

# Pharmaceutical Approval Update

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## Emtricitabine/Tenofovir Disoproxil Fumarate (Truvada) Tablets

**Manufacturer:** Gilead Sciences, Foster City, Calif.

**Indication:** Truvada is indicated for once-daily use to reduce the risk of sexually acquired HIV infection in uninfected individuals at high risk for engaging in sexual activity with an infected partner. In 2004, the FDA approved Truvada in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults, and in 2011, the agency expanded this indication to include the treatment of pediatric patients 12 years of age and older.

**Drug Class:** Truvada is a new fixed-dose combination of emtricitabine (Emtriva), a nucleoside reverse transcriptase inhibitor (NRTI), and tenofovir disoproxil (as fumarate) (Viread), the oral prodrug of tenofovir, a nucleotide reverse transcriptase inhibitor (NtRTI).

The chemical name of emtricitabine is 5-fluoro-1-(2R,5S)-[2(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (–) enantiomer of a thioanalogue of cytidine. It differs from other cytidine analogues in that fluorine is in the 5'-position. Emtricitabine is a synthetic nucleoside analogue of cytidine. Its molecular weight is 247.24.

Tenofovir disoproxil fumarate (DF) is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir DF is 9-(R)-2[[bis[[isopropoxycarbonyl]oxy]-methoxy]phosphinyl]methoxypropyladenine fumarate (1:1). Its molecular weight is 635.52.

**Uniqueness of Drug:** As a synthetic nucleoside analogue of cytidine, emtricitabine is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase 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 polymerase  $\alpha$ ,  $\beta$ , and  $\epsilon$  and mitochondrial DNA polymerase  $\gamma$ .

Tenofovir DF, an acyclic nucleoside phosphonate diester analogue of 5'-adenosine monophosphate, 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 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination.

Truvada must be combined with at least one other anti-HIV drug, usually a protease inhibitor or a non-NRTI (NNRTI).

### Boxed Warning:

**Lactic acidosis/severe hepatomegaly with steatosis.** Lactic acidosis and severe hepatomegaly with steatosis, includ-

ing fatal cases, have been reported with the use of nucleoside analogues (including tenofovir) in combination with other antiretroviral agents.

**Co-infection with HIV-1 and HBV.** Truvada is not approved for the treatment of chronic hepatitis B virus (HBV) infection. The safety and efficacy of Truvada have not been established in patients co-infected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients with HBV and HIV-1 co-infection and who have discontinued Truvada. Hepatic function should be monitored

closely with both clinical and laboratory follow-up for at least several months in these patients, and Truvada should be discontinued. If appropriate, initiation of anti-HBV therapy may be warranted.

### Warnings and Precautions:

**Lactic acidosis/severe hepatomegaly with steatosis.** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues in combination with other antiretroviral agents. Most of these cases have involved women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be taken when nucleoside analogues are administered to patients with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Truvada therapy should be suspended in patients if clinical or laboratory findings suggest lactic acidosis or hepatotoxicity, even in the absence of marked transaminase elevations.

**Co-infection with HIV-1 and HBV.** All patients with HIV-1 infection should be tested for the presence of chronic HBV infection before they begin antiretroviral therapy. Truvada is not approved for patients with chronic HBV infection, and it has not been determined whether the drug is safe and effective for patients with HBV and HIV-1 co-infection.

Severe acute exacerbations of hepatitis B have occurred in patients co-infected with HBV and HIV-1 and who have discontinued Truvada. In some HBV patients who received emtricitabine, the exacerbations of hepatitis B were associated with liver failure. Co-infected patients should undergo laboratory tests for at least several months after they stop taking Truvada. Anti-HBV therapy may be initiated if appropriate.

**Dosage and Administration:** Each film-coated tablet contains 200 mg of emtricitabine and 300 mg of tenofovir DF (equivalent to 245 mg of tenofovir disoproxil). The dose for individuals 12 years of age and older who weigh 35 kg or more (77 pounds or more) is one tablet (200 mg of emtricitabine/300 mg of tenofovir DF) once daily taken orally with or without food.

