sulfate) 300 mg, lamivudine 150 mg and zidovudine 300 mg in each tablet. Product information for ZIAGEN (abacavir (as sulfate) tablets and oral solution), 3TC (lamivudine tablets and oral solution) and RETROVIR (zidovudine capsules and syrup) contain additional information.

Abacavir sulfate is a white to off-white crystalline powder with a solubility of approximately 77 mg/mL in water at 25°C.

Lamivudine is a white to off-white crystalline solid which is highly soluble in water.

Zidovudine is a white to off-white, odourless, crystalline solid.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

TRIZIVIR tablets are blue/green capsule-shaped film-coated tablets, engraved with “GX LL1” on one tablet face.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TRIZIVIR is indicated in antiretroviral therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents over the age of 12 years. TRIZIVIR should not be administered to adults and adolescents who weigh less than 40 kg because it is a fixed-dose tablet, and the dose cannot be adjusted for this patient population.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage in adults

The recommended dose of TRIZIVIR in adults is one tablet twice daily, giving a total daily dose of 600 mg abacavir, 300 mg lamivudine and 600 mg zidouvudine.

Food reduces the C_{max} and extends the T_{max} of lamivudine but the amount of drug absorbed is not reduced. The clinical significance of this is not known (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Therapy should be initiated by a physician experienced in the management of HIV infection.

For situations where discontinuation of therapy with one of the active constituents of TRIZIVIR (abacavir, lamivudine or zidovudine), or dose reduction is necessary, separate preparations of abacavir (ZIAGEN tablets and oral solution), lamivudine (3TC tablets and oral solution) and zidovudine (RETROVIR capsules and syrup) are available.

Monitoring of patients

Haematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of haematologic indices is recommended to detect serious anaemia or granulocytopenia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In patients who experience haematologic toxicity, reduction in haemoglobin may occur as early as 2 to 4 weeks, and granulocytopenia usually occurs after 6 to 8 weeks.

Dose adjustment

Significant anaemia (haemoglobin of < 7.5 g/dL or reduction of > 25% of baseline) and/or significant granulocytopenia (granulocyte count of < 750 cells/mm^3 or reduction of > 50% from baseline) require a dose interruption until evidence of marrow recovery is observed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). For less severe anaemia or granulocytopenia, a reduction in daily dose may be adequate. In patients who develop significant anaemia, dose modification does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose modification, gradual increases in dose may be appropriate depending on haematologic indices and patient tolerance. As dosage adjustment of TRIZIVIR is not possible, separate preparations of abacavir, zidovudine and lamivudine should be used. Physicians should refer to the complete prescribing information for these drugs.

Dosage in the elderly

No specific pharmacokinetic data are available in patients over 65 years of age; however, special care is advised in this age group due to age-associated changes such as the decrease in renal function and alterations in haematological parameters.

Dosage in renal impairment

Whilst no dosage adjustment of abacavir is necessary in patients with renal dysfunction, lamivudine and zidovudine concentrations are increased in patients with renal impairment due to decreased clearance. Therefore, as dosage adjustment of these may be necessary, it

is recommended that separate preparations of abacavir, lamivudine and zidovudine be administered to patients with reduced renal function (creatinine clearance ≤ 50 mL/min) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Dosage in hepatic impairment
Dosage adjustments for both abacavir and zidovudine may be required in patients with mild hepatic impairment (Child-Pugh grade A). As dose reduction is not possible with TRIZIVIR, the separate preparations of abacavir, lamivudine and zidovudine should be used when this is judged necessary. TRIZIVIR is not recommended in patients with moderate and severe hepatic impairment (Child-Pugh grade B or C) (see Section 5.2 PHARMACOKINETIC PROPERTIES - Special populations).

4.3 CONTRAINDICATIONS

TRIZIVIR is contraindicated in patients with known hypersensitivity to TRIZIVIR or any of its components (abacavir, lamivudine or zidovudine), or to any of the excipients of TRIZIVIR tablets.

Due to the active ingredient zidovudine, TRIZIVIR is contraindicated in patients with abnormally low neutrophil counts (< 0.75 x 10^9/L), or abnormally low haemoglobin levels (< 7.5 g/dL or 4.65 mmol/L) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity to abacavir - special warning (see also Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS))
Hypersensitivity to abacavir is a multi-organ clinical syndrome which can occur at any time during treatment, but most often occurs within the first 6 weeks of therapy. Signs or symptom usually present in 2 or more of the following groups although hypersensitivity following the presentation of a single sign or symptom has been reported infrequently.

- fever
- rash
- gastrointestinal, including nausea, vomiting, diarrhoea, or abdominal pain
- constitutional, including generalized malaise, fatigue, or achiness
- respiratory, including dyspnoea, cough, or pharyngitis.

Hypersensitivity reactions may present similarly to pneumonia, bronchitis or pharyngitis, influenza-like illness or gastroenteritis.

- **Discontinue TRIZIVIR as soon as a hypersensitivity reaction is suspected.**
- **If hypersensitivity reaction cannot be ruled out, TRIZIVIR or any other medicinal product containing abacavir must not be restarted.**
- The risk is significantly increased for patients who test positive for the HLA-B*5701 allele. However, abacavir hypersensitivity reactions have been reported at a lower frequency in patients who do not carry this allele.

- **TRIZIVIR is not recommended for use in patients with the HLA-B*5701 allele or in patients who have had a suspected abacavir HSR while taking any medicinal product containing abacavir.**
- Testing for HLA-B*5701 status is recommended before initiating abacavir treatment and also before re-starting abacavir treatment in patients of unknown HLA-B*5701 status who have previously tolerated abacavir.
- The diagnosis of hypersensitivity reaction is based on clinical judgment. **If a hypersensitivity reaction is suspected, TRIZIVIR must be stopped without delay, even in the absence of the HLA-B*5701 allele.** Delay in stopping treatment with abacavir after the onset of hypersensitivity may result in a life-threatening hypotension and death.
- Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity reaction have also experienced life-threatening reactions within hours of re-initiating abacavir therapy. Therefore, if a hypersensitivity reaction is ruled out, the reintroduction of TRIZIVIR or any other abacavir-containing product is recommended only if medical care can be readily accessed.
- Each patient should be reminded to read the Consumer Medicine Information. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.
- Patients who have experienced a hypersensitivity reaction should be instructed to dispose of their remaining TRIZIVIR tablets in order to avoid restarting abacavir.

Lipoatrophy
Treatment with zidovudine has been associated with loss of subcutaneous fat. The incidence and severity of lipoatrophy are related to cumulative exposure. This fat loss, which is most evident in the face, limbs and buttocks, may be only partially reversible and improvement may take several months when switching to a zidovudine-free regimen. Patients should be regularly assessed for signs of lipoatrophy during therapy with zidovudine and other zidovudine containing products (COMBIVIR and RETROVIR), and if feasible therapy should be switched to an alternative regimen if there is suspicion of lipoatrophy development.

Serum lipids and blood glucose
Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Lactic acidosis and severe hepatomegaly with steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including abacavir, lamivudine and zidovudine. A majority of these cases have been in women.

Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).

