PDL DRUG REVIEW

Proprietary Name: Zurampic®
Common Name: lesinurad
PDL Category: Gout

Comparable Products	Preferred Drug List Status
Probenecid	Preferred

Summary

Pharmacology: Lesinurad, the active ingredient of Zurampic®, reduces serum uric acid levels by inhibiting the function of transporter proteins involved in uric acid reabsorption in the kidney. It inhibits the function of 2 apical transporters responsible for uric acid reabsorption, including uric acid transporter 1 (URAT1) and organic anion transporter 4 (OAT4). URAT1 is responsible for most of the reabsorption of filtered uric acid from the renal tubular lumen, while OAT4 is a uric acid transporter associated with diuretic-induced hyperuricemia.

Indications and Usage: In combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone. Zurampic® is not recommended for the treatment of asymptomatic hyperuricemia and should not be used as monotherapy.

There is no pregnancy category associated with this medication; however, the risk summary indicates that there are no available human data on use in pregnant women to inform a drug-associated risk. Animal studies did not show teratogenicity or effects on fetal development when used at higher than recommended doses. The safety and efficacy of use in children under the age of 18 years have not been established.

Dosage Forms: Film-Coated Tablets: 200mg

Recommended Dosage: Zurampic® should be used in combination with a xanthine oxidase inhibitor, including allopurinol or febuxostat. It is recommended to take 200mg QD (maximum dose) in the morning with food and water. Treatment with Zurampic® may be added when target serum uric acid levels are not achieved on an appropriate dose of the xanthine oxidase inhibitor alone. Zurampic® use is not recommended for those taking daily doses of allopurinol less than 300mg (or less than 200mg in patients with estimated creatinine clearance (eCrCl) <60ml/min). If treatment with the xanthine oxidase inhibitor is interrupted, Zurampic® should also be interrupted. Patients should stay well hydrated.

Gout flares may occur after starting urate lowering therapy, including Zurampic®. Gout flare prophylaxis is recommended when starting Zurampic®, per practice guidelines. If a gout flare occurs during Zurampic® treatment, it does not need to be discontinued. The gout flare should be managed concomitantly.

It is recommended to assess renal function prior to starting treatment and periodically thereafter. More frequent renal function monitoring is recommended in patients with an eCrCl <60mL/min. Dose adjustments are not required in those with mild or moderate renal impairment (eCrCL of ≥45mL/min); however, Zurampic® should not be initiated with an eCrCl <45mL/min. Zurampic® should be discontinued when eCrCl is persistently <45mL/min. Dose adjustments are not required in those with mild or moderate hepatic impairment; however, use has not been studied in those with severe hepatic impairment and thus is not recommended in this population.

Drug Interactions: Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when used concomitantly with Zurampic®. It is recommended that females practice additional methods of contraception and not rely on hormonal contraception alone when taking Zurampic®. It is recommended that Zurampic® not be used with inhibitors of epoxide hydrolase (i.e. valproic acid). The potential of reduced efficacy of concomitant drugs that are CYP3A substrates should be considered and their efficacy (e.g. blood pressure with amlodipine or cholesterol levels with HMG-CoA reductase inhibitors) should be monitored. As lesinurad exposure is increased when used concomitantly with CYP2C9 inhibitors and in CYP2C9 poor metabolizers, Zurampic® should be used with caution in patients taking moderate inhibitors of CYP2C9 (e.g. fluconazole, amiodarone) and in CYP2C9 poor metabolizers. A decreased therapeutic effect of Zurampic® may be seen if used concomitantly with moderate inducers of CYP2C9 (e.g. rifampin, carbamazepine). Last, aspirin at doses >325mg per day may decrease the efficacy of Zurampic® in combination with allopurinol; aspirin at doses of 325mg or less per day (ie for cardiovascular protection) does not decrease the efficacy of Zurampic® and thus can be used concomitantly.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Zurampic® tabs + xanthine oxidase inhibitor) minus reported % incidence for placebo + xanthine oxidase inhibitor. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than its comparator.* The most frequently reported adverse events included headache (1.2%), influenza (2.4%), gastroesophageal reflux disease (1.9%), blood creatinine increased (2%), renal failure (0%), and nephrolithiasis (0%). Serum creatinine elevations 1.5X to < 2X baseline were reported (3.9% Zurampic® vs 2.3% placebo) and resolution of serum creatinine elevations by end of study were also reported (90% Zurampic® vs 75% placebo). Serum creatinine elevations ≥2.0X baseline were reported (1.8% [N=9] Zurampic® vs 0% placebo) and resolution of serum creatinine elevations by end of study were also reported (88.9% [N=8/9] Zurampic® vs not applicable for placebo).