Significantly increased drug exposures occurred when emtricitabine or tenofovir was administered to subjects with moderate-to-severe renal impairment. Therefore, the dosing interval of Truvada should be adjusted in patients with a baseline creatinine clearance of 30 to 49 mL/minute. The dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in subjects without HIV infection. These



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dosing adjustment recommendations have not been evaluated in patients with moderate renal impairment; therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Dose recommendations are not available for renally impaired pediatric patients 12 years of age and older.

**Commentary:** Each year, about 50,000 adults and adolescents in the U.S. acquire HIV infection despite the availability of prevention methods, education, and testing. Truvada is the first drug approved to reduce the risk of HIV infection in uninfected individuals who are at high risk of the infection and who might engage in sexual activity with HIV-infected partners.

Truvada was previously approved for HIV-infected patients 12 years of age or older. With the new indication, Truvada is approved as part of a comprehensive HIV-prevention strategy that also includes safe sex practices, risk-reduction counseling, and HIV testing on a regular basis.

**Sources:** [www.fda.gov](http://www.fda.gov); [www.truvada.com](http://www.truvada.com); [www.hivandhepatitis.com](http://www.hivandhepatitis.com)

### Enzalutamide (Xtandi) Capsules

**Manufacturer:** Astellas, Northbrook Ill/Medivation, San Francisco, Calif.

**Indication:** An oral once-daily capsule, enzalutamide is used to treat metastatic castration-resistant prostate cancer in patients who have received docetaxel (Taxotere, Sanofi).

**Drug Class:** Enzalutamide is an androgen-receptor inhibitor.

**Uniqueness of Drug:** Enzalutamide blocks the ability of testosterone to bind to prostate cancer cells and is active in the different steps of the androgen-receptor signaling pathway. It inhibits androgen binding to androgen receptors and blocks androgen-receptor nuclear translocation and interaction with DNA.

A major metabolite (*N*-desmethyl enzalutamide) exhibits *in vitro* activity similar to that of enzalutamide. The drug has been shown to decrease proliferation, induce cell death of prostate cancer cells *in vitro*, and reduce tumor volume in a xenograft mouse model.

**Warnings and Precautions:** In a randomized trial, seven patients of 800 (0.9%) who received enzalutamide 160 mg once daily experienced a seizure (no seizures occurred in the placebo patients). Seizures occurred from 31 to 603 days after initiation of therapy, which was then discontinued permanently. There are no trial data regarding the readministration of enzalutamide to patients who had seizures. Because of the risk of seizure associated with enzalutamide, patients should be advised of the risk of engaging in activities during which a sudden loss of consciousness could cause harm to themselves or others.

**Dosage and Administration:** The recommended dose of enzalutamide is 160 mg (four 40-mg capsules) once daily. The medication can be taken with or without food, and concomitant steroid use is not required.

**Adverse Events.** Common adverse reactions occurring in 5% of patients or more included asthenia, fatigue, back pain, diarrhea, arthralgia, hot flushes, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Grade 3 and higher

adverse reactions were reported among 47% of enzalutamide-treated patients and among 53% of placebo-treated patients.

**Commentary:** Enzalutamide, which was approved 3 months ahead of its goal date, has the potential to prolong the lives of men with advanced metastatic prostate cancer who have received previous chemotherapy. Enzalutamide-treated patients had a statistically significant improvement in median overall survival (18.4 months) compared with the placebo group (13.6 months). Enzalutamide also provided a 37% reduction in risk of death compared with placebo.

As a postmarketing requirement, Medivation and Astellas have agreed to conduct an open-label safety study of enzalutamide 160 mg/day in patients at high risk for seizures and to provide the results in 2019. The drug's cost is expected to be approximately \$7,450 per month.

**Sources:** [www.us.astellas.com](http://www.us.astellas.com); [www.xtandihcp.com](http://www.xtandihcp.com); *The New York Times*, August 31, 2012

### Vincristine Sulfate Liposome Injection (Marqibo)

**Manufacturer:** Talon Therapeutics Inc., South San Francisco, Calif.

**Indication:** Marqibo was approved in August 2012 to treat adults with Philadelphia chromosome–negative acute lymphoblastic leukemia (ALL). Vincristine, a microtubule inhibitor, is approved for ALL and non-Hodgkin's lymphoma (NHL). It is widely used in combination regimens to treat various adult and pediatric hematological and solid-tumor malignancies.

