Emzavir®

Emtricitabine / Tenofovir Disoproxil Fumarate

FORMS AND PRESENTATION

Emzavir®: Film coated tablets: Box of 30.

COMPOSITION

Emzavir®: Each film coated tablet contains Emtricitabine 200mg and Tenofovir Disoproxil Fumarate 300mg Eq. to Tenofovir Disoproxil 245mg.

Excipients: starch, lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, FD&C blue, triacetin, titanium dioxide.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Antivirals for systemic use.

ATC code: J05AR01.

Emtricitabine is a nucleoside analogue of cytidine. Tenofovir Disoproxil Fumarate is converted in vivo to Tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Both Emtricitabine and Tenofovir have activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus.

Emtricitabine and Tenofovir are phosphorylated by cellular enzymes to form Emtricitabine Triphosphate and Tenofovir Diphosphate, respectively. In vitro studies have shown that both Emtricitabine and Tenofovir can be fully phosphorylated when combined together in cells. Emtricitabine Triphosphate and Tenofovir Diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination.

Both Emtricitabine Triphosphate and Tenofovir Diphosphate are weak inhibitors of mammalian DNA polymerases and there was no evidence of toxicity to mitochondria in vitro and in vivo.

Pharmacokinetic properties

Absorption

Following oral administration of Emzavir® to healthy subjects, Emtricitabine and Tenofovir Disoproxil Fumarate are rapidly absorbed and Tenofovir Disoproxil Fumarate is converted to Tenofovir. Maximum Emtricitabine and Tenofovir concentrations are observed in serum within 0.5 to 3.0 h of dosing in the fasted state. Administration of Emzavir® with food resulted in a delay of approximately three quarters of an hour in reaching maximum Tenofovir concentrations and increases in Tenofovir AUC and C_{max} of approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In order to optimize the absorption of Tenofovir, it is recommended that Emzavir® should be taken with food.

Distribution

Following intravenous administration the volume of distribution of Emtricitabine and Tenofovir was approximately 1.4 l/kg and 800 ml/kg, respectively. After oral administration of Emtricitabine or Tenofovir Disoproxil Fumarate, Emtricitabine and Tenofovir are widely distributed throughout the body. In vitro binding of Emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02 to 200 µg/ml.

Biotransformation

There is limited metabolism of Emtricitabine. The biotransformation of Emtricitabine includes oxidation of the thiol moiety to form the 3'-sulphoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). In vitro studies have determined that neither Tenofovir Disoproxil Fumarate nor Tenofovir are substrates for the CYP450 enzymes. Neither Emtricitabine nor Tenofovir inhibited in vitro drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation. Also, Emtricitabine did not inhibit uridine-5'-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.

Elimination

Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and feces (approximately 14%). Thirteen percent of the Emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of Emtricitabine averaged 307 ml/min. Following oral administration, the elimination half-life of Emtricitabine is approximately 10 hours.

Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration. The apparent clearance of Tenofovir averaged approximately 307 ml/min. Renal clearance has been estimated to be approximately 210 ml/min, which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of Tenofovir. Following oral administration, the elimination half-life of Tenofovir is approximately 12 to 18 hours.

INDICATIONS

Emzavir® is a fixed dose combination of Emtricitabine and Tenofovir Disoproxil Fumarate. It is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults aged 18 years and over.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

- Co-administration of other medicinal products: Emzavir® should not be administered concomitantly with other medicinal products containing Emtricitabine, Tenofovir Disoproxil (as Fumarate) or other cytidine analogues, such as lamivudine. Emzavir® should not be administered concomitantly with adefovir dipivoxil.

- Co-administration of Tenofovir Disoproxil Fumarate and didanosine: Is not recommended. Co-administration of Tenofovir Disoproxil Fumarate and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of Tenofovir Disoproxil Fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with Tenofovir Disoproxil Fumarate therapy has been associated with reports of high rates of virological failure within several tested combinations.