Caution should be exercised when administering TRIZIVIR, particularly to those with known

risk factors for liver disease. Treatment with TRIZIVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Immune reconstitution syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia (often referred to as PCP). Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre 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 and sometimes can be an atypical presentation.

Transmission of infection
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Myocardial infarction
Several observational, epidemiological studies have reported an association with abacavir use and the risk of myocardial infarction. Meta-analyses of randomised controlled trials have observed no excess risk of myocardial infarction with abacavir use. To date there is no established biological mechanism to explain a potential increase in risk. In totality the available data from observational studies and from controlled clinical trials show inconsistency and therefore the evidence for a causal relationship between abacavir treatment and the risk of myocardial infarction 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, hyperlipidaemia, diabetes mellitus and smoking).

Patients co-infected with hepatitis C virus
Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. Therefore, the co-administration of ribavirin and zidovudine is not advised and consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This is particularly important in patients with a known history of zidovudine induced anaemia.

Haematological effects
Therapy with zidovudine preparations is commonly associated with haematologic toxicity including granulocytopenia and severe anaemia requiring transfusions particularly in patients with advanced HIV disease (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuation of the drug.

Because anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients with advanced symptomatic HIV disease receiving zidovudine, haematological parameters should be carefully monitored in patients receiving TRIZIVIR (see Section 4.3 CONTRAINDICATIONS). These haematological effects are not usually observed before four to six weeks of therapy. For patients with advanced symptomatic HIV disease, it is generally recommended that blood tests are performed at least every two weeks for the first three months of therapy and at least monthly thereafter.

In patients with early HIV disease haematological adverse reactions are infrequent. Depending on the overall condition of the patient blood tests may be performed less often, for example every one to three months. Decreases in the haemoglobin level of more than 25% from baseline and falls in the neutrophil count of more than 50% from baseline may require more frequent monitoring.

Additionally, dosage adjustment of zidovudine may be required if severe anaemia or myelosuppression occurs during treatment with TRIZIVIR or in patients with pre-existing bone marrow compromise e.g. haemoglobin < 9 g/dL or granulocyte count < 1000 cells/mm^3 (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Separate preparations of abacavir, lamivudine and zidovudine should therefore be administered to these patients. Physicians should refer to the individual product information for these drugs.

Pancreatitis
Cases of pancreatitis have occurred rarely in patients treated with abacavir, lamivudine and zidovudine. However, it is not clear whether these cases were due to the medicinal products or to the underlying HIV disease. Treatment with TRIZIVIR should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

Special precautions for use
It is recommended that separate preparations of abacavir, lamivudine and zidovudine should be administered in cases where dosage adjustment is necessary (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Physicians should refer to the individual product information for these drugs.

Use of other medicines
If TRIZIVIR is co-administered with other drugs metabolised by glucuronidation, careful thought should be given to the possibilities of interactions with zidovudine, because the toxicity of either drug may be potentiated (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Patients should be cautioned about the concomitant use of self-administered medications (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in hepatic impairment
TRIZIVIR should be used with caution in patients with HIV and chronic hepatitis B virus infection. Clinical trial and marketed use of lamivudine have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with decompensated liver disease. If TRIZIVIR is discontinued in a patient with HIV and HBV co-infection, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Use in renal impairment
In patients with moderate to severe renal impairment, the terminal plasma half-life of lamivudine exposure is increased due to decreased clearance. Dosage adjustment in these patients is better controlled using individual abacavir, lamivudine and zidovudine preparations as the dose frequency of lamivudine may need to be reduced (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use
TRIZIVIR should not be administered to children and adolescents who weigh less than 40 kg because it is a fixed-dose combination that cannot be adjusted for this patient population. Physicians should therefore refer to the individual prescribing information for abacavir, lamivudine and zidovudine.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine and lamivudine. As TRIZIVIR contains abacavir, lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur with TRIZIVIR. The potential for P_{450} mediated interactions with other medicinal products involving abacavir is low. *In vitro* studies have shown that abacavir has potential to inhibit cytochrome P_{450} 1A1 (CYP1A1). The likelihood of interactions with lamivudine is low due to limited metabolism and plasma protein binding and almost complete renal clearance. Similarly, zidovudine has limited protein binding but is eliminated primarily by hepatic conjugation to an inactive glucuronidated metabolite. The interactions listed below should not be considered exhaustive but are representative of the classes of medicinal products where caution should be exercised.

Effect of abacavir on the pharmacokinetics of other agents
In vitro, abacavir demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistance protein (BCRP) or P-glycoprotein (Pgp) and minimal inhibition of organic cation transporter 1 (OCT1), OCT2 and multidrug and toxin extrusion protein 2-K (MATE2-K). Abacavir is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters.

Abacavir is an inhibitor of MATE1 *in vitro,* however abacavir has low potential to affect the plasma concentrations of MATE1 substrates at therapeutic drug exposures (up to 600 mg).

Effect of other agents on the pharmacokinetics of abacavir
In vitro, abacavir is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, MATE1, MATE2-K, Multidrug resistance-associated protein 2 (MRP2) or MRP4, therefore drugs that modulate these transporters are not expected to affect abacavir plasma concentrations.

Although abacavir is a substrate of BCRP and Pgp *in vitro,* clinical studies demonstrate no clinically significant changes in abacavir pharmacokinetics when co-administered with lopinavir/ritonovir (Pgp and BCRP inhibitors).

Interactions relevant to abacavir
The potential for drug interactions involving abacavir is low. *In vitro* studies have shown that abacavir has potential to inhibit cytochrome P_{450} 1A1 (CYP1A1). Abacavir shows limited potential to inhibit metabolism mediated by the CYP3A4 enzyme. It has also been shown *in vitro* not to interact with drugs that are metabolised by CYP 2C9 or CYP 2D6 enzymes. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for drug interactions with antiretroviral protease inhibitors and other drugs metabolised by major CYP enzymes.

Ethanol
The metabolism of abacavir is altered by concomitant ethanol resulting in an increase in AUC of abacavir of about 41%. Given the safety profile of abacavir these findings are not considered clinically significant. Abacavir has no effect on the metabolism of ethanol.

Methadone
In a pharmacokinetic study, coadministration of 600 mg abacavir twice daily with methadone showed a 35% reduction in abacavir C_{max} and a one hour delay in t_{max}, but AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study, abacavir increased the mean methadone systemic clearance by 22%. This change is not considered clinically relevant for the majority of patients, however occasionally methadone dose re-titration may be required.

Retinoids
Retinoid compounds such as isotretinoin, are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

Riociguat
In vitro, abacavir inhibits CYP1A1. Concomitant administration of a single dose of riociguat (0.5 mg) to HIV patients receiving the combination of abacavir/dolutegravir/lamivudine (600 mg/50 mg/300 mg once daily) led to an approximately three-fold higher riociguat AUC(0-∞) when compared to historical riociguat AUC(0-∞) reported in healthy subjects. Riociguat dose may need to be reduced, consult the riociguat product labeling for dosing recommendations and for interactions observed in patients receiving highly active antiretroviral therapy.

