Vitricomb®

Emtricitabine / Tenofovir Disoproxil Fumarate / Efavirenz

FORMS AND PRESENTATION
Vitricomb®: Film Coated tablets: Box of 30.

COMPOSITION
Vitricomb®: Each film coated tablet contains Emtricitabine 200mg, Tenofovir Disoproxil Fumarate 300mg equivalent to 245mg of Tenofovir Disoproxil and Efavirenz 600mg.
Excipients: Microcrystalline cellulose, Croscarmellose sodium, Sodium lauryl sulphate, Hydroxy propyl cellulose, Magnesium stearate, Polyvinyl alcohol, Titanium Dioxide, Macrogol, Talc, Red iron oxide non-irradiated, Black iron oxide non-irradiated.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Antiviral for systemic use, antivirals for treatment of HIV infections, combinations.
ATC code: J05AR06.
Mechanism of action
Efavirenz: is an NNRTI of HIV-1. Efavirenz non-competitively inhibits HIV-1 reverse transcriptase (RT) and does not significantly inhibit human immunodeficiency virus-2 (HIV-2) RT or cellular deoxyribonucleic acid (DNA) polymerases (α, β, γ, and δ).
Emtricitabine: is a nucleoside analogue of cytidine.
Tenofovir disoproxil fumarate: is converted in vivo to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate.
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
In HIV infected patients, peak efavirenz plasma concentrations were attained by 5 hours and steady-state concentrations reached in 6 to 7 days. In 35 patients receiving efavirenz 600 mg once daily, steady-state peak concentration (Cmax) was 12.9 ± 3.7 µM (29%) [mean ± standard deviation (S.D.) (coefficient of variation (%CV))], steady-state Cmin was 5.6 ± 3.2 µM (57%), and AUC was 184 ± 73 µM•h (40%).
Emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV infected patients, steady-state Cmax was 1.8 ± 0.7 µg/ml (mean ± S.D.) (39%CV), steady-state Cmin was 0.09 ± 0.07 µg/ml (80%) and the AUC was 10.0 ± 3.1 µg•h/ml (31%) over a 24 hour dosing interval.
Following oral administration of a single 245 mg dose of tenofovir disoproxil fumarate to HIV-1 infected patients in the fasted state, maximum tenofovir concentrations were achieved within one hour and the Cmax and AUC (mean ± S.D.) (%CV) values were 296 ± 90 ng/ml (30%) and 2,287 ± 685 ng•h/ml (30%), respectively. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%.
Distribution
Efavirenz is highly bound (> 99%) to human plasma proteins, predominantly albumin.
In vitro binding of emtricitabine to human plasma proteins is < 4% and independent of concentrations over the range of 0.02 to 200 µg/ml. Following intravenous administration the volume of distribution of emtricitabine was approximately 1.4 l/kg. After oral administration, emtricitabine is widely distributed throughout the body. The mean plasma to blood concentration ratio was approximately 1.0 and the mean semen to plasma concentration ratio was approximately 4.0.
In vitro binding of tenofovir to human plasma or serum protein is < 0.7% and 7.2%, respectively over the tenofovir concentration range 0.01 to 25 µg/ml. Following intravenous administration the volume of distribution of tenofovir was approximately 800 ml/kg. After oral administration, tenofovir is widely distributed throughout the body.
Biotransformation
Studies in humans and in vitro studies using human liver microsomes have demonstrated that efavirenz is principally metabolised by the CYP system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The in vitro studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism and that it inhibits CYP isozymes 2C9, 2C19, and 3A4. In in vitro studies efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 only at concentrations well above those achieved clinically.
Efavirenz plasma exposure may be increased in patients with homozygous G516T genetic variant of the CYP2B6 isozyme. The clinical implications of such an association are unknown; however, the potential for an increased frequency and severity of efavirenz-associated adverse events cannot be excluded.
Efavirenz has been shown to induce CYP3A4 and CYP2B6, resulting in the induction of its own metabolism, which may be clinically relevant in some patients. In uninfected volunteers, multiple doses of 200 to 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 to 42% lower) and a shorter terminal half-life of 40 to 55 hours (single dose half-life 52 to 76 hours). Efavirenz has also been shown to induce UGT1A1. Exposures of raltegravir (a UGT1A1 substrate) are reduced in the presence of efavirenz. Although in vitro data suggest that efavirenz inhibits CYP2C9 and CYP2C19, there have been contradictory reports of both increased and decreased exposures to substrates of these enzymes when co-administered with efavirenz in vivo. The net effect of co-administration is not clear.
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 nor tenofovir are substrates for the CYP enzymes. Neither emtricitabine nor tenofovir inhibited in vitro medicinal product metabolism mediated by any of the major human CYP isoforms involved inbiotransformation of medicinal products. Also, emtricitabine did not inhibit uridine 5'-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.
Elimination
Efavirenz has a relatively long terminal half-life of at least 52 hours after single doses and 40 to 55 hours after multiple doses. Approximately 14 to 34% of a radiolabelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.
Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours. Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (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 tenofovir is approximately 12 to 18 hours. Tenofovir is primarily excreted by the kidneys by both filtration and an active tubular transport system with approximately 70 to 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.

