CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207988Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	December 20, 2015
Reviewer(s):	Jasminder Kumar, PharmD Division of Risk Management (DRISK)
Acting Team Leader:	Jamie Wilkins Parker, Pharm.D., DRISK
Deputy Director:	Reema Mehta, Pharm.D., M.P.H., DRISK
Director:	Cynthia LaCivita, Pharm.D.
Subject:	Review evaluates if a REMS is needed for Zurampic (lesinurad)
Drug Name:	Zurampic (lesinurad)
Therapeutic Class:	Uricosuric agent
Dosage form and route:	200mg tablet for oral administration
Application Type/Number:	NDA 207988
Applicant/Sponsor:	Ardea Biosciences Inc.
OSE RCM #:	2015-52

*** This document contains proprietary and confidential information that should not be released to the public. ***

CONTENTS

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Zurampic (lesinurad) is necessary to ensure the benefits of this product outweigh its risks. Ardea Biosciences, Inc. submitted a New Drug Application (NDA 207988) to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on December 29, 2014, for lesinurad. The proposed indication for lesinurad is treatment of chronic treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor (XOI) for patients who have not achieved target serum uric acid levels with an XOI alone. The applicant submitted a proposed REMS consisting of a Medication Guide (MG) and a communication plan (CP) and a proposed risk management plan consisting of a targeted follow-up questionnaire for reported renal events.

1.1 PRODUCT BACKGROUND

Lesinurad is a uricosuric agent for the proposed indication for treatment of hyperuricemia associated with gout in combination with an XOI. Lesinurad reduces serum uric acid levels by inhibiting the function of carrier proteins involved in uric acid transport. In vitro, lesinurad inhibited the function of two luminal transporters responsible for uric acid reabsorption, uric acid transporter 1 (URAT1) and Organic Anion Transporter 4 (OAT4). URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. Lesinurad also inhibited the in vitro, but not in vivo, function of OAT1 and OAT3, two basolateral transporters responsible for uric acid secretion. The co-administration of an XOI is intended to reduce the amount of uric acid available for excretion.

Lesinurad is available in 200 mg tablets, taken orally once daily in combination with an XOI, including allopurinol or febuxostat. However, doses of allopurinol <300mg (<200mg in patients with CrCl <60mL/min) have not been studied with lesinurad and is not recommended in these patients. Failure to take lesinurad with an XOI may increase the risk of renal adverse reactions (see Section 3.3 for further details). Lesinurad tablets should be taken in the morning with food and water and patients are instructed to stay well hydrated (2 liters of liquids per day). Lesinurad is contraindicated in patients with tumor lysis syndrome and Lesch-Nyhan syndrome and patients with severe renal impairment, end-stage renal disease, and patients on dialysis.

Current proposed labeling indicates no dose adjustment is necessary when administering lesinurad to patients with mild to moderate renal or hepatic impairment ((b) (4)), but should not be initiated in patients with a CrCl < (b) (4) mL/min.

1.2 DISEASE BACKGROUND

Gout is a metabolic disorder characterized by reduced clearance or overproduction of uric acid leading to hyperuricemia, which in turn can result in monosodium urate (MSU) crystal formation around the joints and soft tissues, urate nephropathy, and nephrolithiasis. The prevalence of gout has been increasing over the past few decades, and has been recently estimated to affect approximately 3.9% of adults in the United States (8.3 million).[1] The condition affects primarily

[1] Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: The National Health and Nutrition Examination Survey 2007–2008. Arthritis Rheum. 2011; 63(10):3136–3141.

middle-aged and older men and post-menopausal women. Obesity, hyperlipidemia, diabetes, hypertension, chronic renal insufficiency, metabolic syndrome, and cardiovascular disease are frequent comorbidities in patients with gout. [2] Risk factors for gout include being overweight or obese, having hypertension, alcohol intake (beer and spirits more than wine), diuretic use, a diet rich in meat and seafood, and poor kidney function.[3]

The course of gout is characterized by acute attacks of gouty arthritis alternating with attack-free periods of intercritical gout. A typical course of gouty arthritis attack (or gout flare) is characterized by acute inflammation of the affected joint and surrounding tissues associated with often excruciating pain, tenderness, erythema, and swelling. If left untreated, the acute inflammatory episode is self-limited, typically peaking within 24-48 hours and eventually subsiding within 7-10 days.

