Dolutegravir Tablets (Tivicay)

Manufacturer: GlaxoSmithKline/Viiv, Research Triangle Park, N.C.

Indication: Dolutegravir is indicated, in combination with other antiretroviral agents, once daily for the treatment of HIV-1 infection in treatment-naive adults and in pediatric patients 12 years of age and older who weigh at least 40 kg (about 88 pounds).

Drug Class: The chemical formula for dolutegravir is \((4R,12aS)-N-(2,4-difluorobenzyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1´,2´:4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide. The molecular weight is 419.3821.

Uniqueness of Drug: Dolutegravir is an integrase strand transfer inhibitor (INSTI) that interferes with one of the enzymes necessary for the virus to multiply. The drug blocks HIV replication by preventing viral DNA from integrating into the genetic material of human immune cells, thereby helping to obviate the development of chronic infections.

Warnings and Precautions:

Fat redistribution. Patients receiving antiretroviral therapy have experienced an accumulation of body fat (e.g., central obesity, buffalo hump), peripheral and facial wasting, breast enlargement, and a cushingoid appearance.

Immune reconstitution inflammatory syndrome (IRIS). During the initial phase of combined antiretroviral treatment, patients whose immune systems respond may paradoxically develop an inflammatory response to indolent or residual opportunistic infections (e.g., *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia, or tuberculosis).

Autoimmune disorders (e.g., Graves’ disease, polymyositis, and Guillain-Barré syndrome) have also occurred in the setting of immune reconstitution, although they can occur many months after initiation of treatment.

Hypersensitivity reactions. Rash, fatigue, malaise, and organ dysfunction, including liver injury, have been reported. Therapy should be discontinued immediately if signs or symptoms of hypersensitivity develop. Clinical status, including liver aminotransferases, should be monitored, and appropriate therapy should be initiated. Patients who have experienced a previous hypersensitivity reaction to dolutegravir should not use it.

Liver enzyme elevations and hepatitis B or C co-infection. Patients with underlying hepatitis B or C infection may be at an increased risk for worsening or development of transaminase elevations when they take dolutegravir. These elevations were sometimes consistent with IRIS or hepatitis B reactivation, particularly when anti-hepatitis therapy was withdrawn.

Appropriate laboratory testing before therapy begins and monitoring for hepatotoxicity during therapy are recommended.

Dosage and Administration: Dolutegravir can be taken without regard to meals. The recommended dose for adults and for pediatric patients, 12 years of age and older and weighing at least 40 kg, is 50 mg, administered orally once daily.

Overdose: There is no specific therapy for an overdose. If an overdose occurs, the patient should be monitored and standard supportive treatment applied as required. Because dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Drug Interactions: Patients should take dolutegravir 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron or oral calcium supplements, or buffered medications.

Plasma levels of dolutegravir are reduced when potent UDP glucuronosyltransferase 1A or cytochrome P450 (UGT1A/CYP3A) inducers (e.g., efavirenz, tipranavir/ritonavir, fosamprenavir/ritonavir, or rifampin) are coadministered.

In drug-interaction trials, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of tenofovir, methadone, midazolam, rilpivirine, or oral contraceptives containing norgestimate and ethinyl estradiol. Etravirine significantly reduced plasma concentrations of dolutegravir, but this effect was mitigated by the coadministration of lopinavir/ritonavir or darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir.

Commentary: Dolutegravir is the second approved member of the INSTI class. The first member, raltegravir (Isentress, Merck), was approved in 2007. A third drug in the class, elvitegravir, was approved only in a four-drug combination (Stribild, Gilead).

Like all other HIV medications, dolutegravir is taken with at least two other drugs that attack different aspects of the viral replication cycle. Dolutegravir is regarded as an attractive alternative to raltegravir because it is given once daily, at 50 mg, compared with 400 mg twice daily for the older drug. Dolutegravir has performed as well or better than raltegravir in head-to-head trials and against other potent HIV drug combinations.

The company’s submitted application for FDA approval included data from four pivotal phase 3 clinical trials enrolling 2,557 adults with HIV who received at least one dose of study medication; the trial also included data in children 12 years of age and older. Dolutegravir was used without a pharmacokinetic boosting agent.

Adverse effects have included insomnia and headache. Serious effects have included hypersensitivity reactions and abnormal liver function in HIV patients co-infected with hepatitis B, C, or both.