Effect of lamivudine on the pharmacokinetics of other agents

In vitro, lamivudine demonstrates no or weak inhibition of the drug transporters OATP1B1, OATP1B3, BCRP or Pgp, MATE1, MATE2-K or OCT3. Lamivudine is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters.

Lamivudine is an inhibitor of OCT1 and OCT2 *in vitro* with IC50 values of 17 and 33 uM, respectively, however lamivudine has low potential to affect the plasma concentrations of OCT1 and OCT2 substrates at therapeutic drug exposures (up to 300 mg).

Effect of other agents on the pharmacokinetics of lamivudine
Lamivudine is a substrate of MATE1, MATE2-K and OCT2 *in vitro.* Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations, however this interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

Lamivudine is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

Lamivudine is a substrate of Pgp and BCRP, however due to its high bioavailability it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore co-administration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Interactions relevant to lamivudine
The possibility of interaction with other medicinal products administered concurrently with lamivudine should be considered, particularly when the main route of elimination is active renal secretion especially via the cationic system e.g. trimethoprim.

Sorbitol
Coadministration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14% (9 - 20%), 32% (28 - 37%), and 36% (32 - 41%) in lamivudine exposure (AUC_∞) and 28% (20 - 34%), 52% (47 - 57%), and 55% (50 - 59%) in the C_{max} of lamivudine in adults. When possible, avoid chronic coadministration of sorbitol-containing medicines with lamivudine. Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.

Trimethoprim
An interaction with trimethoprim, a constituent of trimethoprim with sulphamethoxazole causes a 40% increase in lamivudine exposure following administration of one trimethoprim 160 mg / sulfamethoxazole 800 mg tablet once daily for 5 days. The effects of higher doses of trimethoprim on lamivudine plasma levels have not been investigated. However, unless the patient already has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim/sulfamethoxazole. Administration of lamivudine in patients with renal impairment should be assessed carefully. The effect of co-administration of lamivudine with higher doses of trimethoprim/sulfamethoxazole used for the treatment of *Pneumocystis carinii* pneumonia and toxoplasmosis has not been studied.

Emtricitabine
Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these drugs in combination therapy may be limited. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.

In *in vitro* studies, ciprofloxacin, pentamidine and ganciclovir reduced the anti-HIV activity of lamivudine. The clinical significance of this is not known.

Interactions relevant to zidovudine
Atovaquone
Zidovudine does not appear to affect the pharmacokinetics of atovaquone. However, pharmacokinetic data have shown that atovaquone appears to decrease the rate of metabolism of zidovudine to its glucuronide metabolite (steady state AUC of zidovudine was increased by 33% and peak plasma concentration of the glucuronide was decreased by 19%). At zidovudine dosages of 500 or 600 mg/day it would seem unlikely that a three week, concomitant course of atovaquone for the treatment of acute PCP would result in an increased incidence of adverse reactions attributable to higher plasma concentrations of zidovudine. Extra care should be taken in monitoring patients receiving prolonged atovaquone therapy.

Clarithromycin
Clarithromycin tablets reduce the absorption of zidovudine. This can be avoided by separating the administration of zidovudine and clarithromycin by at least two hours.

Lamivudine
Co-administration of zidovudine with lamivudine results in a 13% increase in zidovudine exposure and a 28% increase in peak plasma levels. However overall exposure (AUC) is not significantly altered. This increase is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary. Zidovudine has no effect on the pharmacokinetics of lamivudine (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Phenytoin
Phenytoin blood levels have been reported to be low in some patients receiving zidovudine, while in one case a high level was documented. These observations suggest that phenytoin levels should be carefully monitored in patients receiving TRIZIVIR and phenytoin since many patients with advanced HIV infections have CNS conditions which may predispose them to seizure activity.

Probenecid
Probenecid may reduce renal excretion of glucuronide and zidovudine and, in addition, may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Limited data suggest that probenecid increases the mean half-life and area under the plasma concentration curve of zidovudine by decreasing glucuronidation. Careful thought should be given to the possibilities of drug interactions

before using such drugs, particularly for chronic therapy, in combination with TRIZIVIR.

Ribavirin
The nucleoside analogue ribavirin antagonises the *in vitro* antiviral activity of zidovudine and so concomitant use of TRIZIVIR with this medicinal product should be avoided.

Rifampicin
Limited data suggests that co-administration of zidovudine and rifampicin decreases the AUC of zidovudine by 48% ± 34%. Howeve,r the clinical significance of this is unknown.

Stavudine
Zidovudine may inhibit the intracellular phosphorylation of stavudine when the two medicinal products are used concurrently. Stavudine is therefore not recommended for use in combination with TRIZIVIR.

Other medicinal products, including but not limited to, aspirin, codeine, morphine, methadone, paracetamol, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone and inosine pranobex, may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Careful thought should be given to the possibilities of interactions before using such medicinal products particularly for chronic therapy, in combination with TRIZIVIR.

Co-administration of zidovudine with medicinal products that are potentially nephrotoxic or myelosuppressive or cytotoxic, or which interfere with RBC/WBC number or function (such as pyrimethamine, sulfamethoxazole and trimethoprim, doxorubicin, dapsone, systemic pentamidine, ganciclovir, amphotericin B, flucytosine, vincristine, vinblastine, adriamycin, or interferon) may increase the risk of adverse reactions to zidovudine. If concomitant therapy with TRIZIVIR and any of these medicinal products is necessary then extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more agents should be reduced.

Some experimental nucleoside analogues affecting DNA replication antagonise the *in vitro* antiviral activity of zidovudine against HIV and thus, concomitant use of such medicinal products should be avoided.

Some medicinal products such as trimethoprim and sulfamethoxazole, aerosolised pentamidine, pyrimethamine, and aciclovir may be necessary for the management or prevention of opportunistic infections. In the controlled trial in patients with advanced HIV disease, increased toxicity was not detected with limited exposure to these medicinal products. However, there is one published report of neurotoxicity (profound lethargy) associated with concomitant use of zidovudine and aciclovir (see Interactions relevant to lamivudine).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Abacavir had no adverse effects on the mating performance or fertility of male and female rats at oral doses of up to 427 mg/kg per day, a dose expected to produce exposures approximately 30 fold higher than that in humans at the therapeutic dose based on AUC.

Neither orally administered zidovudine (225 mg/kg BID) nor lamivudine (up to 70 times anticipated clinical exposure based on C_{max}) have shown evidence of impairment of fertility in male and female rats. There are no data on the effect of abacavir, lamivudine or zidovudine on human female fertility. In men zidovudine has not been shown to affect sperm count, morphology or motility.

Use in pregnancy
(Category B3)
Abacavir, lamivudine and zidovudine have been evaluated in the Antiretroviral Pregnancy Registry (APR) in over 2,000, 11,000, and 13,000 women respectively during pregnancy and postpartum. Available human data from the APR do not show an increased risk of major birth defects for abacavir, lamivudine or zidovudine compared to the background rate (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

The safe use of abacavir, lamivudine and zidovudine in human pregnancy has not been established in adequate and well-controlled trials investigating congenital abnormalities. Therefore, administration of abacavir, lamivudine and zidovudine in pregnancy should be considered only if the expected benefit outweighs the possible risk to the foetus.