INDICATIONS
Vitricomb® is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Vitricomb® prior to initiation of their first antiretroviral treatment regimen.

CONTRAINDICATIONS
•Hypersensitivity to the active substances or to any of the excipients of this product.
•Severe hepatic impairment (CPT, Class C).
•Co-administration with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine).
•Co-administration with voriconazole. Efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations. Since Vitricomb® is a fixed-dose combination product, the dose of efavirenz cannot be altered.
•Co-administration with herbal preparations containing St. John's wort (Hypericum perforatum) due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz.
•Co-administration with elbasvir/grazoprevir due to the expected significant decreases in plasma concentrations of elbasvir and grazoprevir. This effect is due to induction of CYP3A4 or P-gp by efavirenz and may result in loss of therapeutic effect of elbasvir/grazoprevir.
•Administration to patients with:
- a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
- a history of symptomatic cardiac arrhythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- severe disturbances of electrolyte balance e.g. hypokalaemia or hypomagnesemia.
•Co-administration with medicinal products that are known to prolong the QTc interval (proarrhythmic). These medicinal products include:
- antiarrhythmics of classes IA and III,
- neuroleptics, antidepressive agents,
- certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,
- certain non-sedating antihistamines (terfenadine, astemizole),
- cisapride,
- flecainide,
- certain antimalarials,
- methadone