Sources: www.fda.gov; www.gsk.com; www.viivhealthcare.com

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A member of P&T’s editorial board, the author is President of Pharmaceutical and Scientific Services at Marvin M. Goldenberg, LLC, in Westfield, N.J. His e-mail address is marvinmgoldenberg@verizon.net.
Topiramate Extended Release Capsules (Trokendi XR)

**Manufacturer:** Supernus Pharmaceuticals, Inc., Rockville, Md.

**Indication:** A once-daily extended-release (ER) formulation of topiramate is now approved for patients with epilepsy. Trokendi XR is intended as an initial monotherapy in patients 10 years of age and older with partial-onset or primary generalized tonic–clonic seizures, as adjunctive therapy in patients 6 years of age and older with partial-onset or primary generalized tonic–clonic seizures, and as an adjunctive therapy in patients 6 years of age and older with Lennox–Gastaut seizures.

Another brand-name version of topiramate, Topamax (Janssen), is used as an anticonvulsant and for the prophylaxis of migraine.

**Drug Class:** Topiramate, USP, is a sulfamate-substituted monosaccharide. Its chemical designation is 2,3:4,5-di-O-isopropylidene-β-D-fructopyranose sulfamate. The drug’s molecular formula is C₁₂H₂₁NO₈S, and the molecular weight is 339.36.

**Uniqueness of Drug:** A white to off-white powder, topiramate is freely soluble in polar organic solvents such as acetonitrile and acetone. It is slightly soluble to practically insoluble in nonpolar organic solvents such as hexanes. The precise mechanisms by which topiramate exerts its anticonvulsant effects are unknown, but at pharmacologically relevant concentrations, the drug appears to block voltage-dependent sodium channels; augment the activity of the neurotransmitter gamma-aminobutyrate (GABA) at some subtypes of the GABA-A receptor; antagonize the AMPA/kainate subtype of the glutamate receptor; and inhibit the carbonic anhydrase enzyme, particularly isozymes II and IV.

**Warnings and Precautions:**

**Acute myopia and glaucoma.** A syndrome consisting of acute myopia, associated with secondary angle-closure glaucoma, has been reported in patients receiving topiramate. Symptoms include an acute onset of decreased visual acuity, ocular pain, or both. Myopia, anterior chamber shallowing, ocular hyperemia, increased intraocular pressure, and mydriasis may occur. The syndrome may be associated with supraciliary effusion, resulting in anterior displacement of the lens and iris.

**Oligohidrosis and hyperthermia.** Decreased sweating and elevated temperature, infrequently resulting in hospitalization, have been reported in association with topiramate. Some cases were reported after exposure to elevated environmental temperatures. Most reports involved pediatric patients.

**Suicidal behavior and ideation.** Antiepileptic drugs, including topiramate, may increase the risk of suicidal thoughts or behavior in patients taking these medications for any indication. Patients using any antiepileptic drug should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

**Metabolic acidosis.** Hyperchloremic, non-anion gap, metabolic acidosis (i.e., abnormally low serum bicarbonate levels) has been associated with topiramate. Metabolic acidosis is caused by renal bicarbonate loss resulting from the drug’s inhibitory effect on carbonic anhydrase. This electrolyte imbalance was observed with topiramate in placebo-controlled clinical trials and in the postmarketing period.

Generally, topiramate-induced metabolic acidosis occurs early in treatment, but it can occur at any time during treatment. Bicarbonate decrements are usually mild to moderate. Rarely, patients may experience severe decrements to values below 10 mEq/L. Factors that predispose patients to acidosis (e.g., renal disease, respiratory disorders, status epilepticus, diarrhea, a ketogenic diet, or a specific drug) may augment the bicarbonate-lowering effects of topiramate.

In adults, the incidence of persistent treatment-emergent decreases in serum bicarbonate (levels below 20 mEq/L) at two consecutive visits or at the final visit in controlled clinical trials for the adjunctive treatment of epilepsy was 32% for 400 mg/day and 1% for placebo. Metabolic acidosis was noted at doses as low as 50 mg/day.

In pediatric patients, the incidence of persistent treatment-emergent decreases in serum bicarbonate was 67% for topiramate (at about 6 mg/kg/day) and 10% for placebo in trials evaluating the adjunctive treatment of Lennox–Gastaut syndrome or refractory partial-onset seizures.

**Cognitive and neuropsychiatric reactions.** The most commonly occurring adverse drug reactions associated with topiramate were related to the central nervous system and were observed in both the epilepsy and migraine patients. In adults, the most frequent events were cognitive problems (e.g., confusion; psychomotor slowing; and concentration, attention, memory, and speech difficulties); psychiatric and behavioral disturbances (e.g., depression and mood changes); and somnolence or fatigue.

