Pharmaceutical Approval Update

Mary Choy, PharmD, BCGP, FASHP

Entrectinib (Rozlytrek)

Manufacturer: Genentech, Inc., South San Francisco, California

Date of Approval: August 15, 2019

Indication: Entrectinib is a kinase inhibitor indicated for the treatment of:
- Adult patients with metastatic non–small-cell lung cancer (NSCLC) whose tumors are ROS1-positive.
- Adult and pediatric patients 12 years of age and older with solid tumors that: 1) have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation; 2) are metastatic or where surgical resection is likely to result in severe morbidity; and 3) have progressed following treatment or have no satisfactory alternative therapy.

Drug Class: Antineoplastics, tyrosine kinase inhibitor

Uniqueness of Drug: Entrectinib is the first treatment approved by the Food and Drug Administration (FDA) designed to target both ROS1 and NTRK that also shows a response in cancer that has spread to the brain. The drug received priority review, breakthrough therapy, and orphan drug designations.

Warnings and Precautions:
- Congestive heart failure (CHF). Assess left ventricular ejection fraction (LVEF) prior to initiating entrectinib in patients with symptoms or known risk factors for CHF. Monitor patients for clinical signs and symptoms of CHF. For patients with myocarditis, or with or without a decreased ejection fraction, magnetic resonance imaging or cardiac biopsy may be required to make the diagnosis. For new-onset or worsening CHF, withhold entrectinib, reassess LVEF, and institute appropriate medical management. Reduce the dose or permanently discontinue entrectinib based on the severity of CHF or worsening LVEF.

- Central nervous system (CNS) effects. CNS adverse reactions, including cognitive impairment, mood disorders, dizziness, and sleep disturbances, can occur with entrectinib. Withhold entrectinib and then resume it at the same or reduced dose upon improvement, or permanently discontinue entrectinib based on severity.

- Skeletal fractures. Entrectinib increases the risk of fractures. Promptly evaluate patients with signs or symptoms of fractures.

- Hepatotoxicity. Monitor liver tests, including alanine aminotransferase and aspartate aminotransferase, every two weeks during the first month of treatment, then monthly thereafter and as clinically indicated. Withhold or permanently discontinue entrectinib based on severity. If entrectinib is withheld, resume it at the same or reduced dose based on severity.

- Hyperuricemia. Assess serum uric acid levels prior to initiation and periodically during treatment with entrectinib. Monitor patients for signs and symptoms of hyperuricemia. Initiate treatment with urate-lowering medications as clinically indicated and withhold entrectinib for signs and symptoms of hyperuricemia. Upon improvement, resume entrectinib at the same or reduced dose based on severity.

- QT interval prolongation. Monitor patients who have or are at risk for QTc interval prolongation. Assess QT interval and electrolytes at baseline and periodically during treatment. Withhold and then resume entrectinib at the same or reduced dose, or permanently discontinue it based on severity.

- Vision disorders. Withhold entrectinib for new visual changes or changes that interfere with activities of daily living until improvement or stabilization. Conduct an ophthalmological evaluation as appropriate. Resume entrectinib at the same or reduced dose upon improvement or stabilization.

- Embryo-fetal toxicity. Entrectinib can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and about the use of effective contraception.

Dosage and Administration:
- Select patients for treatment based on the presence of ROS1 rearrangement(s) or NTRK gene fusion.
- Recommended dosage for ROS1-positive NSCLC: 600 mg orally once daily
- Recommended dosage for NTRK gene fusion–positive solid tumors:
  - Adults: 600 mg orally once daily
  - Pediatric patients 12 years and older: recommended dosage is based on body surface area (BSA):
    - BSA greater than 1.50 m²: 600 mg once daily
    - BSA 1.11 to 1.50 m²: 500 mg once daily
    - BSA 0.91 to 1.10 m²: 400 mg once daily

