Pharmaceutical Approval Update

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Fesoterodine Fumarate Extended-Release Tablets (Toviaz)

**Manufacturer:** Schwarz Pharma, Zwickau, Germany (distributed by Pfizer)

**Indication:** Fesoterodine fumarate is indicated for the treatment of overactive bladder (OAB) in patients with urge urinary incontinence, urgency, and frequency.

**Drug Class:** This agent is designated as isobutyric acid 2-((R)-3-diisopropylammonium-1-phenylpropyl)-4-(hydroxymethyl) phenyl ester hydrogen fumarate.

**Uniqueness of Drug:** Fesoterodine is rapidly de-esterified to its active metabolite, (R)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, or 5-hydroxymethyl tolterodine, a muscarinic receptor antagonist. The active metabolite is further metabolized in the liver to its carboxy, carboxy-N-desisopropyl, and N-desisopropyl metabolites via two major pathways involving cytochrome P450 2D6 and CYP 3A4. None of these metabolites contribute significantly to the antimuscarinic activity of fesoterodine. The extended-release tablet contains either 4 mg or 8 mg of fesoterodine fumarate.

**Precautions:**

- **Bladder outlet obstruction.** Fesoterodine fumarate should be administered with caution to patients with bladder outlet obstruction because of the risk of urinary retention.

- **Decreased gastrointestinal motility.** As with other antimuscarinic drugs, fesoterodine fumarate should be used with caution in patients with decreased gastrointestinal (GI) tract motility (e.g., as in severe constipation).

- **Controlled narrow-angle glaucoma.** Caution should be exercised for patients with narrow-angle glaucoma, and this drug should be prescribed only when the potential benefits outweigh the risks.

- **Reduced hepatic function.** No dosing adjustments are necessary for patients with mild or moderate hepatic impairment. Fesoterodine fumarate has not been studied in patients with severe hepatic impairment and is thus not recommended for this population.

- **Myasthenia gravis.** Caution should be used for patients with myasthenia gravis, which is characterized by decreased cholinergic activity at the neuromuscular junction.

- **Reduced renal function.** There are no dosing adjustments for patients with mild or moderate renal insufficiency. Doses greater than 4 mg are not recommended in patients with severe renal insufficiency.

**Administration with CYP 3A4 inhibitors.** Doses higher than 4 mg are not recommended if patients are taking a potent CYP 3A4 inhibitor, such as ketoconazole (Nizoral, PriCara), itraconazole (Sporanox, PriCara), or clarithromycin (Biaxin, Abbott). If patients are taking weak or moderate CYP 3A4 inhibitors (e.g., erythromycin), careful assessment of tolerability at the 4 mg daily dose is advised before the daily dose is increased to 8 mg. Although the potential for this specific interaction was not examined in a clinical study, some pharmacokinetic interaction is expected, albeit less than that observed with potent CYP 3A4 inhibitors.

**Dosage and Administration:** The recommended starting dose is 4 mg once daily. Depending on the patient’s response and tolerability, the dose may be increased to 8 mg once daily. The daily dose should not exceed 4 mg in patients with severe renal insufficiency (a creatinine clearance [CrCl] below 30 mL/minute) or in those taking potent CYP 3A4 inhibitors.

The tablet is taken with liquid and swallowed whole. It can be taken with or without food and should not be chewed, divided, or crushed.

The extended-release tablet contains either 4 mg or 8 mg of fesoterodine fumarate. Inactive ingredients are glyceral behenate, indigo carmine aluminum lake, lactose monohydrate, soya lecithin, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, t alc, titanium dioxide, and xylitol.

**Contraindications:** Fesoterodine fumarate is not recommended for patients with severe hepatic impairment.

**Commentary:** OAB is a bothersome medical condition that affects an estimated one in six Americans, yet it remains highly undertreated. Fesoterodine fumarate can help regulate involuntary bladder contractions, which cause frequent, sudden urges to urinate. The drug is structurally related to Pfizer’s tolterodine tartrate extended-release capsules (Detrol LA). Two efficacious and well-tolerated doses, 4 mg and 8 mg, allow dosing flexibility to optimize treatment.