**Adults.** Most adverse reactions related to cognition were mild to moderate in severity, frequently occurring in isolation. A rapid titration rate and a higher initial dose were associated with a higher incidence of these reactions. Psychiatric and behavioral disturbances were dose-related for both epilepsy and migraine subjects. Somnolence and fatigue were frequently reported.

**Pediatric patients.** In double-blind clinical studies of adjunctive therapy and monotherapy for epilepsy, the incidence of cognitive and neuropsychiatric adverse reactions in pediatric patients was generally lower than that observed in adults. These reactions included psychomotor slowing and problems with concentration, attention, speech, and language. Somnolence and fatigue were also commonly reported.

**Fetal toxicity.** Topiramate can cause fetal harm when administered during pregnancy. Infants exposed to topiramate in utero have shown an increased risk for cleft lip and cleft palate. When multiple species of pregnant animals received topiramate at clinically relevant doses, the offspring had structural malformations (e.g., craniofacial defects) and low body weight.

**Withdrawal of antiepileptic drugs.** In patients with or without a history of seizures or epilepsy, antiepileptic drugs should be gradually withdrawn to minimize the potential for seizures and their increased frequency.

**Metabolic acidosis.** Patients should be warned about the potential risk for metabolic acidosis, which may be asymptomatic and associated with kidney stones, osteoporosis, and osteomalacia. There is also a risk of rickets, delayed growth, and retardation in children.

**Hyperammonemia and encephalopathy.** Patients should be warned about the possible development of hyperammonemia with or without encephalopathy. Symptoms may include acute
alterations in level of consciousness or cognitive changes with lethargy or vomiting. These conditions can develop with topiramate alone or with topiramate plus valproic acid.

**Kidney stones.** Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of kidney stone formation.

**Dosage and Administration:** Topiramate is available in 25-mg, 50-mg, 100-mg and 200-mg oral ER capsules.

**Partial seizures:**

- **Monotherapy.** The dose is 400 mg orally once daily: initially, 50 mg orally once daily for 1 week, then increased by 50 mg/day each week until 200 mg once daily is given, then increased by 100 mg/day each week.
- **Adjunctive treatment.** The dose is 200 to 400 mg orally once daily: initially, 25 to 50 mg orally once for 1 week, then increased by 25 to 50 mg/day each week.

**Primary generalized tonic-clonic seizures:**

- **Monotherapy.** The dose is 400 mg orally each day: initially, 50 mg orally once daily for 1 week, then increased by 50 mg/day each week until 200 mg each day, then increased by 100 mg/day each week.
- **Adjunctive treatment.** The dose is 400 mg orally each day: initially, 25 to 50 mg each day for 1 week, then increased by 25 to 50 mg/day each week.

**Lennox–Gastaut seizures:**

- **Adjunctive treatment.** The dose is 200 to 400 mg orally each day: initially, 25 to 50 mg for 1 week, then increased by 25 to 50 mg/day each week.

**Commentary:** Trokendi XR is a once-daily ER formulation of topiramate, previously FDA-approved as an antiepileptic drug. The FDA granted a waiver for certain pediatric study requirements for Trokendi XR and a deferral for submission of postmarketing pediatric pharmacokinetic assessments, which are due in 2019, followed by clinical assessments in 2025.

**Sources:** www.trokendixr.com; www.pmpnews.com

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**Ferric Carboxymaltose Injection (Injectafer)**

**Manufacturer:** American Regent/Luitpold Pharmaceuticals, a Daiichi Sankyo Group Company, Shirley, N.Y.

**Indication:** Injectafer, a parenteral iron-replacement product used to treat iron deficiency anemia in adults who do not tolerate or who have not responded satisfactorily to oral iron. This is the first non-dextran intravenous (IV) iron formulation approved for adults with iron-deficiency anemia of various causes as well as for non-dialysis-dependent patients with chronic kidney disease.

**Uniqueness of Drug:** Ferric carboxymaltose is an iron complex that consists of a ferric hydroxide core that is stabilized by a carbohydrate shell, allowing for controlled delivery of iron to target tissues. The drug’s chemical name is polynuclear iron (III) hydroxide 4(R)-(poly-(1(R)4)-O-alpha-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. The relative molecular weight is approximately 150,000 daltons.

**Drug Class:** Ferric carboxymaltose is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron.

**Warnings and Precautions:**

- **Hypersensitivity reactions.** In clinical trials, serious and sometimes life-threatening and fatal anaphylactic and anaphylactoid reactions were reported in 0.1% of subjects receiving ferric carboxymaltose. Other serious reactions that might have been associated with hypersensitivity (e.g., pruritus, rash, urticaria, wheezing, or hypotension) were reported in 1.5% of these subjects.

