Selinexor (Xpovio)

**Manufacturer:** Karyopharm Therapeutics Inc., Newton, Massachusetts

**Date of Approval:** July 3, 2019

**Indication:** Selinexor is indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

**Drug Class:** Nuclear export inhibitor, antineoplastic

**Uniqueness of Drug:** While there is no cure for multiple myeloma, there are FDA-approved treatments to target the cancer and slow its spread. Patients with heavily pretreated multiple myeloma will have a new therapeutic option with selinexor. Selinexor received accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

**Warnings and Precautions:**

- **Thrombocytopenia.** Selinexor can cause thrombocytopenia, leading to potentially fatal hemorrhage. Monitor platelet counts at baseline, during treatment, and as clinically indicated. Manage with dose interruption, reduction, and supportive care.

- **Neutropenia.** Monitor neutrophil counts at baseline, during treatment, and as clinically indicated. Manage with dose interruption and/or reduction and granulocyte colony stimulating factors (G-CSFs).

- **Gastrointestinal toxicity.** Nausea, vomiting, diarrhea, anorexia, and weight loss may occur. Provide antiemetic prophylaxis. Manage with dose interruption and/or reduction, antiemetics, and supportive care.

- **Hyponatremia.** Monitor serum sodium levels at baseline, during treatment, and as clinically indicated. Correct for concurrent hyperglycemia and high serum paraprotein levels.

- **Infections.** In patients receiving selinexor, 52% of patients experienced any grade of infection. Monitor for signs and symptoms of infection and treat promptly.

- **Neurological toxicity.** Avoid taking selinexor with other medications that may cause dizziness or confusion. Avoid situations where dizziness or a confusional state may be a problem. Optimize hydration status, blood counts, and concomitant medications to avoid dizziness or confusion.

- **Embryo-fetal toxicity.** Based on data from animal studies and its mechanism of action, selinexor can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential, or the potential risk to a fetus and use of effective contraception.

**Dosage and Administration:**

- The recommended starting dosage of selinexor is 80 mg (four 20 mg tablets) taken orally on days 1 and 3 of each week until disease progression or unacceptable toxicity.

- The recommended starting dosage of dexamethasone is 20 mg taken orally with each dose of selinexor on days 1 and 3 of each week.

- Each selinexor dose should be taken at approximately the same time of day, and each tablet should be swallowed whole with water. Do not break, chew, crush, or divide the tablets.

- If a dose of selinexor is missed or delayed, instruct patients to take their next dose at the next regularly scheduled time. If a patient vomits a dose of selinexor, the patient should not repeat the dose and the patient should take the next dose on the next regularly scheduled day.

- Monitor complete blood count, standard blood chemistry, and body weight at baseline and during treatment as clinically indicated. Monitor more frequently during the first two months of treatment.

- Advise patients to maintain adequate fluid and caloric intake throughout treatment. Consider intravenous hydration for patients at risk of dehydration. Provide prophylactic concomitant treatment with a 5-HT3 antagonist and/or other antinausea agents prior to and during treatment with selinexor.

**Commentary:** The FDA approval was based on results from the phase 2b STORM study, which analyzed selinexor in combination with dexamethasone among a subgroup of 83 patients with RRMM. The results showed an overall response rate of 25.3% among patients in the subgroup. The median time to first response was four weeks and the median duration of response was 3.8 months. The most common adverse reactions (with an incidence of at least 20%) are thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infection.

**Sources:** Karyopharm Therapeutics Inc., Xpovio prescribing information

**Imipenem, Cilastatin, and Relebactam (Recarbrio)**

**Manufacturer:** Merck & Co., Inc., Whitehouse Station, New Jersey

**Date of Approval:** July 16, 2019

**Indication:** Recarbrio is a combination of imipenem (a penem antibacterial), cilastatin (a renal dehydropeptidase inhibitor), and relebactam (a beta-lactamase inhibitor) indicated in patients 18 years of age and older who have limited or no alternative treatment options for the treatment of the following infections caused by susceptible gram-negative bacteria:
• Complicated urinary tract infections, including pyelonephritis (cUTI)
• Complicated intra-abdominal infections (cIAI)

**Drug Class:** Carbapenems

**Uniqueness of Drug:** Recarbrio is a three-drug combination injection containing imipenem-cilastatin, a previously FDA-approved antibiotic, and relebactam, a new beta-lactamase inhibitor. Use of the combination drug should be limited to cUTI and cIAI among adult patients who have limited or no therapy options.

**Warnings and Precautions:**

**Hypersensitivity reactions.** Hypersensitivity reactions have been reported in patients receiving beta-lactam drugs. Discontinue the drug immediately if a hypersensitivity reaction occurs.

**Seizures and central nervous system (CNS) adverse reactions.** CNS adverse reactions such as seizures have been reported with imipenem/cilastatin. If focal tremors, myoclonus, or seizures occur, evaluate patients to determine whether the drug should be discontinued.

**Increased seizure potential due to interaction with valproic acid.** Concomitant use of imipenem, cilastatin, and relebactam with valproic acid or divalproex sodium may reduce the serum concentration of valproic acid, which may increase the risk of breakthrough seizures. Avoid concomitant use or consider alternative antibacterial drugs other than carbapenems.