Gout is associated with an increased risk of kidney stones, tophi, and general soreness and aching of joints and can lead to increased medical costs, including ambulatory, impatient, prescriptions, ER visits, and chronic disease management. [4] The treatment goals are to end the pain of acute flares and prevent future attacks and the formation of tophi and kidney stones. Therapy for acute flares consists of nonsteroidal anti-inflammatory drugs (NSAIDS), steroids, and colchicine. Diet and lifestyle modifications (weight loss, avoiding alcohol, reducing dietary purine intake) may help prevent future attacks. Changing medications (e.g., stopping diuretics) associated with hyperuricemia may also help. Preventive therapy to lower blood uric acid levels in people with recurrent acute flares or chronic gout usually involves urate lowering therapy or other drugs (febuxostat and pegloticase). Treatment guidelines recommend pharmacologic urate-lowering therapy (ULT) for patients with gout who have 1 or more tophi on clinical examination or imaging study or have frequent attacks of acute gouty arthritis (≥2 attacks per year) and treatment until gout signs and symptoms have resolved and patients can maintain serum uric acid (sUA) levels to <6 mg/dL, or <5 mg/dL, as appropriate.[5] Use of a XOI with either allopurinol or febuxostat as the first line pharmacologic approach is recommended. Probenecid was recommended as an alternative first line therapy, if at least one XOI drug was contraindicated or not tolerated, but probenecid monotherapy was not recommended as a first line approach in those with a creatinine clearance <50 mL/min.

[2] Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men. Arch Intern Med. 2005;165:742–748.

[3] Krishnan E. Chronic kidney disease and the risk of incident gout among middle-aged men. Arthritis Rheum. 2013;65(12):3271–3278.

[4] Centers for Disease Control and Prevention. Gout. http://www.cdc.gov/arthritis/basics/gout html. April 2, 2015. Accessed August 26, 2015.

[5] Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012 Oct. 64(10):1431-46.

Table 1 below lists currently approved agents for the treatment of hyperuricemia.[6]

Table 1 – Treatments for the Management of Hyperuricemia		
Product	**Year of Approval**	**FDA Approved Indication**
Xanthine Oxidase Inhibitors		
Allopurinol	1966	Management of patients with signs and symptoms or primary or secondary gout (i.e., acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)
Febuxostat	2009	Chronic management of hyperuricemia in patients with gout
Uricosuric Agents		
Probenecid	1951	Treatment of the hyperuricemia associated with gout and gouty arthritis
Sulfinpyrazone	1959 (Removed from market 2002)	Treatment of chronic gouty arthritis and intermittent gouty arthritis
Uricase		
Rascburicase	2002	Initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and sold tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid
Pegloticase	2010	Treatment of chronic gout in adult patients refractory to conventional therapy

1.3 Regulatory History

The following is a summary of the regulatory history for NDA 207988 relevant to this review:

- December 29, 2014: The Agency received a NDA submission from Ardea Biosciences Inc. The submission included a proposed REMS with a MG and CP and a proposed risk management plan that included a targeted follow-up questionnaires to monitor renal toxicity.
- June 10, 2015: A Mid-Cycle Meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that there was insufficient information to conclusively determine whether a REMS was necessary to ensure that the benefits of the drug outweigh the risks, but based on the information currently available, the Agency did not believe a REMS was necessary.
- September 18, 2015: A Late-Cycle Meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the benefit-risk evaluation under consideration by the division for lesinurad, DRISK will complete a full evaluation of the need for a REMS for lesinurad after receiving input from the Arthritis Advisory Committee regarding the efficacy and safety of lesinurad.

[6] Neuner R. DPARP. Clinical Review for Zurampic (lesinurad), dated September 17, 2015.