  Patients may present with shock, clinically significant hypotension, and loss of consciousness. Patients should be monitored for signs and symptoms of hypersensitivity during and after the injection for at least 30 minutes and until they are clinically stable after the infusion is completed. Ferric carboxymaltose should be given only when personnel and therapies are readily available to treat serious hypersensitivity reactions.

- **Hypertension.** Hypertension was reported in 3.8% of subjects in two clinical trials. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea, were observed in 6% of subjects in the two trials. These elevations generally occurred immediately after administration and resolved within 30 minutes. Patients should be monitored for signs and symptoms of hypertension after each infusion.

- **Laboratory test alterations.** In the 24 hours after administration of ferric carboxymaltose, serum iron and transferrin bound iron levels may be overestimated if the iron in the medication is also measured.

- **Carcinogenesis.** Carcinogenicity studies have not been performed with ferric carboxymaltose. The drug was not genotoxic in an in vitro microbial mutagenesis (Ames) assay, in an in vitro chromosome aberration test in human lymphocytes, in an in vitro mammalian cell mutation assay in mouse lymphoma L5178Y/TK+/- cells, or an in vivo mouse micronucleus test at single IV doses up to 500 mg/kg.

- **Fertility.** When ferric carboxymaltose was infused over a period of 1 hour to male and female rats at iron doses of up to 30 mg/kg three times per week, there was no effect on mating function, fertility, or early embryonic development. The dose of 30 mg/kg in animals is approximately 40% of the human dose of 750 mg based on body surface area.

- **Fetotoxicity.** Ferric carboxymaltose is a Pregnancy Category C medication. Although adequate and well-controlled studies in pregnant women have not been conducted, the drug caused fetal malformations during organogenesis in rabbits and increased implantation loss at maternal toxic doses of 12% to 23% of the human weekly dose of 750 mg (based on body surface area). The incidence of major malformations in human pregnancies has not been established for ferric carboxymaltose; however, all pregnancies, regardless of exposure to any drug, have a background rate of 2% to 4% for major malformations and of 13% to 20% for pregnancy loss. The drug should be used during pregnancy only if the potential benefits justify the potential risks to the fetus.

**Dosage and Administration:** A single dose of up to 750 mg of ferric carboxymaltose can be given undiluted as an IV push injection at a rate of 100 mg/minute or as an IV infusion in up to 250 mL of 0.9% sodium chloride injection over a period of 15 minutes. This step is followed by a second dose 7 days later, for a total of up to 1,500 mg of iron.

**Patient Counseling.** Patients should be questioned about any history of reactions to parenteral iron products and should be advised to report any signs and symptoms of hypersensitivity.
such as rash, itching, dizziness, lightheadedness, swelling, or breathing problems.

**Commentary:** An estimated 7.5 million people in the U.S. have iron-deficiency anemia. Current therapies are limited to either anemic patients with chronic kidney disease or those who require infusions over the course of several hours. Ferric carboxymaltose (Injectafer) is the first high-dose, non-dextran IV iron indicated for a diverse set of patients with iron-deficiency anemia.

In general, improvements in hemoglobin concentrations were more rapid with ferric carboxymaltose than with oral ferrous sulfate (e.g., Feosol, Meda). In patients with chronic kidney disease undergoing hemodialysis, ferric carboxymaltose was at least as effective as IV iron sucrose injection (e.g., Venofer, American Regent). Ferric carboxymaltose also replenished depleted iron stores and improved health-related quality-of-life scores, serum ferritin levels, and transferrin saturation. The infusions were well tolerated.

Most drug-related adverse events were mild to moderate in severity. Adverse drug-related events include headache, dizziness, nausea, abdominal pain, constipation, diarrhea, rash, and injection-site reactions. The incidence rate of adverse events with IV ferric carboxymaltose was generally similar to that with oral ferrous sulfate.

Rash and local injection-site reactions were more common with ferric carboxymaltose, whereas gastrointestinal adverse events were more frequent with ferrous sulfate. In chronic kidney disease patients undergoing hemodialysis, fewer ferric carboxymaltose patients experienced at least one drug-related adverse event compared with recipients of iron sucrose.

**Sources:** [www.fda.gov](http://www.fda.gov); [www.injectafer.com](http://www.injectafer.com); [www.daiichisankyo.com](http://www.daiichisankyo.com)