**Clostridium difficile-associated diarrhea (CDAD).** CDAD has been reported with use of nearly all antibacterial agents, including imipenem/cilastatin plus relebactam, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. A careful medical history is necessary because CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

**Dosage and Administration:**

- The recommended dosage of Recarbrio is 1.25 g (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) administered by intravenous infusion over 30 minutes every six hours in patients 18 years of age and older with creatinine clearance (CrCl) of 90 mL/min or greater. A dose reduction is recommended for patients with CrCl less than 90 mL/min (Table 1). The severity and location of infection, as well as clinical response, should guide the duration of therapy.
- The recommended duration of treatment with imipenem and cilastatin plus relebactam is four days to 14 days.
- Patients with CrCl less than 15 mL/min should not receive imipenem/cilastatin/relebactam unless hemodialysis is instituted within 48 hours. There is inadequate information to recommend usage of the combination drug for patients undergoing peritoneal dialysis.
- Imipenem/cilastatin/relebactam is cleared from the circulation during hemodialysis. For patients maintained on hemodialysis, administer the combination drug after hemodialysis and at intervals timed from the end of that hemodialysis session.

**Commentary:** The recent FDA approval is based upon two studies examining the efficacy and safety of imipenem-cilastatin for the treatment of cUTI and cIAI. In the cUTI study, 298 adults patients received treatment, with 99 patients receiving the proposed dose of imipenem/cilastatin/relebactam. In the cIAI study, 347 patients were included, with 117 receiving proposed doses of imipenem/cilastatin/relebactam. The most frequently reported adverse reactions (with an incidence of at least 2%) among patients treated with imipenem/cilastatin plus relebactam 250 mg were diarrhea, nausea, headache, vomiting, increased alanine aminotransferase, increased aspartate aminotransferase, phlebitis/infusion site reactions, pyrexia, and hypertension.

**Sources:** Merck & Co., Inc.; Recarbrio prescribing information

**Ferric Maltol (Accrufer)**

**Manufacturer:** Shield Therapeutics, Gateshead Quays, United Kingdom

**Date of Approval:** July 25, 2019

**Indication:** Ferric maltol is indicated for the treatment of iron deficiency in adults.

**Drug Class:** Iron products

**Uniqueness of Drug:** Ferric maltol is a novel, stable, non–salt-based oral treatment for adults with iron deficiency. Iron is absorbed from the ferric maltol molecule and generally does not cause gastrointestinal adverse events typically observed with salt-based therapies.

**Warnings and Precautions:**

**Increased risk of inflammatory bowel disease (IBD) flare.** Avoid use of ferric maltol in patients with an active IBD flare, as there is potential risk of increased inflammation in the gastrointestinal tract.

**Iron overload.** Excessive therapy with iron products can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. Do not administer ferric maltol to patients with evidence of iron overload or patients receiving intravenous

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**Table 1 Dosage Adjustment in Patients With Renal Impairment**

<table>
<thead>
<tr>
<th>Estimated CrCl (mL/min)</th>
<th>Recommended Dose of Recarbrio (Imipenem/Cilastatin/Relebactam)</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>60–89</td>
<td>1 g (imipenem 400 mg, cilastatin 400 mg, and relebactam 200 mg)</td>
<td>Every 6 hours</td>
</tr>
<tr>
<td>30–59</td>
<td>0.75 g (imipenem 300 mg, cilastatin 300 mg, and relebactam 150 mg)</td>
<td></td>
</tr>
<tr>
<td>15–29</td>
<td>0.5 g (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)</td>
<td></td>
</tr>
</tbody>
</table>

1 CrCl calculated using the Cockcroft-Gault formula
2 Administer intravenously over 30 minutes
3 Administration should be timed to follow hemodialysis
iron. Assess iron parameters prior to initiating ferric maltol and monitor iron parameters while on therapy.

**Dosage and Administration:** The recommended dosage is 30 mg twice daily, taken one hour before or two hours after a meal. Do not open, break, or chew capsules. Treatment duration will depend on the severity of iron deficiency, but generally at least 12 weeks of treatment is required. The treatment should be continued as long as necessary until ferritin levels are within the normal range.

**Commentary:** The FDA approval was based on data from three placebo-controlled trials: AEGIS 1 and AEGIS 2 in IBD patients, and AEGIS 3 in chronic kidney disease (CKD) patients. In AEGIS 1 and 2, the safety and efficacy of ferric maltol was evaluated in 128 patients with quiescent IBD and baseline hemoglobin (Hb) concentrations between 9.5 g/dL and 12 g/dL (females) or 13 g/dL (males) and ferritin less than 30 mcg/L. The primary efficacy outcome was the mean difference in Hb concentration from baseline to week 12. Results showed the least square (LS) mean difference from baseline Hb between ferric maltol and placebo was 2.18 g/dL \((P < .0001)\) at week 12. Following the placebo-controlled phase, IBD patients were transitioned to open-label treatment for an additional 52 weeks. During the open-label phase, the mean change in Hb concentration from baseline to week 64 was 3.1 g/dL. In AEGIS 3, 167 patients with nondialysis-dependent CKD and baseline Hb concentrations between 8 g/dL and 11 g/dL were randomized 2:1 to receive ferric maltol or placebo for 16 weeks. The major efficacy outcome was the mean difference in Hb concentration from baseline to week 16. Findings from the study showed that the LS mean difference from baseline Hb between ferric maltol and placebo was 0.52 g/dL \((P = .0149)\). The most common adverse reactions (more than 1%) were flatulence, diarrhea, constipation, discolored feces, abdominal pain, nausea, vomiting, and abdominal discomfort/distension.

**Sources:** Shield Therapeutics, Accrufer prescribing information