- Triple nucleoside therapy: There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when Tenofovir Disoproxil Fumarate was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen. There is close structural similarity between lamivudine and Emtricitabine and similarities in the pharmacokinetics and pharmacodynamics of these two agents. Therefore, the same problems may be seen if Emzavir® is administered with a third nucleoside analogue.

- Opportunistic infections: Patients receiving Emzavir® or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

- Transmission of HIV: Patients must be advised that antiretroviral therapies, including Emzavir®, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.

- Renal impairment: Emtricitabine and Tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Renal failure, renal impairment, elevated creatinine, hypophosphatemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of Tenofovir Disoproxil Fumarate in clinical practice.

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with Emzavir® and renal function (creatinine clearance and serum phosphate) is also monitored every four weeks during the first year and then every three months. In patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function.

- Patients with renal impairment (creatinine clearance < 80 ml/min), including hemodialysis patients: Renal safety with Emzavir® has only been studied to a very limited degree in patients with impaired renal function (creatinine clearance < 80 ml/min). Dose interval adjustments are recommended for patients with creatinine clearance 30-49 ml/min. A careful benefit-risk assessment is needed when Emzavir® is used in patients with creatinine clearance < 60 ml/min, and renal function should be closely monitored. In addition, the clinical response to treatment should be closely monitored in patients receiving Emzavir® at a prolonged dosing interval. The use of Emzavir® is not recommended in patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require hemodialysis since appropriate dose reductions cannot be achieved with the combination tablet.

If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving Emzavir®, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Consideration should also be given to interrupting treatment with Emzavir® in patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).

Use of Emzavir® should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If concomitant use of Emzavir® and nephrotoxic agents is unavoidable, renal function should be monitored weekly.

- Patients with HIV-1 harboring mutations: Emzavir® should be avoided in antiretroviral-experienced patients with HIV-1 harboring the K65R mutation.

- Bone effects: In a 144-week controlled clinical study that compared Tenofovir Disoproxil Fumarate with stavudine in combination with lamivudine and efavirenz in antiretroviral-naïve patients, small decreases in bone mineral density of the hip and spine were observed in both treatment groups. Decreases in bone mineral density of spine and changes in bone biomarkers from baseline were significantly greater in the Tenofovir Disoproxil Fumarate treatment group at 144 weeks. Decreases in bone mineral density of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. If bone abnormalities are suspected then appropriate consultation should be obtained.

- Patients with HIV and hepatitis B or C virus co-infection: Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products.

The safety and efficacy of Emzavir® have not been established for the treatment of chronic HBV infection. Emtricitabine and Tenofovir individually and in combination have shown activity against HBV in pharmacodynamic studies. Limited clinical experience suggests that Emtricitabine and Tenofovir Disoproxil Fumarate have anti-HBV activity when used in antiretroviral combination therapy to control HIV infection.

Discontinuation of Emzavir® therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Emzavir® should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

- Liver disease: The safety and efficacy of Emzavir® have not been established in patients with significant underlying liver disorders. The pharmacokinetics of Emzavir® and Emtricitabine have not been studied in patients with hepatic impairment. The pharmacokinetics of Tenofovir have been studied in patients with hepatic impairment and no dose adjustment is required in these patients. Based on minimal hepatic metabolism and the renal route of elimination for Emtricitabine, it is unlikely that a dose adjustment would be required for Emzavir® in patients with hepatic impairment.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

- Lactic acidosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure. Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

- Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesized. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Tenofovir is structurally related to nucleoside analogues hence the risk of lipodystrophy cannot be excluded.

- Mitochondrial dysfunction: Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or post-natally to nucleoside analogues. The main adverse reactions reported are hematological disorders (anemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behavior). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed in utero to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

- Immune Reactivation Syndrome: In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens 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 CART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

HIV infected patients co-infected with hepatitis B virus may experience acute exacerbations of hepatitis associated with immune reactivation syndrome following the initiation of antiretroviral therapy.