Symptoms of OAB can have a significant impact on workplace productivity, social and sexual activity, and sleep. OAB may also result in falls and fractures, urinary tract infections, skin disorders, and depression. Despite the impact of OAB on patients’ lives, the embarrassment and stigma associated with incontinence can cause patients to try to hide the condition from families, friends, and even their doctors. As a result, many patients with incontinence suffer without seeking help. People with OAB symptoms should be encouraged to speak to their physicians about their problem in order to improve their quality of life.

**Source:** www.pfizer.com

Rufinamide (Banzel)

**Manufacturer:** Eisai, Woodcliff Lake, N.J.

**Indication:** Rufinamide is indicated for the adjunctive treatment of seizures associated with Lennox–Gastaut syndrome in adults and in children four years of age and older.

**Drug Class:** The chemical name is 1-[(2,6-difluoro phenyl)methyl]-1H-1,2,3-triazole-4-carboxamide. Rufinamide, a triazole derivative, is structurally unrelated to currently marketed antiepileptic drugs.


Uniqueness of Product: The precise mechanism by which rufinamide exerts its antiepileptic effect is unknown. In vitro studies suggest that the principal mechanism of action is by modulation of the activity of sodium channels and, in particular, by prolongation of the inactive state of the channel. Rufinamide (≥1 μM) significantly slowed sodium channel recovery from inactivation after a prolonged pre-pulse in cultured cortical neurons and limited sustained repetitive firing of sodium-dependent action potentials.

Warnings:

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

In pooled analyses of 199 placebo-controlled trials (median duration, 12 weeks), patients randomly assigned to receive an antiepileptic drug had approximately twice the risk of suicidal thinking or behavior compared with patients receiving placebo. In these trials, the estimated incidence of suicidal behavior or ideation among 27,863 treated patients was 0.43%, compared with 0.24% among 16,029 placebo patients (an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated). There were four suicides among the treated patients and none in placebo patients, but the number of events was too small to draw a conclusion about the drug’s effect on suicide.

This increased risk was observed as early as one week after treatment started and persisted for at least 24 weeks. Because most trials included in the analysis did not extend beyond 24 weeks, the risk beyond 24 weeks could not be assessed. This risk was consistent among drugs in the data analyzed. The finding of increased risk with antiepileptic drugs of varying mechanisms of action and for a range of indications suggests that the risk applies to all antiepileptic drugs used for any indication. Risk did not vary substantially by age.

The relative risk of suicidal thoughts or behavior was higher in trials of epilepsy than in trials of psychiatric disorders or other conditions. Epilepsy and many other illnesses for which antiepileptics are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. If suicidal thoughts and behavior arise during treatment, prescribers should consider whether the emergence of these symptoms in a patient might be related to the illness being treated.

Patients, their caregivers, and families should be informed that antiepileptic drugs might increase the risk of suicidal thoughts and behavior.

Central nervous system reactions. The use of rufinamide has been associated with central nervous system–related adverse reactions. The most significant of these can be classified into the categories of (1) somnolence or fatigue and (2) coordination abnormalities, dizziness, gait disturbances, and ataxia.

Precautions: In electrocardiographic studies, shortening of the QT interval (up to 20 msec) occurred with rufinamide. In one study, a higher percentage of rufinamide-treated subjects (46% receiving 2,400 mg, 46% receiving 3,200 mg, and 65% receiving 4,800 mg) experienced a QT shortening of more than 20 msec at the time to maximum concentration, compared with placebo (5%–10%). Reductions of the QT interval below 300 msec were not observed in the QT studies with doses up to 7,200 mg/day. Moreover, there was no signal for drug-induced sudden death or ventricular arrhythmias. The degree of QT shortening induced by rufinamide is not linked to any known clinical risk.