Abacavir, lamivudine and zidovudine have been associated with findings in animal reproductive studies. In reproductive studies in animals, abacavir, lamivudine and zidovudine were all shown to cross the placenta. Pregnant women considering using abacavir, lamivudine or zidovudine during pregnancy should be made aware of these findings.

There is no data available on the treatment with a combination of abacavir, lamivudine and zidovudine in animals.

Studies in pregnant rats showed that abacavir is transferred to the foetus through the placenta. Developmental toxicity (depressed foetal body weight and reduced crown-rump length) and increased incidences of foetal anasarca and skeletal malformations were observed when rats were treated with abacavir at doses of 648 mg/kg during organogenesis (approximately 35 times the human exposure at the recommended dose, based on AUC). In a fertility study, evidence of toxicity to the developing embryo and foetuses (increased resorptions, decreased foetal body weights) occurred only at 427 mg/kg per day. The offspring of female rats treated with abacavir at 427 mg/kg (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 foetal malformations at doses up to 453 mg/kg (8.5 times the human exposure at the recommended dose, based on AUC).

There are limited data regarding the use of zidovudine in human pregnancy. It is not known whether zidovudine can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity.

The safety of lamivudine in human pregnancy has not been established. Lamivudine caused an increase in early embryonic deaths in the rabbit at exposures (based on C_{max} and AUC) less than the maximum anticipated clinical exposure. Oral zidovudine caused an increase in foetal resorptions in the rat (75 mg/kg BID) and rabbit (250 mg/kg BID). Lamivudine was not teratogenic in rats and rabbits with exposure (based on C_{max}) up to 40 and 36 times respectively those observed in humans at the clinical dosage. At maternally toxic doses, zidovudine (3000 mg/kg/day) given to rats during organogenesis resulted in an increased incidence of malformations. No evidence of foetal abnormalities was observed at lower doses.

Vaginal tumours have been seen in rodents following 19-month daily oral dosing with zidovudine at exposures (based on AUC) more than 4 times (mouse) and more than 27 times (rat) the estimated clinical exposure (see Section 5.3 PRECLINICAL SAFETY DATA - Carcinogenicity, Genotoxicity). The relevance of these findings to either infected or uninfected infants exposed to zidovudine is unknown. However, pregnant women considering using TRIZIVIR during pregnancy should be made aware of these findings.

There are no adequate and well-controlled studies in pregnant women and TRIZIVIR is not recommended for use in pregnant women.

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure *in utero* or peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Use in lactation

Abacavir and its metabolites are excreted into the milk of lactating rats. Following oral administration of lamivudine or zidovudine to lactating rats, the respective drug was excreted in the milk.

It is expected that abacavir and its metabolites will also be secreted into human milk.

Excretion of zidovudine, abacavir and lamivudine in breast milk has been reported in clinical studies, resulting in sub-therapeutic infant plasma levels. There is no data available on the safety of abacavir and/or lamivudine administered to babies less than three months old.

Breast feeding is not advised because of the potential for HIV transmission from mother to child, and the potential risk of adverse events due to antiretroviral drug excretion in breast milk.

In settings where formula feeding is unsafe or unavailable, the World Health Organisation has provided Guidelines.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of TRIZIVIR, or the active components (abacavir, lamivudine and zidovudine) on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substances. Nevertheless, the clinical status of the patient and the adverse events of TRIZIVIR should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse events have been reported during therapy for HIV disease with abacavir, lamivudine and zidovudine, administered separately or in combination. For many of these adverse events it is unclear whether they are related to abacavir, lamivudine, zidovudine, or to the wide range of medicinal products used in the management of HIV disease or are as a result of the underlying disease process.

Information regarding the safety of TRIZIVIR, abacavir, zidovudine or lamivudine in combination with other antiretroviral drugs is limited. Physicians should refer to the complete product information for the respective antiretroviral therapy for a description of the known associated adverse reactions.

As TRIZIVIR contains abacavir, lamivudine and zidovudine, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of added toxicity following concurrent administration of the three compounds.

Adverse reactions with TRIZIVIR

Clinical trial data

Table 1 lists all adverse reactions, considered possibly related to study medication occurring at an incidence of 5% or more, reported in a controlled pivotal clinical trial (CNAAB3005) in adults.

Table 1: Common adverse reactions (frequency ≥ 5.0%) reported in a pivotal, controlled clinical trial in adults

Drug Related Adverse Reaction	ABC/3TC/ZDV N = 262	IDV/3TC/ZDV N = 264	Total N = 526
	N (%)	N (%)	N (%)
Any Drug-Related Adverse Reaction	206 (79)	225 (85)	431 (82)
GASTROINTESTINAL			
Nausea	137 (52)	144 (55)	281 (53)
Nausea & vomiting	58 (22)	57 (22)	115 (22)
Diarrhoea	40 (15)	38 (14)	78 (15)
Abdominal discomfort & pain	21 (8)	25 (9)	46 (9)
Gaseous symptoms	20 (8)	21 (8)	41 (8)
Abdominal distension	23 (9)	13 (5)	36 (7)
Dyspeptic symptoms	11 (4)	12 (5)	23 (4)
Abnormal liver function tests	13 (5)	9 (3)	22 (4)
Constipation	12 (5)	8 (3)	20 (4)

Drug Related Adverse Reaction	ABC/3TC/ZDV N = 262	IDV/3TC/ZDV N = 264	Total N = 526
	N (%)	N (%)	N (%)
BLOOD AND LYMPHATIC			
Decreased white blood cells	13 (5)	11 (4)	24 (5)
EAR NOSE AND THROAT			
Taste impairment	5 (2)	22 (8)	27 (5)
Hyposalivation (“dry mouth”)	3 (1)	19 (7)	22 (4)
MUSCULOSKELETAL			
Musculoskeletal pain	9 (3)	17 (6)	26 (5)
Muscle pain	9 (3)	13 (5)	22 (4)
NEUROLOGY			
Malaise & fatigue	77 (29)	74 (28)	151 (29)
Headache	47 (18)	39 (15)	86 (16)
Feeding problems (primarily anorexia/loss of appetite)	26 (10)	20 (8)	46 (9)
Dizziness	12 (5)	26 (10)	38 (7)
Sleep disorders	20 (8)	17 (6)	37 (7)
Temperature regulation disturbance (fever &/or chills)	18 (7)	7 (3)	25 (5)
Pain	8 (3)	16 (6)	22 (4)
RENAL			
Renal signs and symptoms	2 (<1)	15 (6)	17 (3)
Dysuria	1 (<1)	12 (5)	13 (2)
SKIN			
Disorders of sweat & sebum (primarily dry skin)	49 (19)	74 (28)	123 (23)
Skin rashes	15 (6)	15 (6)	30 (6)
Pruritus	7 (3)	19 (7)	26 (5)

Adverse reactions reported with the individual components of TRIZIVIR

The following adverse events have been reported with the individual components of TRIZIVIR. Adverse events occurring in at least 5% of patients are listed in bold typeface in Table 2 below.

IMPORTANT: For information on abacavir hypersensitivity refer to the section below.