- October 23, 2015: An Arthritis Advisory Committee Meeting was held to discuss the safety and efficacy of lesinurad. The committee voted 10-4 in favor of recommending approval, 14-0 that there was substantial evidence of clinically meaningful benefit, but 7 -6 (with one abstention) that the safety profile supported approval. The Committee did recommend any additional strategies, beyond labeling, to mitigate the risks of renal toxicity and cardiovascular events risks.
- December 11, 2015: A CDER Regulatory Briefing took place to discuss the risk-benefit of lesinurad in combination with a XOI for the treatment of hyperuricemia associate with gout. The committee concluded that additional data to characterize the risk of renal toxicity and cardiovascular (CV) events was needed. The Committee did recommend any additional strategies, beyond labeling, to mitigate the risks of renal toxicity and cardiovascular events risks. A Post Marketing Requirement for renal safety, which would also include an assessment of CV safety, was recommended.

2 MATERIALS REVIEWED

2.1 SPONSOR'S SUBMISSION

- Ardea Biosciences, Inc. Proposed REMS for Zurampic, received December 29, 2014.

2.2 OTHER MATERIALS INFORMING OUR REVIEW

The following is a list of materials that informed our review:

- Ardea Biosciences, Inc. Clinical Overview for Zurampic (lesinurad), received December 29, 2014.
- Ardea Biosciences, Inc. Summary of Clinical Efficacy for Zurampic (lesinurad), received December 29, 2014.
- Ardea Biosciences, Inc. Summary of Clinical Safety for Zurampic (lesinurad), received December 29, 2014.
- Ardea Biosciences, Inc. 4-Month Safety Update Report for Zurampic (lesinurad), received April 30, 2015.
- Ardea Biosciences, Inc. Proposed Prescribing Information for Zurampic (lesinurad), received December 29, 2014, updated on August 31, 2015, September 19, 2015.
- Neuner R. DPARP. Clinical Review for Zurampic (lesinurad), dated September 17, 2015.

3 REVIEW FINDINGS FOR LESINURAD

3.1 OVERVIEW OF CLINICAL PROGRAM

Clinical efficacy for lesinurad 200 mg and 400 mg was evaluated by three pivotal Phase 3 studies (Study 301, Study 302, and Study 304) and 2 supportive studies (Study 202, Study 303). All studies were randomized, double-blind, multicenter, and placebo-controlled. There are also two ongoing long term extension (OLE) studies, Study 306 (OLE for Study 301 and Study 302) and Study 307 (OLE for Study 304).

Studies 301 (N=603) and 302 (N=610) were 12 month replicate studies that evaluated the safety and efficacy of lesinurad 200 mg daily and 400 mg daily + allopurinol versus placebo + allopurinol in subjects that had uncontrolled gout while on stable, appropriate doses of

allopurinol. These criteria were defined as taking at least 300 mg/day allopurinol (200 mg/day in patients with estimated creatinine clearance of less than 60 ml/min at baseline) for at least 8 weeks and still having a serum uric acid level of 6.5 mg/dL or greater at the screening visit (and >6.0 mg/dL at the Day -7 visit) and also having at least 2 gout flares in the preceding 12 months. The primary endpoint for Studies 301 and 302 was the proportion of subjects achieving the recommended target sUA level of <6.0 mg/dL by Month 6. Study 306 is the ongoing extension study for Studies 301 and 302.

Study 304 (N=324) was a 12 month study that evaluated lesinurad in combination with febuxostat 80 mg in patients who had a sUA level ≥ 6.0 mg/dL, or ≥ 8.0 mg/dL for patients not taking a urate lowering therapy (ULT) and had tophi and at least one target tophus at screening. The primary endpoint for Study 304 was the proportion of subjections achieving sUA target level of <5.0 mg/dL by month 6, a level recommended for patients with greater disease severity and urate burden. Study 307 is an ongoing extension study of Study 304.

