PRESCRIBING INFORMATION
Tenofovir Disoproxil Fumarate, Emtricitabine & Efavirenz Tablets

VIRARAZER®

GENERIC NAME:
Tenofovir Disoproxil Fumarate, Emtricitabine & Efavirenz Tablets

COMPOSITION:
Each Filmcoated Tablet contains:
Tenofovir Disoproxil Fumarate 300mg
Emtricitabine …… 200mg
Efavirenz … …….. 600mg
Colours : Titanium Dioxide and Indigo Carmine

DETAILED PHARMACOLOGY
Efavirenz: Efavirenz is a non-nucleoside reverse transcriptase (RT) inhibitor of human immunodeficiency virus type 1 (HIV-1). Efavirenz is predominantly a non-competitive inhibitor of HIV-1 RT. HIV-2 RT and human cellular DNA polymerases α, β, γ, and δ are not inhibited by efavirenz.
Emtricitabine: Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, ε, and mitochondrial DNA polymerase γ.
Tenofovir DF: Tenofovir DF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir di phosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.
Antiviral Activity Efavirenz, emtricitabine and tenofovir DF:
In combination studies evaluating the in vitro antiviral activity of emtricitabine and efavirenz together, efavirenz and tenofovir together and emtricitabine and tenofovir together, additive to synergistic antiviral effects were observed.
Efavirenz: The clinical significance of in vitro susceptibility of HIV-1 to efavirenz has not been established. The in vitro antiviral activity of efavirenz was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures enriched from PBMCs. The concentration of efavirenz inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90–95% (EC90−95) ranged from 1.7 to ≤25nM. Efavirenz demonstrated additive to synergistic antiviral activity against HIV-1 in cell culture when combined with non-nucleoside reverse transcriptase inhibitors NNRTIs) (delavirdine and nevirapine), nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine, stavudine, zalcitabine, and zidovudine), protease inhibitors (PIs) (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), and the fusion inhibitor enfuvirtide. Efavirenz demonstrated antiviral activity against most nonclade B isolates (subtypes A, AE, AG, C, D, F, G, J, and N), but had reduced antiviral activity against group O viruses.
Emtricitabine: The in vitro antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The EC_{50} values for emtricitabine were in the range of 0.0013−0.64 μM (0.0003−0.158 μg/mL). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zalcitabine, and zidovudine), nonnucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, and nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Emtricitabine displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007−0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007−1.5 μM).
Tenofovir DF: The in vitro antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC50 values for tenofovir were in the range of 0.04−8.5 μM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, and zidovudine), nonnucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, and nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Tenofovir displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, G, and O (IC50 values ranged from 0.5−2.2 μM).

Resistance Efavirenz, emtricitabine and tenofovir DF:
HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture and in clinical studies. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT. In a clinical study of treatment-naïve patients (Study 934, see Clinical Studies) resistance analysis was performed on HIV isolates from all virologic failure patients with >400 copies/mL of HIV-1 RNA at Week 144 or early discontinuations. The resistance analysis population consisted of 19/244 (8%) patients in the emtricitabine + tenofovir DF group and 29/243 (12%) patients in the zidovudine/lamivudine fixed-dose combination group with available genotypic data. Genotypic resistance to efavirenz, predominantly the K103N mutation, was the most common form of resistance that developed. Resistance to efavirenz occurred in 13/19 (68%) analyzed patients (13/244, 5% of total patients) in the emtricitabine + tenofovir DF group and in 21/29 (72%) analyzed patients (21/243, 9% of total patients) in the zidovudine/lamivudine fixed-dose combination group.
The M184V amino acid substitution, associated with resistance to emtricitabine, was observed in 2/19 (11%) analyzed patient isolates (2/244, 0.8% of total patients) in the emtricitabine + tenofovir DF group and in 10/29 (34%) analyzed patient isolates (10/243, 4.1% of total patients) in the zidovudine/lamivudine group; this difference was statistically significant (p=0.021). Through 144 weeks of Study 934, no patients developed a detectable K65R mutation in their HIV as analyzed through standard genotypic analysis.
Only limited resistance data are available from a clinical study of treatment-experienced patients with stable virologic suppression and no history of virologic failure (Study 073, see CLINICAL TRIALS section) since virologic failure was observed in only 3 subjects in the TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS treatment group. One of the 3 subjects who experienced virologic failure on TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS had confirmed development of resistance, specifically the K103N efavirenz resistance mutation only.
In a clinical study of treatment-naïve patients, isolates from 8/47 (17%) analyzed patients receiving tenofovir DF developed the K65R substitution through 144 weeks of therapy; 7
of these occurred in the first 48 weeks of treatment and one at Week 96. In treatment experienced patients, 14/304 (5%) of tenofovir DF treated patients with virologic failure through Week 96 showed >1.4 fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution
Efavirenz: HIV-1 isolates with reduced susceptibility to efavirenz (>380-fold increase in EC90) compared to baseline emerged rapidly under selection in cell culture in the presence of drug.
Genotypic characterization of these viruses identified mutations resulting in single amino acid substitutions L100I or V179D, double substitutions L100I/V108I and triple substitutions L100I/V179D/Y181C in RT. Other resistance mutations observed to emerge commonly included L100I (7%), K101E/Q/R(14%), V108I (11%), G190S/T/A(7%), P225H(18%), and M230I/L(11%). Phenotypic (N=26) changes in evaluable HIV-1 isolates and genotypic (N=104) changes in plasma virus from selected patients treated with efavirenz in combination with indinavir, or with zidovudine plus lamivudine, were monitored. Clinical isolates with reduced susceptibility in vitro to efavirenz have been obtained. One or more RT mutations at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190 and 225, and 227 were observed in all 102 of 104 patients with a frequency of at least 9% compared to baseline. The mutation at RT amino acid position 103 (lysine to asparagine) was the most frequently observed (≥90%). A mean loss in susceptibility (EC90) to efavirenz of 47-fold was observed in 26 clinical isolates. Five clinical isolates were evaluated for both genotypic and phenotypic changes from baseline. Decreases in efavirenz susceptibility (range from 9 to >312-fold increase in EC90) were observed for these isolates in vitro compared to baseline. All 5 isolates possessed at least one of the efavirenz-associated RT mutations. The clinical relevance of phenotypic and genotypic changes associated with efavirenz therapy has not been established.