Table 2: Adverse Reactions Reported with the Individual Components of TRIZIVIR

	Abacavir	Lamivudine	Zidovudine
Cardiovascular			Cardiomyopathy
Gastrointestinal tract	**Nausea, vomiting, diarrhoea,** anorexia.	**Nausea, vomiting, diarrhoea, upper abdominal pain**	**Nausea, vomiting, anorexia,** diarrhoea, abdominal pain, oral mucosa pigmentation, dyspepsia and flatulence.
Haematological		Anaemia, neutropenia, thrombocytopenia Pure red cell aplasia	Anaemia, neutropenia and leucopenia and aplastic anaemia (see below for further details*),

	Abacavir	Lamivudine	Zidovudine
			thrombocytopenia, and pancytopenia with marrow hypoplasia and pure red cell aplasia.
Liver/pancreas	Pancreatitis.	Transient rises in liver enzymes (AST, ALT), rises in serum amylase, pancreatitis.	Liver disorders such as severe hepatomegaly with steatosis, rises in blood levels of liver enzymes and bilirubin, pancreatitis.
Metabolic/endocrine	Lactic acidosis[1]	Lactic acidosis[1]	Lactic acidosis[1]
	Hyperlactataemia	Hyperlactataemia	Hyperlactataemia
			Lipoatrophy[2]
Musculoskeletal		**Muscle disorders**, rarely rhabdomyolysis arthralgia	**Myalgia,** myopathy.
Neurological/ psychiatry	**Headache.**	**Headache,** peripheral neuropathy, paraesthesia	**Headache, insomnia,** paraesthesia, dizziness, somnolence, loss of mental acuity, convulsions, anxiety, depression.
Respiratory tract			Cough, dyspnoea.
Skin	Rash without systemic symptoms. Very rarely erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis.	**Rash, alopecia.**	Rash, nail and skin pigmentation, urticaria, pruritus, sweating.
Miscellaneous	**Fever, lethargy, fatigue.**	**Fever, malaise, fatigue**.	**Malaise,** fever, urinary frequency, taste perversion, generalised pain, chills, chest pain, influenza-like syndrome, gynaecomastia, asthenia.

[1] Lactic acidosis: see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.
[2] Lipoatrophy: Treatment with zidovudine has been associated with loss of subcutaneous fat (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Description of selected adverse reactions

Adverse events with abacavir

Many of the adverse events listed above for abacavir (nausea, vomiting, diarrhoea, fever, fatigue, rash) occur commonly as part of abacavir hypersensitivity. Therefore, patients with any of these symptoms should be carefully evaluated for the presence of this hypersensitivity reaction. If TRIZIVIR has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart TRIZIVIR, this should be done only under direct medical supervision (see Special considerations following an interruption of

TRIZIVIR therapy).

Hypersensitivity **(see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)**
Abacavir hypersensitivity reaction (HSR) has been identified as a common adverse reaction with abacavir therapy. The signs and symptoms of this hypersensitivity reaction are listed below. These have been identified either from clinical studies or post marketing surveillance. Those reported in **at least 10% of patients** with a hypersensitivity reaction are in bold text.

Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however, reactions have occurred without rash or fever. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.

Skin:	**Rash** (usually maculopapular or urticarial)
Gastrointestinal tract:	**Nausea, vomiting, diarrhoea, abdominal pain,** mouth ulceration
Respiratory tract:	**Dyspnoea, cough,** sore throat, adult respiratory distress syndrome, respiratory failure
Miscellaneous:	**Fever, fatigue, malaise,** oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/psychiatry:	**Headache,** paraesthesia
Haematological:	Lymphopenia
Liver/pancreas:	**Elevated liver function tests,** hepatic failure
Musculoskeletal:	**Myalgia,** rarely myolysis, arthralgia, elevated creatine phosphokinase
Urology:	Elevated creatinine, renal failure

Restarting abacavir following an abacavir HSR results in a prompt return of symptoms within hours. This recurrence of the HSR is usually more severe than on initial presentation, and may include life-threatening hypotension and death. Reactions have also occurred infrequently after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity (see above) prior to stopping abacavir; and on very rare occasions have also been seen in patients who have restarted therapy with no preceding symptoms of a HSR (i.e., patients previously considered to be abacavir tolerant).

For details of clinical management in the event of a suspected abacavir HSR see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Haematological adverse events with zidovudine
Anaemia (which may require transfusions), neutropenia and leucopenia occurred more frequently at higher dosages (1200-1500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment) and particularly in

patients with CD4 cell counts less than 100/mm^3. Dosage reduction or cessation of therapy may become necessary (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). The anaemia appeared to be the result of impaired erythrocyte maturation as evidenced by increasing macrocytosis (MCV) while on drug.

The incidence of neutropenia was also increased in those patients whose neutrophil counts, haemoglobin levels and serum vitamin B_{12} levels were low at the start of zidovudine therapy.

Post marketing data

Metabolism and nutrition disorders
Hyperlactataemia (common)

Lactic acidosis (rare, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no experience of overdosage with TRIZIVIR. However, there are limited data available on the consequences of ingestion of acute overdoses of either lamivudine or zidovudine in humans. No fatalities occurred, and all patients recovered. No specific signs or symptoms have been identified following such overdosage apart from those listed in Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). Single doses up to 1200 mg and daily doses up to 1800 mg of abacavir have been administered to patients in clinical studies. No unexpected adverse reactions were reported. The effects of higher doses are not known.

Treatment
Patients should be observed closely for evidence of toxicity (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) and given the necessary supportive therapy.

Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied. Haemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine. The primary metabolite, GAZT, appears to be more efficiently removed by haemodialysis than peritoneal dialysis. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

For more details, physicians should refer to the individual product information for abacavir, lamivudine and zidovudine.

For information on the management of overdose, contact the Poison Information Centre on 131 126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Abacavir, lamivudine and zidovudine are all nucleoside analogue reverse transcriptase inhibitors.

Abacavir is a selective antiretroviral agent against HIV-1 and HIV-2, including HIV-1 isolates that are resistant to zidovudine, lamivudine, zalcitabine, didanosine or nevirapine. Zidovudine is an inhibitor of the *in vitro* replication of some retroviruses including HIV, whereas lamivudine is a potent, selective inhibitor of HIV-1 and HIV-2 replication *in vitro.* All three drugs are metabolised sequentially by intracellular kinases to their 5'-triphosphate (TP) derivatives. Carbovir 5'-triphosphate, lamivudine 5'-triphosphate and zidovudine 5'-triphosphate are substrates for and competitive inhibitors of HIV reverse transcriptase. However, their main antiviral activity is through incorporation of the monophosphate (MP) form into the viral DNA chain, resulting in chain termination. Abacavir, lamivudine and zidovudine triphosphates show significantly less affinity for host cell DNA polymerases.

The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir. No antagonistic effects *in vitro* were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine, zalcitabine, and zidovudine). No antagonistic effects *in vitro* were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine, lamivudine and interferon-alpha).

The relationships between *in vitro* susceptibility of HIV to lamivudine and zidovudine and the clinical response to therapy remain under investigation. *In vitro* sensitivity testing has not been standardised and results may vary according to methodological factors.