- Osteonecrosis: Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

- Elderly: Emzavir® has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with Emzavir®.

- Emzavir® contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with both Emtricitabine and Tenofovir Disoproxil Fumarate.

PREGNANCY AND LACTATION

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicates no malformations or fetal/neonatal toxicity associated with Emtricitabine and Tenofovir Disoproxil Fumarate. Animal studies on Emtricitabine and Tenofovir Disoproxil Fumarate do not

Disoproxil Fumarate. Animal studies on Emtricitabine and Tenofovir Disoproxil Fumarate do not indicate reproductive toxicity. Therefore the use of Emzavir® may be considered during pregnancy, if necessary.
Emtricitabine and Tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of Emtricitabine and Tenofovir in newborns/infants. Therefore Emzavir® should not be used during breast-feeding.
As a general rule, it is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV to the infant.
No human data on the effect of Emzavir® are available. Animal studies do not indicate harmful effects of Emtricitabine or Tenofovir Disoproxil Fumarate on fertility.

DRUG INTERACTIONS

As Emzavir® contains Emtricitabine and Tenofovir Disoproxil Fumarate, any interactions that have been identified with these agents individually may occur with Emzavir®. Interaction studies have only been performed in adults.
The steady-state pharmacokinetics of Emtricitabine and Tenofovir were unaffected when Emtricitabine and Tenofovir Disoproxil Fumarate were administered together versus each medicinal product dosed alone.
In vitro and clinical pharmacokinetic interaction studies have shown the potential for CYP450 mediated interactions involving Emtricitabine and Tenofovir Disoproxil Fumarate with other medicinal products is low.
- Concomitant use not recommended: Due to similarities with Emtricitabine, Emzavir® should not be administered concomitantly with other cytidine analogues, such as lamivudine.
As a fixed combination, Emzavir® should not be administered concomitantly with other medicinal products containing any of the components, Emtricitabine or Tenofovir Disoproxil Fumarate.
Emzavir® should not be administered concomitantly with adefovir dipivoxil.
- Renally eliminated medicinal products: Since Emtricitabine and Tenofovir are primarily eliminated by the kidneys, co-administration of Emzavir® with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of Emtricitabine, Tenofovir and/or the co-administered medicinal products.
Use of Emzavir® should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2.
- Protease inhibitors: The concomitant administration of atazanavir 300 mg once daily, ritonavir 100 mg once daily and Tenofovir Disoproxil Fumarate 300 mg once daily decreased atazanavir AUC by 25%, C_{max} by 28% and C_{min} by 26% and increased Tenofovir AUC by 37%, C_{max} by 34% and C_{min} by 29%. No dose adjustment is recommended. The increased exposure of Tenofovir could potentiate Tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored.
The concomitant administration of darunavir 300 mg once daily, ritonavir 100 mg once daily and Tenofovir Disoproxil Fumarate 300 mg once daily increased Tenofovir AUC by 22% and C_{min} by 37%. No dose adjustment is recommended. The increased exposure of Tenofovir could potentiate Tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored.
The concomitant administration of lopinavir 400 mg twice daily, ritonavir 100 mg twice daily and Tenofovir Disoproxil Fumarate 300 mg once daily increased Tenofovir AUC by 32% and C_{min} by 51%. No dose adjustment is recommended. The increased exposure of Tenofovir could potentiate Tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored.
- Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs): Co-administration of Tenofovir Disoproxil Fumarate and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk for didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of Tenofovir Disoproxil Fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with Tenofovir Disoproxil Fumarate therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection. Co-administration of Emzavir® and didanosine is not recommended.