PRECAUTIONS
Co-administration with other medicinal products
•As a fixed combination, Vitricomb® should not be administered concomitantly with other medicinal products containing the same active components, emtricitabine or tenofovir disoproxil fumarate. Vitricomb® should not be co-administered with products containing efavirenz unless needed for dose adjustment e.g. with rifampicin. Due to similarities with emtricitabine, Vitricomb® should not be administered concomitantly with other cytidine analogues, such as lamivudine. Vitricomb® should not be administered concomitantly with adefovir dipivoxil or with medicinal products containing tenofovir alafenamide.
•Co-administration of Vitricomb® and didanosine is not recommended.
•Co-administration of Vitricomb® and sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir is not recommended since plasma concentrations of velpatasvir and voxilaprevir are expected to decrease following co-administration with efavirenz leading to reduced therapeutic effect of sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir.
•Concomitant use of Ginkgo biloba extracts is not recommended.
Switching from a PI-based antiretroviral regimen
Currently available data indicate a trend that in patients on a PI-based antiretroviral regimen the switch to Vitricomb® may lead to a reduction of the response to the therapy. These patients should be carefully monitored for rises in viral load and, since the safety profile of efavirenz differs from that of protease inhibitors, for adverse reactions.
Opportunistic infections
Patients receiving Vitricomb® 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
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.
Effect of food
The administration of Vitricomb® with food may increase efavirenz exposure and may lead to an increase in frequency of adverse reactions. It is recommended that Vitricomb® be taken on an empty stomach, preferably at bedtime.
Liver disease
The pharmacokinetics, safety and efficacy of Vitricomb® have not been established in patients with significant underlying liver disorders. Vitricomb® is contraindicated in patients with severe hepatic impairment and not recommended in patients with moderate hepatic impairment. Since efavirenz is principally metabolised by the CYP system, caution should be exercised in administering Vitricomb® to patients with mild hepatic impairment. These patients should be carefully monitored for efavirenz adverse reactions, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals.
Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease or persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with Vitricomb® needs to be weighed against the potential risks of significant liver toxicity. In such patients, interruption or discontinuation of treatment must be considered.
In patients treated with other medicinal products associated with liver toxicity, monitoring of liver enzymes is also recommended.
Patients with HIV and hepatitis B (HBV) or C virus (HCV) co-infection
Patients with chronic hepatitis B or C and treated with CART are at an increased risk for severe and potentially fatal hepatic adverse reactions.
The safety and efficacy of Vitricomb® have not been studied 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 an anti-HBV activity when used in antiretroviral combination therapy to control HIV infection. Discontinuation of Vitricomb® 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 Vitricomb® must be closely monitored with both clinical and laboratory follow-up for at least four months after stopping treatment with Vitricomb®. If appropriate, resumption of anti-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.
Psychiatric symptoms
Psychiatric adverse reactions have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of serious psychiatric adverse reactions. In particular, severe depression was more common in those with a history of depression. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation, they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risk of continued therapy outweighs the benefits.
Nervous system symptoms
Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies. Dizziness was also seen in clinical studies with emtricitabine and tenofovir disoproxil fumarate. Headache has been reported in clinical studies with emtricitabine. Nervous system symptoms associated with efavirenz usually begin during the first one or two days of therapy and generally resolve after the first two to four weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.
Seizures
Convulsions have been observed in patients receiving efavirenz, generally in the presence of a known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolized by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz. Caution must be taken in any patient with a history of seizures.
Renal impairment
Vitricomb® is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min). Patients with moderate or severe renal impairment require a dose adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet. Use of Vitricomb® should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If concomitant use of Vitricomb® and nephrotoxic agents (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin-2) is unavoidable, renal function must be monitored weekly.
Bone effects
Alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures.
Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. If bone abnormalities are suspected then appropriate consultation should be obtained.
Skin reactions
Mild-to-moderate rash has been reported with the individual components of the fixed-dose combination of efavirenz/emtricitabine/tenofovir disoproxil. The rash associated with the efavirenz component usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve tolerability and hasten the resolution of rash.
Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Efavirenz/Emtricitabine/Tenofovir disoproxil must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. This medicine is not recommended for patients who have had a life-threatening cutaneous reaction (e.g. Stevens-Johnson syndrome) while taking an NNRTI.
Weight and metabolic parameters
An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.
Mitochondrial dysfunction following exposure in utero
Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed in utero to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology, particularly neurologic findings. 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 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

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when necessary.
Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.
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 CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.
Patients with HIV-1 harbouring mutations
Vitricomb® should be avoided in patients with HIV-1 harbouring the K65R, M184V/I or K103N mutation.
Elderly
Vitricomb® has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased hepatic or renal function; therefore caution should be exercised when treating elderly patients with Vitricomb®.
Effects on ability to drive and use machines
Dizziness has been reported during treatment with efavirenz, emtricitabine and tenofovir disoproxil fumarate. Efavirenz may also cause impaired concentration and/or somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and operating machinery.
FERTILITY, PREGNANCY AND LACTATION
Women of childbearing potential
Pregnancy should be avoided in women receiving Vitricomb®. Women of childbearing potential should undergo pregnancy testing before initiation of Vitricomb®.
Contraception in males and females
Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives) while on therapy with Vitricomb®. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of Vitricomb® is recommended.
Pregnancy
Vitricomb® should not be used during pregnancy unless the clinical condition of the woman requires treatment with efavirenz/emtricitabine/tenofovir disoproxil fumarate.
Breast-feeding
Efavirenz, emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of efavirenz, emtricitabine and tenofovir in newborns/infants. A risk to the infants cannot be excluded. Therefore Vitricomb® should not be used during breast-feeding.
As a general rule, it is recommended that HIV infected women do not breast-feed their infants in order to avoid transmission of HIV to the infant.
Fertility
No human data on the effect of Vitricomb® are available. Animal studies do not indicate harmful effects of efavirenz, emtricitabine or tenofovir disoproxil fumarate on fertility.