Commentary: The FDA approval was based on data from four clinical trials of 54 adults with NTRK gene fusion–positive tumors—including cancers of the lung, salivary gland, breast, thyroid, and colon/rectum—and one trial of 51 patients with ROS1-positive NSCLC. Those with the NTRK gene fusion–positive tumors experienced substantial tumor shrinkage, and tumors completely disappeared in 7.4% of patients. Tumor shrinkage persisted for nine months or longer in 61% of patients with a response. In those with ROS1-positive NSCLC, the overall response rate (those who had a complete or partial response to treatment) was 78%, with a complete response of 5.9%. Tumor shrinkage persisted for at least one year in 55% of those who responded to treatment with entrectinib. The most common adverse reactions (20% or more) were fatigue, constipation, dysgeusia, edema, dizziness, diaphoresis, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight,

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cough, vomiting, pyrexia, arthralgia, and vision disorders.
Sources: Genentech, Inc., Rozlytrek prescribing information

Upadacitinib (Rinvoq)
Manufacturer: AbbVie, Inc., North Chicago, Illinois
Date of Approval: August 16, 2019
Indication: Upadacitinib is a Janus kinase (JAK) inhibitor indicated for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate.

Limitation of Use: Use of upadacitinib in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Drug Class: DMARDs, JAK inhibitors
Uniqueness of Drug: Upadacitinib is convenient to administer because it is an oral medication taken once daily. The packaging was designed to make it convenient for individuals with RA to remove pills from the bottle.

Warnings and Precautions:
Boxed warning: Serious infections, malignancy, and thrombosis
- Serious infections leading to hospitalization or death, including tuberculosis (TB) and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving upadacitinib.
- If a serious infection develops, interrupt upadacitinib until the infection is controlled.
- Prior to starting upadacitinib, perform a test for latent TB; if it is positive, start treatment for TB prior to starting upadacitinib.
- Monitor all patients for active TB during treatment, even if the initial latent TB test is negative.
- Lymphoma and other malignancies have been observed in patients treated with upadacitinib.
- Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions.

Serious infections. Avoid use of upadacitinib in patients with active, serious infection, including localized infections.
Malignancy. Consider the risks and benefits of upadacitinib treatment prior to initiating therapy in patients with a known malignancy.
Thrombosis. Consider the risks and benefits prior to treating patients who may be at increased risk of thrombosis.Promptly evaluate patients with symptoms of thrombosis and treat appropriately.
Gastrointestinal perforations. Use with caution in patients who may be at increased risk.
Laboratory monitoring. Recommended monitoring of laboratory tests due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids.
Embryo-fetal toxicity. Upadacitinib may cause fetal harm based on animal studies. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.
Vaccinations. Avoid use of upadacitinib with live vaccines.

Dosage and Administration:
- The recommended oral dose of upadacitinib is 15 mg once daily with or without food.
- Upadacitinib may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs.
- Avoid initiation or interrupt upadacitinib if the absolute lymphocyte count is less than 500 cells/mm³, absolute neutrophil count is less than 1,000 cells/mm³, or hemoglobin level is less than 8 g/dL.

Commentary: The FDA based the approval of upadacitinib on data from the SELECT program, a collection of five phase 3 studies that included approximately 4,400 patients with RA across all treatment arms. The studies assessed efficacy, safety, and tolerability in a variety of patients with RA, including those who were unresponsive to or intolerant of biologic DMARDs, and those who had not received methotrexate or had an inadequate response to it. The most common adverse reactions (1% or more) were upper respiratory tract infections, nausea, cough, and pyrexia. Upadacitinib achieved all primary and ranked secondary endpoints across all five SELECT phase 3 studies, including:
- SELECT-EARLY: 52% of patients who had not received methotrexate and were treated with upadacitinib demonstrated ACR50 (an American College of Rheumatology [ACR] 50% improvement), compared with 28% of those treated with methotrexate, at week 121.
- SELECT-MONOTHERAPY: 68% of patients who had an inadequate response to methotrexate and were treated with upadacitinib achieved ACR20 (an ACR 20% improvement), compared with 41% of those who continued with methotrexate, at week 141.
- SELECT-COMpare: 71% of patients who had an inadequate response to methotrexate and were treated with upadacitinib plus methotrexate demonstrated ACR20, compared with 36% treated with placebo plus methotrexate, at week 121.
- SELECT-NEXT: 64% of patients who had an inadequate response to conventional synthetic DMARDs and were treated with upadacitinib plus conventional synthetic DMARDs achieved ACR20, compared to 36% of those treated with placebo plus conventional synthetic DMARDs, at week 121.
- SELECT-BEYOND: 65% of patients with an inadequate response to biologics who were treated with upadacitinib plus conventional synthetic DMARDs demonstrated ACR20, compared with 28% of those treated with placebo plus conventional synthetic DMARDs, at week 12.