Familial short QT syndrome is associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation. Such events in this syndrome are believed to occur primarily when the corrected QT interval falls below 300 msec. Nonclinical data also indicate that QT shortening is associated with ventricular fibrillation. Patients with familial short QT syndrome should not use rufinamide. Caution should be used when rufinamide is given with other drugs that shorten the QT interval.

Multigorgan hypersensitivity reactions. A serious condition sometimes induced by antiepileptic drugs, multiorgan hypersensitivity syndrome has occurred in association with rufinamide. One patient experienced rash, urticaria, facial edema, fever, elevated eosinophils, a stuporous state, and severe hepatitis beginning on day 29 of therapy and extending over a course of 30 days of continued therapy; symptoms resolved 11 days after therapy was discontinued. Rash, fever, elevated liver enzymes, hematuria, and lymphadenopathy were also noted. These cases occurred in children younger than 12 years of age within four weeks of starting treatment and resolved or improved upon discontinuation of therapy. This syndrome has been reported with other anticonvulsants. Patients sometimes present with fever and rash associated with other organ system involvement. Because this disorder is variable in expression, other organ system signs and symptoms may occur. If this reaction is suspected, rufinamide should be discontinued and a different treatment should be started. If a rash develops, the patient must be closely supervised.

Withdrawal of antiepileptic drugs. As with all antiepileptic drugs, rufinamide should be withdrawn gradually to minimize the risk of precipitating or exacerbating seizures or status epilepticus. If the drug must be stopped abruptly, the transition to another drug should be closely supervised. In clinical trials, discontinuation was achieved by reducing the dose by approximately 25% every two days.

Status epilepticus. It is difficult to estimate the incidence of treatment-emergent status epilepticus among the rufinamide patients because standard definitions were not employed. In a controlled trial involving patients with Lennox–Gastaut syndrome, three of 74 rufinamide-treated patients (4.1%) had status epilepticus–like episodes compared with none of the 64 placebo patients. In all controlled trials that included patients with different types of epilepsy, 11 of 1,240 rufinamide-treated patients (0.9%) had episodes that could be described as status epilepticus, compared with none of 635 placebo patients.

Dosage and Administration: The tablets are scored on both sides. They can be taken whole, as half-tablets, or crushed. Rufinamide should be taken with food.

Children four years of age and older with Lennox–Gastaut syndrome: Initial treatment should be a daily dose of approximately 10 mg/kg per day, given in two equally
divided doses. The dose should be increased by increments of approximately 10 mg/kg every other day to a target dose of 45 mg/kg per day or 3,200 mg/day, whichever is less, in two equally divided doses. It is not known whether doses lower than the target doses are effective.

**Adults with Lennox–Gastaut syndrome:** Treatment is initiated at a daily dose of 400 to 800 mg/day, taken in two equally divided doses. The dose should be increased by 400 to 800 mg/day every two days until a maximum daily dose of 3,200 mg/day, taken in two equally divided doses, is reached. It is not known whether doses lower than 3,200 mg are effective.

**Patients with renal impairment.** Renally impaired patients (with a CrCl below 30 mL/minute) do not require any dose adjustments.

**Patients undergoing hemodialysis.** Hemodialysis may reduce exposure to a limited extent (about 30%). Accordingly, adjusting the rufinamide dose during the dialysis process can be considered.

**Patients with hepatic disease.** The use of rufinamide in patients with hepatic impairment has not been studied, and it is therefore not recommended for patients with severe hepatic impairment. Caution should be exercised in treating patients with mild-to-moderate hepatic impairment.