ADVERSE EFFECTS

The most frequently reported adverse reactions considered possibly or probably related to Emtricitabine and/or Tenofovir Disoproxil Fumarate were nausea (12%) and diarrhea (7%) in an open-label randomized clinical trial. The safety profile of Emtricitabine and Tenofovir Disoproxil Fumarate in this study was consistent with the previous experience with these agents when each was administered with other antiretroviral agents.
In patients receiving Tenofovir Disoproxil Fumarate, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Emzavir®.
Lactic acidosis, severe hepatomegaly with steatosis and lipodystrophy are associated with Tenofovir Disoproxil Fumarate and Emtricitabine.
Co-administration of Tenofovir Disoproxil Fumarate and didanosine is not recommended as this may result in an increased risk of adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.
Discontinuation of Emzavir® therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis.
The adverse reactions considered at least possibly related to treatment with the components of Emzavir® from clinical trial and post-marketing experience are listed by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) or rare (≥ 1/10,000 to < 1/1,000).

Emtricitabine

- Blood and lymphatic system disorders: Neutropenia (common); anemia (uncommon).
- Immune system disorders: Allergic reaction (common).
- Metabolism and nutrition disorders: Hyperglycemia, hypertriglyceridemia (common).
- Psychiatric disorders: Insomnia, abnormal dreams (common).
- Nervous system disorders: Headache (very common); dizziness (common).
- Gastrointestinal disorders: Diarrhea, nausea (very common); elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia (common).
- Hepatobiliary disorders: Elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), hyperbilirubinemia (common).
- Skin and subcutaneous tissue disorders: Vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discoloration (increased pigmentation) (common); angioedema (uncommon).
- Musculoskeletal and connective tissue disorders: Elevated creatine kinase (very common).
- General disorders and administration site conditions: Pain, asthenia (common).

Tenofovir Disoproxil Fumarate

- Metabolism and nutrition disorders: Hypophosphatemia (very common); hypokalemia (uncommon); lactic acidosis (rare).
- Nervous system disorders: Dizziness (very common); headache (common).
- Gastrointestinal disorders: Diarrhea, vomiting, nausea (very common); abdominal pain, abdominal distension, flatulence (common); pancreatitis (uncommon).
- Hepatobiliary disorders: Increased transaminases (common); hepatic steatosis, hepatitis (rare).
- Skin and subcutaneous tissue disorders: Rash (very common); angioedema (rare).
- Musculoskeletal and connective tissue disorders: Rhabdomyolysis, muscular weakness (uncommon); osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy (rare).
- Renal and urinary disorders: Increased creatinine, proteinuria (uncommon); renal failure (acute and chronic), acute tubular necrosis, proximal renal tubulopathy including Fanconi syndrome, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus (rare).
- General disorders and administration site conditions: Asthenia (very common).

Hypophosphatemia, hypokalemia, rhabdomyolysis, muscular weakness, osteomalacia and myopathy may occur as a consequence of proximal renal tubulopathy. They are not considered to be causally associated with Tenofovir Disoproxil Fumarate in the absence of this condition.
Anemia was common and skin discoloration (increased pigmentation) was very common when Emtricitabine was administered to pediatric patients.
- Renal impairment: As Emzavir® may cause renal damage monitoring of renal function is recommended.
- Interaction with didanosine: Co-administration of Tenofovir Disoproxil Fumarate and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.
- Lipids, lipodystrophy and metabolic abnormalities: Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolemia, insulin resistance, hyperglycemia and hyperlactatemia.
Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).
- Immune Reactivation Syndrome: In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.
- Osteonecrosis: Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown.
- Lactic acidosis and severe hepatomegaly with steatosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.
- Pediatric population: Insufficient safety data are available for children below 18 years of age. Emzavir® is not recommended in this population.
- Elderly: Emzavir® has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with Emzavir®.
- Patients with renal impairment: Since Tenofovir Disoproxil Fumarate can cause renal toxicity, close monitoring of renal function is recommended in any patient with renal impairment treated with Emzavir®.
- HIV/HBV or HCV co-infected patients: The adverse reaction profile of Emtricitabine and Tenofovir Disoproxil Fumarate in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without co-infection. However, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.
- Exacerbations of hepatitis after discontinuation of treatment: In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis have occurred after discontinuation of treatment.