Resistance
In vitro selection of abacavir-resistant isolates of HIV-1 is associated with specific genotypic changes in the reverse transcriptase (RT) codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro* and *in vivo,* requiring multiple mutations to reach an eight fold increase in IC_{50} of the wild-type virus. Isolates resistant to abacavir may also show reduced sensitivity to lamivudine, zalcitabine and/or didanosine, but remain sensitive to zidovudine and stavudine. Treatment failure following initial therapy with abacavir, lamivudine and zidovudine is mainly associated with the M184V alone, thus maintaining many therapeutic options for a second line regimen.

Cross-resistance between abacavir, zidovudine or lamivudine and protease inhibitors or non-nucleoside reverse transcriptase inhibitors is unlikely. Reduced susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors.

Individually, lamivudine and zidovudine therapy has resulted in HIV clinical isolates which

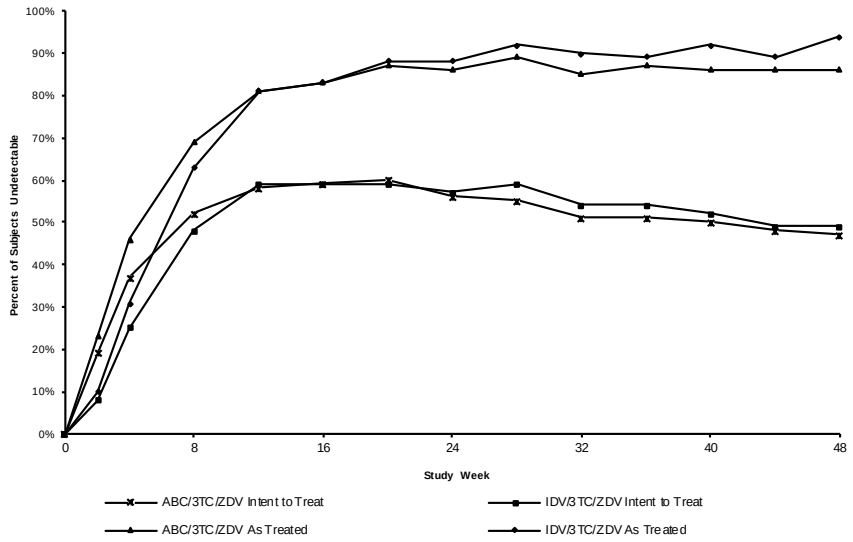
show reduced sensitivity *in vitro* to the nucleoside analogue to which they have been exposed. However *in vitro* studies also indicate that zidovudine-resistant virus isolates may become sensitive again to zidovudine when they simultaneously acquire resistance to lamivudine. Furthermore *in-vivo* there is clinical evidence that lamivudine plus zidovudine delays the emergence of zidovudine resistance in anti-retroviral naive patients.

Clinical trials

Antiretroviral-naïve subjects

Antiretroviral-naïve adults: CNAAB3005 is a randomised, double-blind, multicentre study in which 562 HIV-infected antiretroviral-naïve adults were randomised to receive either 300 mg abacavir sulfate (ABC) tablets, twice daily and a COMBIVIR tablet (containing 150 mg lamivudine (3TC) and 300 mg zidovudine (ZDV)) twice daily, or 800 mg indinavir (IDV) every 8 hours plus a COMBIVIR tablet twice daily. The duration of treatment was 48 weeks. Approximately 87% of study participants in each group were male with a total of 73% white, 15% black, 9% American Hispanics and 2% Asians. The median age was 36 years. The median baseline CD4+ cell counts were 359 and 360 cells/mm^3 for the ABC/3TC/ZDV and IDV/3TC/ZDV treatment groups respectively, while median baseline plasma HIV-1 RNA concentrations were 4.85 and 4.82 log_{10} copies/mL respectively. The proportion of patients with plasma HIV-1 RNA ≤ 400 copies/mL (using Roche Amplicor HIV-1 Monitor® test) through 48 weeks of treatment are summarised in Figure 1.

Figure 1: Proportion of Subjects with Undetectable Viral Load (≤400 copies/mL) by Study Week



In Intent To Treat (ITT) analysis at 48 weeks the combination of abacavir, lamivudine and zidovudine showed an equivalent anti-viral effect (plasma HIV-1 RNA ≤ 400 copies/mL) to a combination of indinavir, lamivudine and zidovudine (47% vs 49% respectively; 95% CI of difference in proportions (-10%, 7%)). Overall, the proportion of ITT subjects with plasma HIV-1 RNA ≤ 50 copies/mL were comparable between the two groups at week 48 (37% vs 43% respectively; 95% CI of difference in proportions (-15, 2)).

Subjects with baseline HIV-1 RNA > 100,000 copies/mL demonstrated comparable antiretroviral activity between the abacavir, lamivudine and zidovudine (ABC/LAM/ZDV) treatment group and the indinavir, lamivudine and zidovudine (IND/LAM/ZDV) treatment group (as measured by ≤ 400 copies/mL assay). Although a difference in favour of IND/LAM/ZDV was observed at 48 weeks using a ≤ 50 copies/mL assay (ITT 29% ABC/LAM/ZDV vs 44% IND/LAM/ZDV; 95% CI -27, -1) this did not translate into a difference in time to viral rebound between the two groups.

In antiretroviral-naïve patients the triple combination of abacavir, lamivudine and zidovudine was superior in terms of durability of viral load response over 48 weeks to lamivudine and zidovudine (study CNAAB3003). In a similar antiretroviral-naïve patient population durability of antiviral response over 120 weeks was demonstrated in approximately 70% of subjects (study CNAB2002).

In antiretroviral-naïve patients treated with a combination of abacavir, lamivudine, zidovudine and efavirenz, the proportion of patients with undetectable viral load (< 400 copies/mL) was approximately 90% with 80% having < 50 copies/mL after 24 weeks of treatment (study CNAF3008).

In another clinical study over 16 weeks in antiretroviral-naïve patients, the combination of abacavir, lamivudine and zidovudine showed a similar antiviral effect to the combination with nelfinavir, lamivudine and zidovudine (study CNAF3007).

Antiretroviral experienced subjects
Virological suppression (< 50 copies/mL) was maintained over 24 weeks in antiretroviral experienced patients receiving therapy with highly active antiretroviral therapy including a protease inhibitor, who changed to therapy with abacavir, lamivudine and zidovudine (study CH 96 06 - Swiss Maintenance Study).

In moderately antiretroviral experienced patients with a low baseline viral load (< 50,000 copies/mL), treatment intensification with abacavir, lamivudine and zidovudine provided significant therapeutic benefit with an undetectable viral load (< 400 copies/mL) achieved in approximately 50% of patients at 48 weeks (study NZTA4005 - Target study).

In heavily NRTI experienced patients, the degree of benefit of this nucleoside combination will depend on the nature and duration of prior therapy that may have selected for HIV-1 variants with cross-resistance to abacavir, zidovudine or lamivudine.