**Commentary:** Lennox–Gastaut syndrome is a difficult-to-treat form of childhood-onset epilepsy. Seizures usually start between two and five years of age but may also start before age two. Seizures may be tonic, atonic, atypical absence, and myoclonic. Most affected children experience impaired intellectual functioning or information processing along with developmental delays and behavioral disturbances. Severe myoclonic epilepsy in infancy is considered a chronically debilitating condition. From 1,400 to 4,500 new cases of the syndrome are diagnosed each year in the U.S. Complete recovery is unusual, and there is no known cure.

In clinical trials, rufinamide reduced the frequency and types of seizures. Patients seemed to tolerate the drug well, but it is not clear whether these results will ultimately change prognosis. Treated patients experienced a 32.7% median reduction in total seizure frequency per 28 days relative to baseline, compared with an 11.7% median decrease with placebo. There was a 42.5% median reduction in the frequency of tonic–atonic seizures per 28 days relative to the baseline in the rufinamide group, compared with a 1.4% median increase for the placebo group. A significantly higher percentage of the rufinamide patients (42.5%) responded to treatment, compared with placebo patients (16.7%), experiencing a reduction of 50% or more in the frequency of tonic–atonic seizures, a secondary endpoint of the study. Frequently reported adverse drug events included somnolence, fever, vomiting, and diarrhea.

**Sources:** www.eisai.com; www.emea.europa.com; www.redorbit.com

**Eltrombopag (Promacta) Tablets**

**Manufacturer:** GlaxoSmithKline, Research Triangle Park, N.C.

**Indication:** Eltrombopag is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. This drug should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk of bleeding. Eltrombopag should not be used in an attempt to normalize platelet counts.

**Drug Class:** Eltrombopag is a nonpeptide thrombopoietin receptor agonist.

**Uniqueness of Drug:** As an oral, once-daily agent, eltrombopag is designed to stimulate the proliferation and differentiation of megakaryocytes (bone marrow cells that give rise to blood platelets).

**Boxed Warning:** Eltrombopag may cause hepatotoxicity. Serum levels of aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin should be measured before therapy begins, every two weeks during the dose-adjustment phase, and monthly after a stable dose is established. If bilirubin is elevated, fractionation is performed. Abnormal serum liver tests are evaluated with more testing within three to five days. If the abnormalities are confirmed, liver function tests are monitored weekly until the abnormalities resolve, stabilize, or return to baseline levels.

Eltrombopag should be discontinued if ALT levels increase to more than three times the upper limit of normal (ULN) and if they are progressive, persist for four weeks or more, or are accompanied by increased direct bilirubin or by clinical symptoms of liver injury or evidence of hepatic decompensation.

**Warnings and Precautions:** Increased levels of serum ALT, AST, and bilirubin have been observed. Liver chemistries must be measured before therapy begins and regularly during treatment. Caution is needed for patients with hepatic impairment.

Eltrombopag may increase the risk of development of or progression of reticulin fiber deposition within bone marrow. Peripheral blood should be monitored for signs of marrow fibrosis.

Discontinuation of therapy may result in worsened thrombocytopenia than was present before therapy. Complete blood counts (CBCs), including platelet counts, should be monitored for at least four weeks after discontinuation. Excessive doses of this agent may increase platelet counts to a level that produces thrombotic or thromboembolic complications.

Eltrombopag may increase the risk of hematological malignancies, especially in patients with myelodysplastic syndrome. CBCs, platelet counts, and peripheral blood smears should be monitored weekly during the dose-adjustment phase and then monthly after a stable dose is established.

Because of the risk for hepatotoxicity, eltrombopag is available only through a restricted distribution program called Promacta Cares. Prescribers, pharmacies, and patients, respectively, must be registered to be able to prescribe, dispense, and receive eltrombopag.

**Risk of hepatotoxicity.** In controlled clinical studies, one patient experienced grade 4 elevations in serum liver test values during therapy, worsening of underlying cardiopulmonary disease, and death. No placebo patients experienced grade 4 liver test abnormalities. Overall, serum liver test abnormalities (predominantly grade 2 or less in severity) were reported in 10% of the eltrombopag patients and in 8% of the placebo groups. In the controlled studies, two treated patients (1%) and
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two placebo patients (3%) discontinued treatment because of hepatobiliary laboratory abnormalities.