Secondary endpoints in Studies 301, 302, and 304 included the proportion of subjects with ≥ 1 target tophus at baseline who experienced complete resolution (CR) of ≥ 1 target tophus by month 12. For studies 301 and 302, an additional secondary endpoint was the mean rate of gout flares requiring treatment from the end of month 6 to the end of month 12. For Study 304, additional secondary endpoints were the proportion of subjects who experienced complete or partial resolution (CR/PR) of ≥ 1 target tophus by Month 12 and the proportion of subjects with at least 0.25 improvements in the Health Assessment Questionnaire – Disability Index (HAQ-DI). In Study 301, 302, and 304, subjects received gout flare prophylaxis with colchicine 0.5 or 0.6 mg daily, or with NSAIDs, for those who were intolerant of or had a contraindication to colchicine

Study 202 (N=123) was a 28 day, Phase 2b dose response study of lesinurad 200 mg, 400 mg, and 600 mg daily as monotherapy and Study 303 (N=214) was a 6 month, Phase 3 study of lesinurad 400 mg daily as monotherapy in patients with gout who were intolerant of or had a contraindication to an XOI, with a sUA level ≥ 6.5 mg/dL (Study 303). The primary endpoint for Study 202 and Study 303 was the proportion of subjects with a sUA level <6.0 mg/dL at month 6. Of note, the open label extension trial of Study 303 was terminated early based on the observed renal safety profile.

3.2 SUMMARY OF EFFICACY

In Studies, 301 and 302, more patients achieved the target of sUA <6.0 mg/dL with lesinurad in combination with allopurinol compared with allopurinol alone by Month 6. In Study 301, 54.2% of patients in the lesinurad 200 mg + allopurinol and 59.2% in the lesinurad 400 mg + allopurinol achieved the target sUA compared to 27.9% in the placebo group ($p<0.001$). In Study 302, 55.4% of patients in the lesinurad 200 mg + allopurinol and 66.5% in the lesinurad 400 mg + allopurinol achieved the target sUA compared to 23.3% in the placebo group ($p<0.001$). The benefit of lesinurad 200 mg or 400 mg in combination with allopurinol was consistent across all subgroups, including subjects with renal impairment, those with tophi, and those receiving thiazide diuretics at baseline.

There was no statistically significant difference ($p<0.05$) between treatment groups for the rate of gout flares requiring treatment for the 6-month period after gout flare prophylaxis was

discontinued from the end of Month 6 to Month 12, in both Study 301 and 302, which was a key secondary endpoint.

In Study 304, the number of patients achieving the target of sUA <5.0 mg/dL by Month 6 was only statistically significant for lesinurad 400 mg + febuxostat (76.1%, p<0.0001) but not lesinurad 200 mg +febuxostat (56.6% p=0.1298) compared to febuxostat alone (46.8%, for both 200 mg and 400 mg).

The proportion of subjects who achieved CR of ≥ 1 target tophus, a key secondary endpoint, by Month 12 was greater in the lesinurad 200 mg and 400 mg + febuxostat groups compared with febuxostat alone, in a dose-ordered manner, 25.5%, 30.3%, compared with 21.1%, respectively, but the differences were not statistically significant.

During Study 202, a higher proportion of subjects treated with lesinurad at each dose level (200 mg, 400 mg, and 600 mg daily) achieved the primary endpoint of sUA level < 6.0 mg/dL compared with subjects who received placebo (7.4%, 27.6%, 44.8%, 0%, respectively; p<0.01 for lesinurad 400 mg and 600 mg only). The difference for lesinurad 200 mg was not statistically significant.

In Study 303, lesinurad 400 mg as monotherapy taken daily (for up to 6 months) demonstrated superior efficacy compared with placebo at lowering sUA to achieve target goal of sUA <6.0 mg/dL (29.9% vs. 1.9%, respectively; p<0.0001), but was associated with a greater increase in adverse events, including renal events (See Section 3.3 for further details). Based on the data from Study 202 and 303, the Applicant only proposed lesinurad 200 mg in combination with an XOI for the indicated population.

