Pharmaceutical Approval Update

Mary Choy, PharmD, BCGP, FASHP

Hydrocodone Bitartrate (Vantrela ER)

Manufacturer: Teva Pharmaceuticals, Inc., North Wales, Pennsylvania

Date of Approval: January 17, 2017

Indication: Vantrela ER is an opioid agonist used for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment. Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release (ER) opioid formulations, Vantrela ER should be reserved for use in patients for whom alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. This medication is not indicated as an as-needed analgesic.

Drug Class: Opioid analgesics

Uniqueness of Drug: Vantrela ER (CII), formulated with Teva’s proprietary abuse-deterrence technology, is expected to reduce, but not totally prevent, oral, intranasal, and intravenous abuse of the drug when the tablets are manipulated.

Warnings and Precautions:

Boxed Warnings:

• Addiction, abuse, and misuse. Vantrela ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk before prescribing, and monitor regularly for these behaviors and conditions.

• Life-threatening respiratory depression. Serious, life-threatening, or fatal respiratory depression may occur. Monitor patients closely, especially upon initiation or following a dose increase. Instruct patients to swallow the medication whole to avoid exposure to a potentially fatal dose of hydrocodone.

• Accidental ingestion. Accidental ingestion of even one dose, especially by children, can result in a fatal overdose of hydrocodone.

• Neonatal opioid withdrawal syndrome. Prolonged use during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of this syndrome, and ensure that appropriate treatment will be available.

• Cytochrome P450 (CYP) 3A4 interaction. Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of hydrocodone.

• Risks from concomitant use with benzodiazepines or other central nervous system (CNS) depressants. Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

Adrenal insufficiency. If diagnosed, treat with physiological replacement of corticosteroids, and wean patient off of the opioid.


Risks of use in patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness. Monitor for sedation and respiratory depression. Avoid use in patients with impaired consciousness or coma.

QTc prolongation. Consider this observation when making clinical decisions regarding monitoring of patients with congestive heart failure, bradycardias, or electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. Avoid use in patients with congenital long QTc syndrome. In patients who develop QTc prolongation, consider reducing the dose. Do not exceed a dose of 90 mg every 12 hours (180 mg per day) because higher doses have not been studied.

Dosage and Administration: Vantrela ER 90-mg tablets, a single dose greater than 60 mg, or a total daily dose greater than 120 mg are indicated only for patients in whom tolerance to an opioid of comparable potency has been established. Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. For opioid-naive and opioid non-tolerant patients, initiate with 15-mg tablets orally every 12 hours. Increase the dose every three to seven days as needed. Do not abruptly discontinue therapy in a physically dependent patient.

For patients with mild-to-moderate hepatic impairment or moderate-to-severe renal impairment and end-stage renal disease, initiate therapy with one-half of the recommended initial dose and titrate carefully. Use alternative analgesia for patients requiring less than 15 mg; and monitor closely.

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse.

Tablets must be swallowed intact and are not to be crushed, dissolved, or chewed due to the risk of overdose or death. To
Etelcalcetide (Parsabiv)

**Manufacturer:** Amgen, Inc., Thousand Oaks, California  
**Date of Approval:** February 7, 2017

**Indication:** Etelcalcetide is a calcium-sensing receptor agonist indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis. Etelcalcetide has not been studied in adult patients with parathyroid carcinoma, primary HPT, or with CKD who are not on hemodialysis, and it is not recommended for use in these populations.

**Drug Class:** Calcimimetics

**Uniqueness of Drug:** Etelcalcetide is the first new treatment in more than a decade for secondary HPT in adults on hemodialysis. It is the only calcimimetic that can be administered intravenously (IV) by the dialysis health care team three times a week at the end of the hemodialysis session.

**Warnings and Precautions:**

- **Hypocalcemia.** Etelcalcetide lowers serum calcium and can lead to hypocalcemia. Severe hypocalcemia can cause paresthesias, myalgias, muscle spasms, seizures, QT prolongation, and ventricular arrhythmias. Patients predisposed to QT interval prolongation, ventricular arrhythmias, and seizures may be at increased risk and require close monitoring. Educate patients on the symptoms of hypocalcemia, and advise them to contact a health care provider if symptoms occur. If corrected serum calcium falls below the lower limit of normal or if symptoms of hypocalcemia develop, start or increase calcium supplementation. It may also be necessary to reduce the etelcalcetide dose or discontinue therapy.

- **Worsening heart failure.** Reductions in corrected serum calcium may be associated with congestive heart failure; however, a causal relationship to etelcalcetide could not be completely excluded. Patients should be closely monitored for worsening signs and symptoms of heart failure.

- **Upper gastrointestinal (GI) bleeding.** Patients with risk factors for upper GI bleeding may be at increased risk. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with etelcalcetide and for signs and symptoms of GI bleeding and ulcerations during therapy. Promptly evaluate and treat any suspected GI bleeding.