DRUG INTERACTIONS
As Vitricomb® contains efavirenz, emtricitabine and tenofovir disoproxil fumarate, any interactions that have been identified with these agents individually may occur with Vitricomb®. Interaction studies with these agents have only been performed in adults.
As a fixed combination, Vitricomb® should not be administered concomitantly with other medicinal products containing the components, emtricitabine or tenofovir disoproxil.
Vitricomb® should not be co-administered with products containing efavirenz unless needed for dose adjustment e.g. with rifampicin. Due to similarities with emtricitabine, Vitricomb® should not be administered concomitantly with other cytidine analogues, such as lamivudine. Vitricomb® should not be administered concomitantly with adefovir dipivoxil or with medicinal products containing tenofovir alafenamide.
Efavirenz exposure may be increased when given with medicinal products (for example ritonavir) or food (for example, grapefruit juice) which inhibit CYP3A4 or CYP2B6 activity. Compounds or herbal preparations (for example Ginkgo biloba extracts and St. John's wort) which induce these enzymes may give rise to decreased plasma concentrations of efavirenz. Concomitant use of St. John's wort is contraindicated. Concomitant use of Ginkgo biloba extracts is not recommended.
In vitro and clinical pharmacokinetic interaction studies have shown the potential for CYP-mediated interactions involving emtricitabine and tenofovir disoproxil fumarate with other medicinal products is low.
Cannabinoid test interaction
Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been reported with some screening assays in uninfected and HIV infected subjects receiving efavirenz. Confirmatory testing by a more specific method such as gas chromatography/mass spectrometry is recommended in such cases.
Contraindications of concomitant use
•Vitricomb® must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events.
•Elbasvir/grazoprevir: Co-administration of Vitricomb® with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir.
•Voriconazole: Co-administration of standard doses of efavirenz and voriconazole is contraindicated. Since Vitricomb® is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and Vitricomb® must not be co-administered.
•St. John's wort (Hypericum perforatum): Co-administration of Vitricomb® and St. John's wort or herbal preparations containing St. John's wort is contraindicated. Plasma levels of efavirenz can be reduced by concomitant use of St. John's wort due to induction of drug metabolizing enzymes and/or transport proteins by St. John's wort. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John's wort. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment.
QT Prolonging medicinal products: Vitricomb® is contraindicated with concomitant use of medicinal products that are known to prolong the QTc interval and could lead to Torsade de Pointes, such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride, flecainide, certain antimalarials and methadone.
Concomitant use not recommended
•Atazanavir/ritonavir: Insufficient data are available to make a dosing recommendation for atazanavir/ritonavir in combination with Vitricomb®. Therefore co-administration of atazanavir/ritonavir and Vitricomb® is not recommended.
•Didanosine: Co-administration of Vitricomb® and didanosine is not recommended.
•Sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir: Co-administration of Vitricomb® and Sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir: is not recommended.
•Renally eliminated medicinal products: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of Vitricomb® 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 Vitricomb® 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.

ADVERSE EFFECTS
Adverse reactions were generally consistent with those seen in previous studies of the individual components. The most frequently reported adverse reactions considered possibly or probably related to Vitricomb® were psychiatric disorders, nervous system disorders, and gastrointestinal disorders.
Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme; neuropsychiatric adverse reactions (including severe depression, death by suicide, psychosis-like behaviour, seizures); severe hepatic events; pancreatitis and lactic acidosis (sometimes fatal) have been also reported.
Rare events of renal impairment, renal failure and uncommon events of proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have also been reported.
Discontinuation of Vitricomb® therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis.
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).
Adverse reactions associated with Vitricomb® listed by the component(s) of Vitricomb® are the following:
Efavirenz:
Immune system disorders: hypersensitivity (uncommon).
Metabolism and nutrition disorders: hypertriglyceridaemia (common); hypercholesterolaemia (uncommon).
Psychiatric disorders: depression, anxiety, abnormal dreams, insomnia (common); suicide attempt, suicide ideation, psychosis, mania, paranoia, hallucination, euphoric mood, affect lability, confusional state, aggression catatonia (uncommon); completed suicide, delusion, neurosis (rare).
Nervous system disorders: cerebellar coordination and balance disturbances, somnolence, headache, disturbance in attention, dizziness (common); convulsions, amnesia, thinking abnormal, ataxia, coordination abnormal, agitation, tremor (uncommon).
Eye disorders: vision blurred (uncommon).
Ear and labyrinth disorders: tinnitus, vertigo (uncommon).
Vascular disorders: flushing (uncommon).
Gastrointestinal disorders: diarrhoea, vomiting, abdominal pain, nausea (common); pancreatitis (uncommon).
Hepatobiliary disorders: elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), elevated gamma-glutamyltransferase (GGT) (common); hepatitis acute (uncommon); hepatic failure (rare).
Skin and subcutaneous tissue disorders: rash (very common); pruritus (common); Stevens-Johnson syndrome, erythema multiforme, severe rash (uncommon); photoallergic dermatitis (rare).
Reproductive system and breast disorders: gynaecomastia (uncommon).
General disorders and administration site conditions: fatigue (common).
Emtricitabine:
Blood and lymphatic system disorders: neutropenia (common); anaemia (uncommon).
Immune system disorders: allergic reaction (common).
Metabolism and nutrition disorders: hyperglycaemia, hypertriglyceridaemia (common).
Psychiatric disorders: abnormal dreams, insomnia (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 AST and/or elevated serum ALT, hyperbilirubinaemia (common).
Skin and subcutaneous tissue disorders: vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (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: hypophosphataemia (very common); hypokalaemia (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, proximal renal tubulopathy including Fanconi syndrome (uncommon); renal failure (acute and chronic), acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus (rare).
General disorders and administration site conditions: asthenia (very common).