Sources: AbbVie, Inc., Rinvoq prescribing information

Lefamulin (Xenleta)
Manufacturer: Nabriva Therapeutics US, Inc., King of Prussia, Pennsylvania
Date of Approval: August 19, 2019
Indication: Lefamulin is a pleuromutilin antibacterial indicated for the treatment of adults with community-acquired bacterial pneumonia (CABP) caused by susceptible microorganisms. To reduce the development of drug-resistant bacteria and maintain the effectiveness of lefamulin and other
antibacterial drugs, lefamulin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

**Drug Class:** Pleuromutilin

**Uniqueness of Drug:** The FDA approved lefamulin for both its oral and intravenous (IV) formulations to treat CABP. It is the first IV and oral antibiotic with a new mechanism of action approved in almost 20 years.

**Warnings and Precautions:**

- **QT prolongation.** Avoid use in patients with known QT prolongation, ventricular arrhythmias including torsades de pointes, and patients receiving drugs that prolong the QT interval, such as antiarrhythmic agents.
- **Embryo-fetal toxicity.** Based on findings from animal studies, lefamulin may cause fetal harm when administered to pregnant women. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception.
- **Clostridium difficile–associated diarrhea (CDAD).** CDAD has been reported with the use of nearly all antibacterial agents, including lefamulin, and may range in severity from mild diarrhea to fatal colitis. 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 more than 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:** For treatment of adults with CABP, the recommended dosage of lefamulin is described in Table 1.

### Table 1 Dosage of Lefamulin in Adult CABP Patients

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Treatment Duration</th>
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<tbody>
<tr>
<td>150 mg every 12 hours by intravenous infusion over 60 minutes*</td>
<td>5 to 7 days</td>
</tr>
<tr>
<td>600 mg orally every 12 hours</td>
<td>5 days</td>
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*With the option to switch to lefamulin tablets 600 mg every 12 hours to complete the treatment course.

**Dosage adjustment for patients with hepatic impairment.** Monitor patients with hepatic impairment for adverse reactions associated with lefamulin injection and tablets throughout the treatment period.

- **Lefamulin injection.** Reduce the dosage of injection to 150 mg infused intravenously over 60 minutes every 24 hours for patients with severe hepatic impairment (Child-Pugh Class C). No dosage adjustment of lefamulin injection is needed for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.
- **Lefamulin tablets.** Lefamulin tablets have not been studied in and are not recommended for patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. No dosage adjustment of lefamulin tablets is needed for patients with mild hepatic impairment (Child-Pugh Class A).

**Important administration instructions**

- **Lefamulin injection.** Administer injection by IV infusion over 60 minutes. The practitioner must dilute it in a 250-mL solution of 10-mM citrate-buffered 0.9% sodium chloride for injection supplied with lefamulin injection before use.
- **Lefamulin tablets.** Take tablets at least one hour before a meal or two hours after a meal. Swallow tablets whole with water (6 to 8 ounces). Do not crush or divide tablets.
- **Missed dose.** If a dose is missed, the patient should take the dose as soon as possible and anytime up to eight hours prior to the next scheduled dose. If less than eight hours remain before the next scheduled dose, do not take the missed dose, and resume dosing at the next scheduled dose.

**Commentary:** The FDA approval was based on results of two clinical trials assessing a total of 1,289 people with CABP. In these trials, lefamulin was compared with moxifloxacin with and without linezolid. Patients who received lefamulin had rates of treatment success similar to those taking moxifloxacin alone or moxifloxacin plus linezolid. The most common adverse reactions (2% or more) are:

- **Lefamulin injection:** administration site reactions, hepatic enzyme elevation, nausea, hypokalemia, insomnia, and headache
- **Lefamulin tablets:** diarrhea, nausea, vomiting, and hepatic enzyme elevation

**Sources:** Nabriva Therapeutics US, Inc., Xenleta prescribing information