In the extension study, seven treated patients with hepatobiliary laboratory abnormalities were re-exposed to eltrombopag. Six of these patients again experienced liver test abnormalities (mostly grade 1), resulting in discontinuation of therapy in one patient. In the extension study, one additional patient discontinued eltrombopag because of liver test abnormalities (grade 3 or lower).

ALT, AST, and bilirubin should be measured before therapy begins, every two weeks during the dose-adjustment phase, and monthly after the establishment of a stable dose. If serum liver test results are abnormal, the test is repeated within three to five days. If the abnormalities are confirmed, serum liver tests are monitored weekly until the abnormality resolves, stabilizes, or returns to baseline levels. Eltrombopag should be discontinued if ALT levels increase to more than three times the ULN, are progressive, persist for four weeks or more, and are accompanied by increased direct bilirubin or by symptoms of liver injury or evidence of hepatic decompensation.

Re-initiating treatment with eltrombopag is not recommended, but if the potential benefit is considered to outweigh the risk for hepatotoxicity, the drug can be cautiously re-introduced. Serum liver tests should be measured weekly during the dose-adjustment phase. If liver tests abnormalities persist, worsen or recur, eltrombopag should be permanently discontinued.

A lower starting dose is used in patients with moderate-to-severe hepatic disease.

Bone marrow reticulin formation and risk of bone marrow fibrosis. Thrombopoietin receptor agonists increase the risk for development of or progression of reticulin fiber deposition in bone marrow.

In the extension study, seven patients undergoing bone marrow biopsies had reticulin fiber, including two patients who also had collagen fiber deposition. The fiber deposition was not associated with cytopenias and did not necessitate discontinuation of eltrombopag. However, clinical studies have not excluded a risk of bone marrow fibrosis with cytopenias.

Before therapy begins, the peripheral blood smear should be closely examined to establish a baseline level of cellular morphological abnormalities. After a stable dose of eltrombopag has been identified, peripheral blood smears and CBCs are examined monthly to check for new or worsening morphological abnormalities, such as teardrop and nucleated red blood cells, immature white blood cells, or cytopenia. If new or worsening morphological abnormalities or cytopenia develops, treatment is discontinued, and a bone marrow biopsy, including staining for fibrosis, should be considered.

Worsened thrombocytopenia and risk of hemorrhage after cessation of therapy. Discontinuing eltrombopag may result in thrombocytopenia of a greater severity than that which was present before therapy. This worsened thrombocytopenia may increase the risk of bleeding, particularly if the drug is discontinued while the patient is taking anticoagulants or antiplatelet agents. In controlled studies, transient decreases in platelet counts to levels lower than baseline were observed after treatment was discontinued in 10% of the eltrombopag patients and in 6% of the placebo patients. Serious hemorrhagic events requiring the use of supportive ITP medications occurred in three severely thrombocytopenic patients within one month after the drug was stopped; no events were reported in the placebo group. After discontinuation, weekly CBCs, including platelet counts for at least four weeks, are obtained. Alternative treatments for worsening thrombocytopenia should be considered.

Thrombotic and thromboembolic complications. Complications can result from excessive increases in platelet counts. Excessive doses of eltrombopag, or medication errors that result in excessive doses of eltrombopag, may increase platelet counts to a level that produces thromboses or thromboembolism. In controlled studies, one such complication was reported in patients who received eltrombopag but none were observed within the placebo groups. In the extension study, seven patients experienced complications.

Caution should be used for patients with known risk factors for thromboembolism, such as factor V Leiden and antiphospholipid syndrome. To minimize the risk of thrombotic or thromboembolic complications, eltrombopag should not be used in an attempt to normalize platelet counts. The dose-adjustment guidelines should be followed to achieve and maintain a platelet count of 50 × 10^9/L or higher.