**Drug Class:** Vincristine, a commonly used anti-cancer drug, was approved in 1963. A vinca alkaloid, it is derived from the periwinkle flower. Marqibo is a sphingomyelin/cholesterol liposome-encapsulated formulation of vincristine sulfate.

**Uniqueness of Drug:** Talon's Optisome nanoparticle-encapsulation technology prolongs the circulation of vincristine in the blood and accumulation at the tumor site. Vincristine is encased within a liposome, a drug-delivery vehicle composed of material similar to that of cell membranes.

**Boxed Warning:** Marqibo is indicated for intravenous (IV) use only and can be fatal if given by other routes. Death has occurred with intrathecal administration. The dosage recommendations for Marqibo injection differ from those for vincristine sulfate injection. The drug name and dose should be verified before preparation and administration to avoid overdosage.

#### Warnings and Precautions:

**Extravasation tissue injury.** Marqibo should be administered only via a secure, free-flowing venous access line. If extravasation is suspected, the infusion should be discontinued immediately and local treatment measures should be considered.

**Neurological toxicity.** Sensory and motor neuropathies are common and cumulative. Patients should be monitored for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, hyporeflexia, areflexia, neuralgia, jaw pain, decreased vibratory sense, cranial neuropathy, ileus, a burning sensation, arthralgia, myalgia, muscle spasm, and weakness, both before and during treatment. Orthostatic hypotension may occur.

The risk of neurological toxicity is increased in patients with pre-existing neuromuscular disorders and in those receiving other drugs that carry a risk of neurological toxicity. In studies

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of relapsed or refractory ALL, grade 3 or greater neuropathy occurred in 32.5% of patients. Marqibo therapy should be delayed, reduced, or discontinued if the patient experiences worsening neuropathy.

**Myelosuppression.** The complete blood count should be monitored before each dose. If grade 3 or 4 neutropenia, thrombocytopenia, or anemia develops, modifying or reducing the dose, as well as initiating supportive care measures, should be considered.

**Tumor lysis syndrome.** Tumor lysis syndrome may occur in patients with ALL who receive Marqibo. This condition should be anticipated, monitored, and managed.

**Constipation and bowel obstruction.** Ileus, bowel obstruction, colonic pseudo-obstruction, and constipation have occurred with Marqibo. A prophylactic bowel regimen should be instituted to lessen the risk of these conditions.

Adequate dietary fiber intake, hydration, and the routine use of stool softeners (docusate) are recommended. Additional treatments, such as senna, bisacodyl, milk of magnesia, magnesium citrate, and lactulose, may also be considered.

**Fatigue.** If Marqibo causes severe fatigue, it might be necessary to delay, reduce, or discontinue therapy as necessary.

**Hepatotoxicity.** Fatal liver toxicity and elevated levels of aspartate aminotransferase (grade 3 or higher) have occurred. Hepatic function tests should be monitored, and therapy should be reduced or interrupted if hepatic toxicity occurs.

**Embryofetal toxicity.** Marqibo can cause fetal harm when administered to pregnant women. The injection was teratogenic or caused embryofetal death in animals. Women of childbearing age should avoid becoming pregnant while using Marqibo. No adequate or well-controlled studies of Marqibo have been conducted in pregnant women, and there were no reports of pregnancy in the clinical studies in the clinical development program. If Marqibo is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

**Dosage and Administration:** The recommended dose of Marqibo is 2.25 mg/m<sup>2</sup>, administered intravenously by a health care professional over a period of 1 hour once every 7 days.

**Commentary:** Marqibo is approved for Philadelphia chromosome–negative ALL that has recurred two or more times or has progressed after two or more regimens of antileukemia therapy. ALL is a rapidly progressing form of blood and bone marrow cancer that is more common in children than adults. According to the National Cancer Institute, ALL is expected to be diagnosed in approximately 6,000 men and women during 2012.

Marqibo contains vincristine, encased within a liposome. The drug's effectiveness was evaluated in a single clinical trial that enrolled patients experiencing at least two relapses of ALL despite standard treatments and who had at least one previous treatment response lasting at least 90 days.

Administered once weekly, Marqibo was approved under the FDA's accelerated approval program and received an orphan-product designation for the treatment of a rare disease. The projected cost is \$45,000 for a typical course of treatment.

**Sources:** [www.fda.gov](http://www.fda.gov); [www.talontx.com](http://www.talontx.com) ■