Antiretroviral Pregnancy Registry
The Antiretroviral Pregnancy Registry (APR) has received prospective reports of over 2,000 exposures to abacavir during pregnancy resulting in live birth. These consist of over 900 exposures during the first trimester, over 1,200 exposures during the second/third trimester and included 29 and 33 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 2.9% (2.0, 4.2%) and in the second/third trimester, 2.6% (1.8, 3.7%).

The APR has received reports of over 11,000 exposures to lamivudine during pregnancy resulting in live birth. These consist of over 4,500 exposures during the first trimester, over

7,200 exposures during the second/third trimester and included 143 and 207 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.1% (2.6, 3.7%) and in the second/third trimester, 2.9% (2.5, 3.3%).

The APR has received reports of over 13,000 exposures to zidovudine during pregnancy resulting in live birth. These consist of over 4,100 exposures during the first trimester, over 9,300 exposures during the second/third trimester and included 133 and 264 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.2% (2.7, 3.8%) and in the second/third trimester, 2.8% (2.5, 3.2%).

These proportions are not significantly higher than those reported in the two population based surveillance systems (2.72 per 100 live births and 4.17 per 100 live births respectively). The Antiretroviral Pregnancy Registry does not show an increased risk of major birth defects for abacavir, lamivudine or zidovudine compared to the background rates.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Abacavir, lamivudine and zidovudine are rapidly and well absorbed from the gastro-intestinal tract following oral administration. The absolute bioavailability of oral abacavir, lamivudine and zidovudine in adults is about 83%, 80 - 85% and 60 - 70% respectively.

In a pharmacokinetic study in HIV-1 infected patients, the steady state pharmacokinetic parameters of abacavir, lamivudine and zidovudine were similar when either TRIZIVIR alone or ZIAGEN (abacavir) and COMBIVIR (lamivudine and zidovudine) in combination were administered. The steady state parameters were also similar to the values obtained in the bioequivalence study of TRIZIVIR in healthy volunteers.

A bioequivalence study compared TRIZIVIR with lamivudine 150 mg, zidovudine 300 mg and abacavir 300 mg taken together. The effect of food on the rate and extent of absorption was also studied. TRIZIVIR was shown to be bioequivalent to abacavir 300 mg, lamivudine 150 mg and zidovudine 300 mg given as separate tablets for AUC_{∞} and C_{max}. Food decreased the rate of absorption of all three components of TRIZIVIR (slight decrease in C_{max} (mean 18 - 32%) and increased T_{max} (approximately 1 hour)), but not the extent of absorption (AUC_{∞}). The changes observed with food are not considered to be clinically significant.

Distribution

Intravenous studies with lamivudine, abacavir and zidovudine showed that the mean apparent volume of distribution is 1.3, 0.8 and 1.6 L/kg respectively. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 36% serum albumin *in vitro).* Zidovudine plasma protein binding is 34% to 38%. Plasma protein binding studies *in vitro* indicate that abacavir binds only low to moderately (~49%) to human plasma proteins at therapeutic concentrations. This indicates a low likelihood for interactions with other medicinal products through plasma protein binding displacement. Drug interactions involving binding site displacement are therefore not anticipated with TRIZIVIR.

Data show that lamivudine, abacavir and zidovudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). The mean ratios of CSF/serum lamivudine and zidovudine concentrations 2 - 4 hours after oral administration were approximately 0.12 and 0.5 respectively. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

Studies in HIV infected patients have shown good penetration of abacavir into the cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44%. In a Phase I pharmacokinetic study, the penetration of abacavir into the CSF was investigated following administration of abacavir 300 mg twice a day. The mean concentration of abacavir achieved in the CSF 1.5 hours post dose was 0.14 µg/mL. In a further pharmacokinetic study of 600 mg twice a day, the CSF concentration of abacavir increased over time, from approximately 0.13 µg/mL at 0.5 to 1 hour after dosing, to approximately 0.74 µg/mL after 3 to 4 hours. While peak concentrations may not have been attained by 4 hours, the observed values are 9 fold greater than the IC_{50} of abacavir of 0.08 µg/mL or 0.26 µM.

Metabolism

Abacavir is primarily metabolised by the liver with less than 2% of the administered dose being renally excreted, as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the dose in the urine.

The likelihood of adverse drug interactions with lamivudine is low due to limited metabolism (< 10% hepatic) and plasma protein binding and almost complete renal elimination.

Zidovudine is rapidly metabolised during first pass to 3'-azido-3'-deoxy-5'-O-β-D-glucopyranuronosylthymidine (GAZT) which has an apparent elimination half-life of 1 hour (range 0.61 to 1.73 hours). Following oral administration, urinary recoveries of zidovudine and GAZT accounted for 14 and 74% of the dose, respectively, and the total urinary recovery averaged 90% (range 63 to 95%), indicating a high degree of absorption.

Limited data has identified 3'-amino-3'deoxythymidine (AMT) as a metabolite of zidovudine following intravenous and oral dosing. A small *in vitro* study showed that AMT reduced the growth of haemopoietic progenitor cells; the clinical significance of this finding is unknown.

Excretion

The mean half-life of abacavir is about 1.5 hours. Following multiple oral doses of abacavir 300 mg twice a day there is no significant drug accumulation. Elimination of abacavir is via hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir account for about 83% of the administered abacavir dose in the urine; the remainder is eliminated in the faeces.

Mean terminal half-life of elimination of lamivudine is 5 to 7 hours and mean systemic clearance is approximately 0.32 L/h/kg, with predominantly renal clearance (> 70%) via the organic cationic transport system, but little (< 10%) hepatic metabolism.

Studies in patients with renal impairment show lamivudine elimination is affected by renal

dysfunction. Dose reduction is required for patients with creatinine clearance < 50 mL/min (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Lamivudine crosses the placenta in rats and rabbits.

From studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours and the mean systemic clearance was 1.6 L/h/kg. Renal clearance of zidovudine is estimated to be 0.34 L/h/kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure. Limited data indicate that zidovudine crosses the placenta and is found in amniotic fluid and foetal blood. Zidovudine has also been detected in semen.

Special populations

Hepatically impaired
There are no data available on the use of TRIZIVIR in hepatically impaired patients. Limited data in patients with cirrhosis suggest that accumulation of zidovudine may occur, because of decreased glucuronidation. Dosage adjustment of zidovudine is required in patients with severe hepatic impairment. Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6). The results showed that there was a mean increase of 1.89 fold in the abacavir AUC and 1.58 fold in the half-life of abacavir. The AUCs of the metabolites were not modified by the liver disease. However, the rates of formation and elimination of these were decreased. Dosage reduction of abacavir is likely to be required in patients with mild hepatic impairment. The pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment, and TRIZIVIR is therefore not recommended in these patient groups.

Renally impaired
Abacavir is primarily metabolised by the liver with less than 2% of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function. Therefore, no dose reduction is required in patients with renal impairment.

A single dose pharmacokinetic study of lamivudine (n=16) in HIV-infected patients with normal renal function and with moderate (creatinine clearance < 30 mL/min and > 10 mL/min) or end stage renal impairment (creatinine clearance < 10 mL/min) showed there was a linear relationship between lamivudine clearance and renal function.

Zidovudine concentrations have also been shown to be increased in patients with advanced renal failure. Dosage adjustment of zidovudine is required in patients with advanced renal failure.