The DPARP Medical Officer concluded that there does appear to be adequate statistical evidence to support the efficacy of both the 200 mg and 400 mg dose in the broader population of gout patients, and to support the proposed indication of treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor.[7]

3.3 SUMMARY OF SAFETY CONCERNS

Data from Study 301, Study 302, Study 304, and their respective extension studies were included in the pooled safety analysis. All patients who received at least one dose of randomized study medication were included in the safety population (N=1332). Study 303 was not included in this pooled analysis since the 200 mg dose of lesinurad was not evaluated in that trial and lesinurad was administered without a concomitant XOI (allopurinol or febuxostat). Of note, gout flares, new tophi or enlarging tophi that were not clinically adverse, were considered part of the efficacy analyses and were not captured as adverse events (AEs). For a comprehensive safety evaluation, data from the 120 Day Safety Update Report, submitted on April 30, 2015, was also evaluated.

A majority of patients experienced at least 1 AE over the course of the trial. Overall, lesinurad 400 mg was associated with an increased incidence of AEs, serious adverse events (SAEs), serious renal AEs, major cardiovascular adverse events (MACE), and death, compared to placebo. Lesinurad 200 mg was not associated with an increased incidence of SAEs, including

[7] Neuner R. DPARP. Clinical Review for Zurampic (lesinurad), dated September 17, 2015.

death, renal SAEs, or MACE, compared to placebo; lesinurad 200 mg was associated with a smaller increased risk of AEs compared to lesinurad 400 mg, suggesting toxicity is dose-related.

Common Adverse Events

The most common adverse reactions in 12-month controlled clinical trials (occurring in greater than or equal to 2% of patients treated with lesinurad in combination with an XOI and more frequently than on an XOI alone) were headache, influenza and gastroesophageal reflux disease. The proportions of subjects experiencing a treatment emergent adverse event (TEAE) were higher in the lesinurad 200 mg + XOI and 400 mg + XOI treatment groups as compared to the placebo + XOI for the pooled, 12-month, controlled studies (75.5%, 79.8%, and 70.3%, respectively) and the 6-month monotherapy trial. The incidences of the most common TEAEs was similar for patients who received lesinurad in the core +extension studies to those in the monotherapy study, with the exception of a higher incidence of blood creatinine increase in both the lesinurad 200 mg and 400 mg doses (13.5% vs. 8.5% in the core studies).

3.3.1 Serious Adverse Events (SAEs)

There were 6 deaths reported in the phase 3 placebo-controlled studies and 9 deaths in the phase 3 uncontrolled extension studies. All of the deaths reported during the 12-month controlled studies and the 6-month monotherapy study occurred in patients randomized to the lesinurad treatment groups with numerically more deaths occurring in patients treated with lesinurad 400 mg +XOI (2 deaths in the lesinurad 200 mg +XOI group and 4 deaths in the lesinurad 400 mg +XOI group). No deaths were considered to be related to treatment with lesinurad by the investigator. The clinical reviewer concluded that the although there was a numeric imbalance against lesinurad in deaths that occurred during the controlled trials, the exposure-adjusted incidence rates for death in the lesinurad groups were low overall, with highly overlapping confidence intervals, making it difficult to draw definitive conclusions.[8]

Overall, the incidence of SAEs for lesinurad 200 mg +XOI was comparable to placebo +XOI (4.7% vs. 5.6%, respectively), and lower compared to lesinurad 400 mg XOI (8.6%). Similarly, in the 6-monotherapy study, the exposure-adjusted incidence rate for SAEs for the lesinurad 400 mg group was nearly 2.5 times higher as for placebo treated subjects.

In the combined Phase 3 core and extension studies, 31.1% of patients discontinued study treatment. The primary reasons for the 200 mg and 400 mg lesinurad groups included: noncompliance/protocol violation (10.4% and 9.2%, respectively), AE (6.9% and 9.2%, respectively), and consent withdrawn (6.9% and 7.1%, respectively). Discontinuation rates were similar in the lesinurad 200 mg +XOI group compared with placebo +XOI (6.3% and 5.4%, respectively), but higher in the 400 mg +XOI group (9.4%).