Malignancies. Eltrombopag’s stimulation of the thrombopoietin receptor on the surface of hematopoietic cells may increase the risk of hematological malignancies. In clinical studies, no hematological malignancies were reported for patients receiving eltrombopag for a maximum of six weeks. One hematological malignancy (non-Hodgkin’s lymphoma) was reported in the extension study. Eltrombopag is not indicated for the treatment of thrombocytopenia resulting from etiologic factors (e.g., myelodysplasia or chemotherapy) other than chronic ITP.

Cataracts. In controlled studies, cataracts developed or worsened in five patients (5%) who received 50 mg of eltrombopag daily and two placebo patients (3%). In the extension study, cataracts developed or worsened in 4% of patients who underwent an eye examination before receiving eltrombopag. Cataracts were also observed in studies of eltrombopag in rodents.

A baseline ocular examination should be performed before therapy begins, and patients should be monitored during therapy for signs and symptoms of cataracts.

Dosage and Administration: Only health care providers who have enrolled in the Promacta Cares Program may prescribe eltrombopag.

The 25-mg tablets are round, biconvex, and orange; each tablet contains eltrombopag olamine, equivalent to 25 mg of eltrombopag free acid. The 50-mg tablets are round, biconvex, and blue; each tablet contains eltrombopag olamine, equivalent to 50 mg of eltrombopag free acid.

Eltrombopag is initiated at a dose of 50 mg once daily. For patients of East Asian ancestry or those with moderate-to-severe hepatic impairment, the dose should be reduced to 25 mg once daily. The lowest possible dose should be used to achieve and maintain a platelet count of 50 × 10^9/L or more to reduce the risk of bleeding. Ertomopag should not be used in an attempt to normalize platelet counts.

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Liver enzymes (ALT, AST, and bilirubin) and CBCs, including platelet counts and peripheral blood smears, should be monitored before and throughout therapy. If bilirubin is elevated, fractionation should be performed. The CBC should be monitored for at least four weeks following discontinuation of eltrombopag. In clinical studies, platelet counts generally increased within one to two weeks after therapy begins and decreased within one to two weeks after eltrombopag is discontinued.

Eltrombopag is taken on an empty stomach, one hour before or two hours after a meal. Patients should allow at least a four-hour interval before they take other medications (e.g., antacids, calcium-rich foods) or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc.

Monitoring and dose adjustments. The dose should not exceed 75 mg daily. Hematology and liver tests should be monitored throughout therapy, and the dosage should be modified according to the platelet count. During therapy, the CBC is assessed weekly until a stable platelet count has been achieved; after that, the CBC is obtained monthly. Dosages of concomitant ITP medications, as medically appropriate, should be adjusted to avoid excessive increases in platelet counts during therapy. Patients should not take more than one dose within any 24-hour period.

Discontinuation of therapy. Patients should stop taking this drug if the platelet count does not increase to a level sufficient to avoid bleeding after four weeks of therapy at the maximum daily dose of 75 mg. If platelet count responses or liver test abnormalities occur, eltrombopag should be discontinued.

Commentary: Eltrombopag is an oral platelet growth factor agent developed to treat chronic immune (idiopathic) thrombocytopenic purpura, or ITP, a rare disorder characterized by increased platelet destruction or inadequate platelet production. Patients with chronic ITP often bleed from small blood vessels, resulting in bruises, nosebleeds, or even fatal GI tract or intracerebral bleeding. Between 50,000 and 100,000 individuals in the U.S. have chronic ITP.

The goal of therapy is to keep the platelet count at about 50 × 10^9/L in order to lower the risk of bleeding, but eltrombopag is not indicated for normalizing the platelet count. During therapy, the dose may need to be modified. Blood platelet counts are performed before, during, and after therapy. Eltrombopag is available only through a restricted program.

Sources: www.promactacares.com; http://us.gsk.com

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