Lesinurad (Zurampic)

**Manufacturer:** AstraZeneca, Wilmington, Delaware  
**Date of Approval:** December 22, 2015  
**Indication:** Zurampic is indicated in combination with a xanthine oxidase inhibitor (XOI) for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with an XOI alone.  
**Drug Class:** Lesinurad is a uric acid transporter 1 (URAT1) inhibitor.  
**Uniqueness of Drug:** URAT1 is responsible for the majority of the renal reabsorption of uric acid. By inhibiting URAT1, lesinurad increases uric acid excretion, thereby lowering serum uric acid. Lesinurad also inhibits organic anion transporter (OAT) 4, a uric acid transporter involved in diuretic-induced hyperuricemia. Lesinurad does not inhibit OAT1 and OAT3, which are drug transporters in the kidney associated with drug–drug interactions.  
**Warnings and Precautions:**  
**Boxed warning.** The labeling for Zurampic includes a boxed warning regarding the risk for acute renal failure, which is more common when the drug is used without an XOI or at higher-than-approved doses.  
**Renal events.** Treatment with Zurampic 200 mg in combination with an XOI was associated with an increased incidence of serum creatinine elevations, most of which were reversible.  
**Cardiovascular events.** In clinical trials, major adverse cardiovascular events (defined as cardiovascular deaths, nonfatal myocardial infarctions, or nonfatal strokes) were observed with Zurampic. A causal relationship with Zurampic has not been established.  
**Dosage and Administration:** Zurampic tablets should be coadministered with an XOI, including allopurinol or febuxostat. The recommended starting dosage of Zurampic is 200 mg once daily. This is also the maximum daily dose. Zurampic should be taken by mouth in the morning with food and water. The drug may be added when target serum uric acid levels are not achieved on the medically appropriate dose of the XOI alone. The use of Zurampic is not recommended in patients taking daily doses of allopurinol of less than 300 mg (or less than 200 mg in patients with an estimated creatinine clearance of less than 60 mL/min).  
**Commentary:** In clinical trials, less than 50% of patients treated with allopurinol 300 mg reached serum uric acid target levels of less than 6 mg/dL. For patients who cannot reach the target on an XOI alone, the current American College of Rheumatology guidelines recommend adding an agent that increases uric acid excretion (such as Zurampic).  
**Sources:** AstraZeneca, Zurampic prescribing information

Selexipag (Uptravi)

**Manufacturer:** Actelion Pharmaceuticals U.S., South San Francisco, California  
**Date of Approval:** December 21, 2015  
**Indication:** Uptravi is indicated for the treatment of pulmonary arterial hypertension (PAH, World Health Organization [WHO] group I) to delay disease progression and to reduce the risk of hospitalization for PAH. The drug’s effectiveness was established in a long-term study in PAH patients with WHO functional class II–III symptoms.  
**Drug Class:** Selexipag is a selective nonprostanoid IP prostacyclin receptor agonist.  
**Uniqueness of Drug:** Selexipag is the first medication in its class. It acts by relaxing muscles in the walls of blood vessels to dilate the vessels and reduce the elevated pressure in vessels supplying blood to the lungs.  
**Warnings and Precautions:**  
**Pulmonary edema.** If signs of pulmonary edema occur, clinicians should consider the possibility of associated pulmonary veno-occlusive disease. If confirmed, Uptravi should be discontinued.  
**Dosage and Administration:** The recommended starting dosage of Uptravi is 200 mcg twice daily. Tolerability may be improved when the drug is taken with food. The dosage is increased in increments of 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dosage (up to 1,600 mcg twice daily). If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous tolerated dose.  
**Commentary:** In a pivotal phase 3 study, selexipag reduced the risk of a morbidity/mortality event by 40% compared with placebo (P < 0.0001). The observed efficacy was consistent across the key subgroups: age, gender, WHO functional class, PAH etiology, and background PAH therapy. Patients were treated for up to 4.2 years. The tolerability profile of selexipag was consistent with that of prostacyclin therapies.  
**Sources:** FDA, Uptravi prescribing information

Sugammadex (Bridion)

**Manufacturer:** Merck, Kenilworth, New Jersey  
**Date of Approval:** December 15, 2015  
**Indication:** Bridion injection is indicated for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery.  
**Drug Class:** Sugammadex is a modified gamma cyclo-dextrin.  
**Uniqueness of Drug:** The neuromuscular blocking agents rocuronium and vecuronium cause temporary paralysis by interfering with the transmission of nerve impulses to the muscle and are used to paralyze the vocal cords during tracheal intubation. They can also be used to prevent patients from moving during surgery while they are receiving general anesthesia. Neuromuscular blocking drugs are also sometimes used to prevent the body from breathing automatically when a patient has to be placed on a ventilator.

Sugammadex forms a complex with rocuronium and vecuronium, and it reduces the amount of these neuromuscular blocking agents that is available to bind to nicotinic cholinergic receptors in the neuromuscular junction. This results in the
reversal of neuromuscular blockade induced by rocuronium and vecuronium.