DOSAGE AND ADMINISTRATION

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

Adults

The recommended dose of Emzavir® is one tablet, taken orally, once daily. In order to optimize the absorption of Tenofovir, it is recommended that Emzavir® should be taken with food. Even a light meal improves absorption of Tenofovir from the combination tablet.
Where discontinuation of therapy with one of the components of Emzavir® is indicated or where dose modification is necessary, separate preparations of Emtricitabine and Tenofovir Disoproxil Fumarate are available.
If a patient misses a dose of Emzavir® within 12 hours of the time it is usually taken, the patient should take Emzavir® with food as soon as possible and resume their normal dosing schedule. If a patient misses a dose of Emzavir® by more than 12 hours and it is almost time for their next dose, the patient should not take the missed dose and simply resume the usual dosing schedule.
If the patient vomits within 1 hour of taking Emzavir®, another tablet should be taken. If the patient vomits more than 1 hour after taking Emzavir® they do not need to take another dose.

Elderly

No data are available on which to make a dose recommendation for patients over the age of 65 years. However, no adjustment in the recommended daily dose for adults should be required unless there is evidence of renal insufficiency.

Renal impairment

Emtricitabine and Tenofovir are eliminated by renal excretion and the exposure to Emtricitabine and Tenofovir increases in patients with renal dysfunction. There are limited data on the safety and efficacy of Emzavir® in patients with moderate and severe renal impairment (creatinine clearance < 50 ml/min) and long-term safety data has not been evaluated for mild renal impairment (creatinine clearance 50-80 ml/min). Therefore, in patients with renal impairment Emzavir® should only be used if the potential benefits of treatment are considered to outweigh the potential risks. Patients with renal impairment may require close monitoring of renal function. Dose interval adjustments are recommended for patients with creatinine clearance between 30 and 49 ml/min. These dose adjustments have not been confirmed in clinical studies and the clinical response to treatment should be closely monitored in these patients.
- Mild renal impairment (creatinine clearance 50-80 ml/min): Limited data from clinical studies support once daily dosing of Emzavir® in patients with mild renal impairment.
- Moderate renal impairment (creatinine clearance 30-49 ml/min): Administration of Emzavir® every 48 hours is recommended, based on modelling of single-dose pharmacokinetic data for Emtricitabine and Tenofovir Disoproxil Fumarate in non-HIV infected subjects with varying degrees of renal impairment.
- Severe renal impairment (creatinine clearance < 30 ml/min) and hemodialysis patients: Emzavir® is not recommended for patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require hemodialysis because appropriate dose reductions cannot be achieved with the combination tablet.

Hepatic impairment

The pharmacokinetics of Emzavir® and Emtricitabine have not been studied in patients with hepatic impairment. The pharmacokinetics of Tenofovir have been studied in patients with hepatic impairment and no dose adjustment is required for Tenofovir Disoproxil Fumarate in these patients. Based on minimal hepatic metabolism and the renal route of elimination for Emtricitabine, it is unlikely that a dose adjustment would be required for Emzavir® in patients with hepatic impairment.
If Emzavir® is discontinued in patients co-infected with HIV and HBV; these patients should be closely monitored for evidence of exacerbation of hepatitis.

Pediatric population

The safety and efficacy of Emzavir® in children under the age of 18 years have not been established.

Method of administration

Emzavir® tablets should be taken once daily, orally with food.
If patients have difficulty in swallowing, Emzavir® can be disintegrated in approximately 100 ml of water, orange juice or grape juice and taken immediately.

OVERDOSAGE

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.
Up to 30% of the Emtricitabine dose and approximately 10% of the Tenofovir dose can be removed by hemodialysis. It is not known whether Emtricitabine or Tenofovir can be removed by peritoneal dialysis.

STORAGE CONDITIONS

Store below 30°C.
Keep in original pack in intact conditions.

Date of revision: December 2016.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

Manufactured by Hetero Labs Limited, India
Packed by **Benta S.A.L.**, Lebanon

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