INTERACTIONS WITH THIS MEDICATION
Drugs that must not be taken with TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS :
Propulsid (cisapride)*, Versed (midazolam), Halcion (triazolam), ergot medications (for example Wigraine and Cafergot), Hismanal (astemizole)*, Seldane (terfenadine)*, Vascor (bepridil)* or Orap (pimozide). Taking these medications with TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS could create the potential for serious or life-threatening side effects.
Vfend (voriconazole) since it may lose its effect or may increase the chance of having side effects from TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS .
PROPER USE OF THIS MEDICATION
Stay under a doctor's care when taking TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS . Do not change your treatment or stop treatment without first talking with your doctor. Take TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS exactly as your doctor prescribed it. Follow the directions from your doctor, exactly as written on the label.Set up a dosing schedule and follow it carefully.
Usual Adult Dose:
The usual dose of TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS is one tablet orally (by mouth) once a day, in combination with other anti-HIV medicines.
TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS may be taken with or without a meal.

Over dosage:
In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional poison control centre, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM
The most common side effects are:
Nervous system symptoms such as dizziness, trouble sleeping, drowsiness, trouble concentrating, unusual dreams
• Headache
• Diarrhea
• Nausea
• Vomiting
• Rash
• Flatulence (intestinal gas)
• Tiredness
• Itching
• Allergic reaction (including swelling of the face, lips, tongue or throat)
• Abdominal pain
Other side effects may include pancreatitis (inflammation of the pancreas) and shortness of breath.
Skin discoloration (small spots or freckles) may also happen with TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS .
A small number of patients taking efavirenz, one of the components of TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS , have had severe depression, strange thoughts, or angry behavior. Some patients have
had thoughts of suicide and a few patients have actually committed suicide. These problems tend to occur more often in patients with a history of mental illness. Contact your doctor immediately if you think you are having these symptoms so your doctor can decide whether you should continue to take TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS .
Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amounts of fat in the upper back and neck
("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.
Some patients have experienced serious liver problems including liver failure resulting in transplantation or death. Most of these serious side effects occurred in patients with a chronic liver disease such as a hepatitis infection, but there have also been a few reports in patients without any existing liver disease.
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HOW TO STORE IT
TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS should be stored at 15–30 °C (59-86 °F). It should remain stable until the expiration date printed on the label.
Keep TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS and all other medications out of reach of children.
Do not keep your medicine in places that are too hot or cold.
Keep TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE & EFAVIRENZ TABLETS in its original container and keep the container tightly closed.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT: If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

PACKING: HDPE Bottle pack of 30 tablets and packed in a unit carton along with package insert.

SHELF LIFE: Refer label for shelf life.

STORAGE INSTRUCTIONS:
Store below 30ºC. Protect from light.
Keep this medicine out of the sight and reach of children.
Do not store above 30°C. Store in the original container.
Do not use this medicine after the expiry date which is stated on the bottle.
The expiry date refers to the last day of that month.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

MARKETED BY:

APRAZER

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