Key Warnings and Precautions:
- Anaphylaxis and hypersensitivity. Clinicians should be prepared for the possibility of drug hypersensitivity reactions (including anaphylactic reactions) when using Bridion and should take the necessary precautions.
- Marked bradycardia. Cases of marked bradycardia, some of which have resulted in cardiac arrest, have been observed within minutes after the administration of Bridion.
- Monitoring of respiratory function during recovery. Ventilatory support is mandatory for patients until adequate spontaneous respiration is restored and the ability to maintain a patent airway is assured.
- Risk of prolonged neuromuscular blockade. In clinical trials, a small number of patients experienced a delayed or minimal response to the administration of sugammadex. Therefore, it is important to monitor ventilation until recovery occurs.
- Risk of coagulopathy and bleeding. In healthy volunteers, sugammadex doses of up to 16 mg/kg were associated with increases of up to 25% for up to one hour in two coagulation parameters: activated partial thromboplastin time and prothrombin time/international normalized ratio.
- Renal impairment. Bridion is not recommended for use in patients with severe renal impairment, including those requiring dialysis.

Dosage and Administration:

For rocuronium and vecuronium: A 4-mg/kg dose of Bridion is recommended if spontaneous recovery of the twitch response has reached one to two post-tetanic counts and there are no twitch responses to train-of-four (TOF) stimulation following rocuronium- or vecuronium-induced neuromuscular blockade. A Bridion dose of 2 mg/kg is recommended if spontaneous recovery has reached the reappearance of the second twitch in response to TOF stimulation after rocuronium- or vecuronium-induced neuromuscular blockade.

For rocuronium only: A 16-mg/kg dose of Bridion is recommended if there is a clinical need to reverse neuromuscular blockade soon (approximately three minutes) after the administration of a single 1.2-mg/kg dose of rocuronium. The efficacy of the 16-mg/kg dose of Bridion after the administration of vecuronium has not been established.

Commentary: For seven years prior to the approval of Bridion, the FDA repeatedly declined to clear the product largely because of concerns about potentially dangerous allergic reactions. Doctors were also warned to monitor for bradycardia, which could lead to cardiac arrest. Those safety concerns spurred demands for new studies as well as periodic regulatory delays.

Sources: Merck, Bridion prescribing information, Reuters, FierceBiotech

Alectinib (Alecensa)

Manufacturer: Genentech, South San Francisco, California
Date of Approval: December 11, 2015

Indication: Alecensa is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non–small-cell lung cancer (NSCLC) who have progressed on or are intolerant of crizotinib.

Drug Class: Alectinib is a tyrosine kinase inhibitor that targets the ALK and RET kinase genes.

Uniqueness of Drug: In nonclinical studies, alectinib inhibited ALK phosphorylation and ALK-mediated activation of the downstream signaling proteins STAT3 and AKT, and decreased tumor cell viability in multiple cell lines harboring ALK fusions, amplifications, or activating mutations. Alectinib also demonstrated in vitro activity against multiple mutant forms of the ALK enzyme, including some mutations identified in NSCLC tumors in patients who had progressed on crizotinib (Xalkori, Pfizer).

Warnings and Precautions:
- Hepatotoxicity. Elevations of aspartate aminotransferase (AST) greater than five times the upper limit of normal (ULN) occurred in 3.6% of patients, and elevations of alanine transaminase (ALT) greater than five times the ULN occurred in 4.8% of patients. Elevations of bilirubin greater than three times the ULN occurred in 2.8% of patients.
- Interstitial lung disease (ILD)/pneumonitis. Severe ILD (grade 3) occurred in one (0.4%) of 253 patients exposed to alectinib in clinical trials.
- Bradycardia. Cases of bradycardia (7.5%) have been reported in patients treated with alectinib. Twenty percent of 221 patients treated with alectinib for whom serial electrocardiograms were available had heart rates of less than 50 beats per minute.

Severe myalgia and creatine phosphokinase (CPK) elevation. Myalgia or musculoskeletal pain occurred in 29% of patients in clinical studies of alectinib. The incidence of grade 3 myalgia/musculoskeletal pain was 1.2%. Elevations of CPK occurred in 43% of 218 patients.

Embryo-fetal toxicity. Based on findings from animal studies and its mechanism of action, alectinib can cause fetal harm when administered to pregnant women.

Dosage and Administration: The recommended dosage of alectinib is 600 mg orally twice daily with food. Alectinib should be administered until disease progression or unacceptable toxicity occurs.

Commentary: An ALK gene mutation can occur in several different types of cancer cells, including lung cancer cells. ALK gene mutations are present in approximately 5% of patients with NSCLC. In patients with metastatic ALK-positive NSCLC, the brain is a common target for the spread of disease.

The safety and efficacy of alectinib were studied in two single-arm clinical trials of patients with metastatic ALK-positive NSCLC whose disease was no longer controlled by treatment with crizotinib. The study participants received alectinib twice daily to measure the drug’s effect on their lung cancer tumors. In the first study, 38% of participants experienced a partial shrinkage of their NSCLC tumors, an effect that lasted for an average of 7.5 months. In the second study, 44% of participants experienced a partial shrinkage of their NSCLC tumors, lasting for an average period of 11.2 months.

Sources: FDA, Alecensa prescribing information