In clinical trials, major adverse cardiovascular events (defined as cardiovascular deaths, non-fatal myocardial infarctions, or non-fatal strokes) were seen with Zurampic®; however, a causal relationship with Zurampic® has not been established.

Zurampic® has a box warning regarding the risk of acute renal failure, and it was more common when Zurampic® was given alone. The warning adds that Zurampic® should be used in combination with a xanthine oxidase inhibitor.

Contraindications: In severe renal impairment (eCrCl <30mL/min), end stage renal disease, kidney transplant recipients, or patients on dialysis; With Tumor Lysis Syndrome or Lesch-Nyhan syndrome

Manufacturer: AstraZeneca Pharmaceuticals LP

Analysis: The safety and efficacy of Zurampic® were assessed in 3 multicenter, randomized, double-blind, placebo-controlled studies that included adult patients with hyperuricemia and gout and used in combination with allopurinol or febuxostat. The studies were 12 months in duration and patients were provided prophylaxis for gout flares with colchicine or NSAIDs during the first 5 months of Zurampic® treatment.

Study 1 and Study 2 included patients on a stable dose of allopurinol of at least 300mg but with serum uric acid >6.5mg/dL and had reported at least 2 gout flares in the prior 12 months. In both studies, significantly more in the Zurampic® plus allopurinol group achieved serum uric acid target (<6mg/dL) as compared with placebo plus allopurinol at month 6. The results are illustrated in the table below, which was adapted from the prescribing information.

Study	Time-point	Patients Achieving Serum Uric Acid Target		Difference of Proportion
		Placebo + Allopurinol	Zurampic® 200mg + Allopurinol	
Study 1 (N=603)	Month 6	28%	54%	0.26
Study 2 (N=610)	Month 6	23%	55%	0.32

The reduction in average serum uric acid levels to <6mg/dl was noted for the Zurampic® 200mg plus allopurinol group at the month 1 visit and was maintained throughout the 12-month study.

Study 3 included gout patients with measurable tophi who received Zurampic® or placebo in combination with febuxostat 80mg QD. Patients were given febuxostat 80mg QD for 3 weeks prior to being randomized to placebo or Zurampic®, and 50% of patients did not reach target serum uric acid <5mg/dl at baseline after 3 weeks of febuxostat treatment. Results suggested that there was not statistical evidence of a difference in the proportion of patients treated with Zurampic® 200mg plus febuxostat achieving a serum uric acid <5mg/dl as compared with the placebo plus febuxostat group by month 6. However, the average decrease in serum uric acid with Zurampic® 200mg in Study 3 was similar to that seen in Study 1 and Study 2. The table below illustrates the results, which was adapted from the prescribing information.

Study	Time-point	Patients Achieving Serum Uric Acid Target		Difference of Proportion
		Placebo + Febuxostat	Zurampic® 200mg + Febuxostat 80mg	
Study 3	Month 6	47%	57%	0.10

The reduction in average serum uric acid levels to <5mg/dL was noted for Zurampic® 200mg plus febuxostat at the month 1 visit and was maintained throughout the 12-month study.

Results also suggested that in each of the 3 studies above, the rates of gout flare needing treatment from the end of month 6 to the end of month 12 were not statistically different between Zurampic® 200mg (in combination with allopurinol or febuxostat) as compared with placebo (in combination with allopurinol or febuxostat). In addition, the proportion who had a complete resolution of ≥1 target tophus in Study 3 was not statistically different between Zurampic® 200mg in combination with febuxostat as compared with febuxostat plus placebo.

Place in Therapy: Zurampic® is indicated to be used in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in those who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone. It should not be used as monotherapy and is not recommended for the treatment of asymptomatic hyperuricemia. In two clinical trials that included patients with an inadequate response to allopurinol, Zurampic® in combination with allopurinol was found to be superior to allopurinol monotherapy for lowering serum uric acid to <6mg/dL at month 6. None of the currently reported studies demonstrated that the addition of Zurampic® significantly reduced the rate of gout flares needing treatment or increased the rate of tophi resolution from month 6-12 of treatment.

There is no evidence at this time to support that Zurampic® is safer or more effective than the currently available medications. It is therefore recommended that Zurampic® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Zurampic [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2016.