- **Adynamic bone.** Adynamic bone may develop if parathyroid hormone (PTH) levels are chronically suppressed. If PTH levels fall below the recommended target range, the dose of vitamin D sterols and/or etelcalcetide should be reduced or discontinued. After discontinuation, therapy can be resumed at a lower dose to maintain PTH levels in the target range.

**Dosage and Administration:** The recommended starting dose of etelcalcetide is 5 mg administered by IV bolus injection three times per week at the end of hemodialysis treatment. The maintenance dose is individualized and determined by titration based on PTH levels and corrected serum calcium response. The dose range is 2.5–15 mg three times per week. The dose may be increased in 2.5-mg or 5-mg increments no more frequently than every four weeks.

Ensure corrected serum calcium is at or above the lower limit of normal prior to initiation, dose increase, or reinitiation. Measure serum calcium within one week after initiation or dose adjustment and every four weeks for maintenance. Obtain a PTH level four weeks after initiation or dose adjustment. The dose of etelcalcetide should be decreased or temporarily discontinued in patients with PTH levels below the target range. In patients with a corrected serum calcium below the lower limit of normal but at or above 7.5 mg/dL without symptoms of hypocalcemia, the dose of etelcalcetide should be decreased or temporarily discontinued or concomitant therapies can be used to increase the corrected serum calcium. Discontinue etelcalcetide and treat hypocalcemia if the corrected serum calcium falls below 7.5 mg/dL or if patients report symptoms of hypocalcemia.

**Commentary:** The Food and Drug Administration’s approval of etelcalcetide was based on data from two placebo-controlled phase 3 clinical trials in patients with CKD and secondary HPT on hemodialysis. In both studies, etelcalcetide achieved a greater reduction from baseline in PTH than placebo. Etelcalcetide offers convenient IV delivery at the end of hemodialysis and has effectively demonstrated reduction in levels of PTH, corrected calcium, and phosphate. The most common adverse reactions were blood calcium decrease, muscle spasms, diarrhea, nausea, vomiting, headache, hypocalcemia, and paresthesia.

**Sources:** Teva Pharmaceuticals, Inc., Vantrela ER prescribing information

---

**Deflazacort (Emflaza)**

**Manufacturer:** Marathon Pharmaceuticals, LLC, Northbrook, Illinois  
**Date of Approval:** February 10, 2017

**Indication:** Deflazacort is a corticosteroid indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 5 years of age and older.

**Drug Class:** Corticosteroids

**Uniqueness of Drug:** Deflazacort tablets and oral suspension are indicated to treat DMD, a rare genetic disorder that causes progressive muscle deterioration and weakness. This is the first Food and Drug Administration (FDA) approval of any corticosteroid to treat DMD. Deflazacort also received an FDA orphan drug designation.

**Warnings and Precautions:**

- **Alterations in endocrine function.** Hypothalamic–pituitary–adrenal axis suppression, Cushing’s syndrome, and hyperglycemia can occur; patients should be monitored for these conditions with chronic use of deflazacort.

- **Immunosuppression and increased risk of infection.** There is an increased risk of new infections and of exacerbation, dissemination, or reactivation of latent infections, which can be severe and sometimes fatal. The signs and symptoms of infection may be masked.

continued on page 255
Alterations in cardiovascular and renal function. Monitor patients for elevated blood pressure and sodium levels and for decreased potassium levels.

Gastrointestinal (GI) perforation. Patients with certain GI disorders are at increased risk of GI perforation. The signs and symptoms may be masked.

Behavioral and mood disturbances. Deflazacort may cause euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis.

Effects on bones. Monitor patients for decreases in bone mineral density with chronic use of deflazacort.

Ophthalmic effects. Deflazacort may cause cataracts, infections, and glaucoma. Monitor intraocular pressure if deflazacort is continued for more than six weeks.

Vaccination. Do not administer live or live attenuated vaccines to patients receiving immunosuppressive doses of corticosteroids.

Serious skin rashes. Discontinue at the first sign of rash, unless the rash is clearly unrelated to deflazacort.

Dosage and Administration: The recommended once-daily dosage of deflazacort is approximately 0.9 mg/kg per day administered orally. The medication should be discontinued gradually when administered for more than a few days.

Commentary: The effectiveness of deflazacort for the treatment of DMD was established in a multicenter, randomized, double-blind, placebo-controlled, 52-week study conducted in the United States and Canada. The study included 196 male pediatric patients 5 to 15 years of age who were ambulatory and nonambulatory. The change in average muscle strength score between baseline and week 12 was significantly greater for the deflazacort 0.9-mg/kg per day group (the recommended dose) than for the placebo group \( (P = 0.017) \). The most common adverse reactions were Cushingoid appearance, increased weight and appetite, upper respiratory tract infection, cough, pollakiuria, hirsutism, central obesity, and nasopharyngitis.

Sources: Marathon Pharmaceuticals, LLC, Emflaza prescribing information