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

Dosage
Adults
The recommended dose of Vitricomb® is one tablet taken orally once daily.
If a patient misses a dose of Vitricomb® within 12 hours of the time it is usually taken, the patient should take Vitricomb® as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Vitricomb® by more than 12 hours and it is almost time for the 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 Vitricomb®, another tablet should be taken. If the patient vomits more than 1 hour after taking Vitricomb® he/she does not need to take another dose.
It is recommended that Vitricomb® be taken on an empty stomach since food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions. In order to improve the tolerability to efavirenz with respect to undesirable effects on the nervous system, bedtime dosing is recommended.
It is anticipated that tenofovir exposure (AUC) will be approximately 30% lower following administration of Vitricomb® on an empty stomach as compared to the individual component tenofovir disoproxil when taken with food.
Where discontinuation of therapy with one of the components of Vitricomb® is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil are available. Please refer to the Summary of Product Characteristics for these medicinal products.
If therapy with Vitricomb® is discontinued, consideration should be given to the long half-life of efavirenz and long intracellular half-lives of emtricitabine and tenofovir. Because of interpatient variability in these parameters and concerns regarding development of resistance, HIV treatment guidelines should be consulted, also taking into consideration the reason for discontinuation.
Dose adjustment: If Vitricomb® is co-administered with rifampicin to patients weighing 50 kg or more, an additional 200 mg/day (800 mg total) of efavirenz may be considered .
Special populations
Elderly: Vitricomb® should be administered with caution to elderly patients .
Renal impairment: Vitricomb® is not recommended for patients with moderate or severe renal impairment (creatinine clearance (CrCl) < 50 ml/min). Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir disoproxil that cannot be achieved with the combination tablet.
Hepatic impairment: The pharmacokinetics of Vitricomb® have not been studied in patients with hepatic impairment. Patients with mild liver disease (Child-Pugh-Turcotte (CPT), Class A) may be treated with the normal recommended dose of Vitricomb®. Patients should be monitored carefully for adverse reactions, especially nervous system symptoms related to efavirenz .
If Vitricomb® is discontinued in patients co-infected with HIV and HBV, these patients should be closely monitored for evidence of exacerbation of hepatitis .
Paediatric population: The safety and efficacy of Vitricomb® in children under the age of 18 years have not been established.

Method of administration:
Vitricomb® tablets should be swallowed whole with water, once daily.

OVERDOSAGE
Some patients accidentally taking 600 mg efavirenz twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.
If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.
Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to remove significant quantities of it from blood.
Up to 30% of the emtricitabine dose and approximately 10% of the tenofovir dose can be removed by haemodialysis. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

STORAGE CONDITIONS
Store below 30°C. Protect from moisture.
Keep in original pack in intact conditions.

Date of Revision:
October 2020

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

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

Benta S.A.L.,
Dbayeh - Lebanon