As dosage reduction of lamivudine and zidovudine may be necessary in renally impaired patients it is recommended that separate preparations of zidovudine, lamivudine and abacavir be administered to patients with reduced renal function (creatinine clearance ≤ 50 mL/min).

Elderly
The pharmacokinetics of TRIZIVIR have not been studied in patients over 65 years of age. When treating elderly patients consideration needs to be given to the greater frequency of decreased hepatic, renal and cardiac function, and concomitant disease or other drug therapy.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Abacavir was inactive in *in vitro* tests for gene mutation in bacteria but it showed clastogenic activity against human lymphocytes *in vitro* and in an *in vivo* mouse micronucleus test. 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. Abacavir was not mutagenic in bacterial mutagenicity assays.

With zidovudine no evidence of mutagenicity (with or without metabolic activation) was observed in the *Salmonella* mutagenicity assay. In a mutagenicity assay conducted in L5178Y/TK+/- mouse lymphoma cells, zidovudine was weakly mutagenic in the presence and absence of metabolic activation. In an *in vitro* cytogenetic study performed in cultured human lymphocytes, zidovudine induced dose-related structural chromosomal abnormalities. Zidovudine was clastogenic in *in vivo* micronucleus tests in rats and mice. Zidovudine gave positive results in an *in vitro* mammalian cell transformation assay.

Lamivudine was not active in a microbial mutagenicity screen but did induce mutations at the thymidine kinase locus of mouse lymphoma L5178Y cells without metabolic activation. Lamivudine was clastogenic in human peripheral blood lymphocytes *in vitro,* with or without metabolic activation. In rats, lamivudine did not cause chromosomal damage in bone marrow cells *in vivo* or cause DNA damage in primary hepatocytes.

Carcinogenicity
The carcinogenic potential of a combination of abacavir, lamivudine and zidovudine has not been tested.

Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver, urinary bladder, lymph nodes and the subcutis of female rats. Nonmalignant tumours occurred in the liver of mice and rats, Harderian gland of female mice, and thyroid gland of rats. In rats, there were also increased incidences of urothelial hyperplasia and urinary bladder tumours, associated with increased urinary calculi.

The majority of these tumours occurred at the highest abacavir dose of 330 mg/kg/day in mice and 600 mg/kg/day in rats. These dose levels were equivalent to 24 to 32 times the expected systemic exposure in humans. The exception was the preputial gland tumour which occurred at a dose of 110 mg/kg. This is equivalent to six times the expected human systemic exposure.

Zidovudine was administered orally to separate groups of mice and rats at doses up to 40

and 300 mg/kg/day, respectively. In mice, seven late-appearing (after 19 months) vaginal neoplasms (5 non-metastasising squamous cell carcinomas, one squamous cell papilloma, and one squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle dose animal. No vaginal tumours were found at the lowest dose. In rats, two late-appearing (after 20 months), non-metastasising vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumours occurred at the low or middle dose in rats. No other drug related tumours were observed in either sex of either species. At doses that produced tumours in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 4 times (mouse) and 27 times (rat) the estimated human exposure at the recommended therapeutic dose of one tablet twice daily.

When lamivudine was administered orally to separate groups of rodents at doses up to 2000 mg/kg/day (mice and male rats) and 3000 (female rats) mg/kg/day, there was no evidence of a carcinogenic effect due to lamivudine in the mouse study. In the rat study there was an increased incidence of endometrial tumours at the highest dose (approximately 70 times the estimated human exposure at the recommended therapeutic dose of one tablet twice daily, based on AUC). However, the relationship of this increase to treatment is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose
Sodium starch glycollate
Magnesium stearate
Hypromellose
Titanium dioxide
Macrogol 400
Indigo carmine aluminium lake
Iron oxide yellow.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C in a dry place.

6.5 NATURE AND CONTENTS OF CONTAINER

Tablets are available in white Aclar blister packs or opaque white child-resistant* foil Aclar blister packs or plastic HDPE bottles with a child-resistant closure. Each pack type contains 60 tablets.

*complies with European Standard *EN 14375:2003 Child-resistant Non-reclosable Packaging for Pharmaceutical Products - Requirements And Testing.*

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

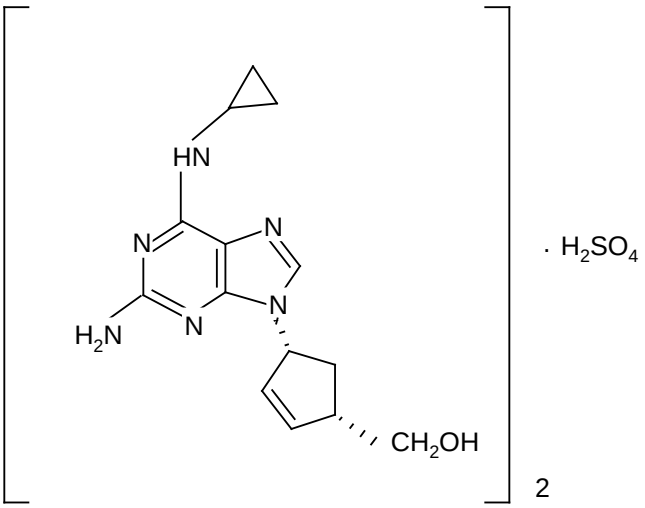
6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name of abacavir sulfate is [4R-(2-Amino-6-cyclopropylamino-purin-9-yl)-cyclopent-2-en-1S-yl]-methanol sulfate (2:1). The molecular formula of abacavir sulfate is $(C_{14}H_{18}N_6O)2.H_2SO_4$ and it has a relative molecular mass of 670.76.

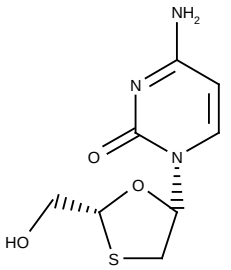
Lamivudine is the free base of (2R-cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine has a molecular weight of 229.3 and molecular formula $C_8H_{11}N_3O_3S$.

The chemical name of zidovudine (formerly called azidothymidine (AZT)) is 3'-azido-3'-deoxythymidine. Zidovudine has a molecular weight of 267.24 and molecular formula $C_{10}H_{13}N_5O_4$.

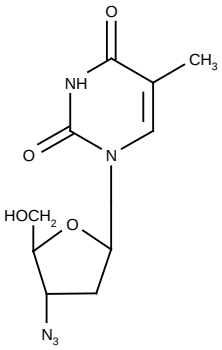
Chemical structure
Abacavir sulfate has the following structural formula:



Lamivudine has the following structural formula:



Zidovudine has the following structural formula:



CAS number
188062-50-2 (abacavir sulfate); 134678-17-4 (lamivudine); 30516-87-1 (zidovudine).

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

ViiV Healthcare Pty Ltd
Level 4, 436 Johnston Street
Abbotsford, Victoria, 3067
Australia

9 DATE OF FIRST APPROVAL

06 June 2001

10 DATE OF REVISION

28 September 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Update to Transmission of Infection
4.5	Addition of a potential drug-drug interaction between abacavir and riociguat

Version 15.0