3.3.2 Adverse Events of Special Interest (AESIs)

3.3.2.1 Renal Toxicity

In the core studies, lesinurad 200 mg +XOI and placebo +XOI had a similar rate of renal-related AEs, but were higher for lesinurad 400 +XOI, suggesting toxicity was dose-dependent. The most

[8] Neuner R. Clinical DPARP. Clinical Review for Zurampic (lesinurad), dated September 17, 2015.

common renal-related AE was increased sCr. Additionally, there was an increased risk of other renal-related AEs in the lesinurad monotherapy trial. There were 7 subjects in the pooled, 12-month, phase 3, controlled lesinurad +XOI studies, 5 subjects in the 6-month, monotherapy study, and 10 patients in the long-term extension studies that developed serious renal AEs. The majority of patients experiencing the serious renal AEs were taking various medications that can adversely affect renal function and/or had underlying chronic kidney disease or other medical conditions that affect the kidney. However, no patient died as a result of renal-related toxicity.

Lesinurad 200 mg +XOI was not associated with an increased incidence of SAEs compared to placebo, but was associated with increases in sCr, with 1.8% of patients experiencing elevations >2x baseline. The elevations were mostly transient in nature and resolved without treatment interruption of lesinurad. However, two patients receiving lesinurad 200 mg +allopurinol in the long term extension studies underwent hemodialysis and treatment with lesinurad was discontinued. Of note, these patients had underlying medical conditions affecting the kidney and the events were also confounded by the concomitant use of medications that can adversely affect kidney function. In the overall populations, increases in sCr $\geq$2x baseline were associated with renal AEs (e.g., renal impairment, renal failure).

Lesinurad 400 mg +XOI was associated with a higher incidence of renal AE, serious renal AE, serum creatinine elevations, and kidney stone AE, compared to placebo, suggesting that renal toxicity is dose dependent. One patient in the long term extension study developed acute renal failure and received a renal biopsy indicating acute tubular cell injury. However, this case was confounded by the concomitant use of medications that affect renal function and other medical conditions that increase the risk of renal failure. Overall, severe and life-threatening events (Grades 3 and 4) were reported for 10.2%, 13.1%, and 9.3% of subjects in the lesinurad 200 mg + XOI, 400 mg + XOI, and placebo + XOI groups, respectively. Events that were classified as Renal and Urinary Disorders were reported at a higher rate for the lesinurad 400 mg + XOI group (2.4 events/100 person-years of exposure (PYE)) compared with the lesinurad 200 mg + XOI group (1.1 events/100 PYE). Of the patients that experienced transient increases in sCr elevations, 57.5% resolved without interruption of lesinurad. The incidence of renal-related TEAEs was comparable for subjects on XOI alone and patients on lesinurad 200 mg +XOI, but was higher for patients taking lesinurad 400 mg +XOI (4.5%, 5.7%, and 11.8%, respectively), suggesting this adverse event was dose related. There was a marked increase in renal adverse events in the lesinurad 400 mg monotherapy study, compared to placebo.

In the monotherapy trials, all cases of renal toxicity, including sCr elevations, renal impairment, acute renal failure, and renal failure occurred in the lesinurad 400 mg group. There was one patient, during the controlled period of the trial, that underwent a renal biopsy, but the results did not clarify the etiology of the renal failure. This case was also confounded by the concomitant use of medications that affect renal function and other medical conditions that increase the risk of renal failure. Based on the renal safety profile seen in Study 303, the lesinurad 400 mg monotherapy trial, Study 305, which is the open label extension trial for Study 303, was terminated prematurely.

The clinical reviewer noted that although there were multiple confounding factors involved in all renal failure cases, it is difficult to exclude lesinurad as another contributing factor since these patients' renal function appeared to be fairly stable until they entered these trials.[9]

An independent Renal Events Adjudication Committee (REAC) reviewed all AEs of acute renal failure that were serious or led to study drug discontinuation. The REAC concluded that while more sCr elevations occurred in lesinurad-treated subjects, they were transient and most resolved without treatment interruption. The REAC also concluded that lesinurad 200 mg daily in combination with an XOI is the optimum dose for the chronic treatment of hyperuricemia associated with gout. Overall, the clinical reviewer concluded that that lesinurad treatment is associated with an increased risk of renal adverse events, including reversible and non-reversible creatinine elevation and serious renal-related adverse events. The risk appears to be dose-dependent, with the highest risk being with use of lesinurad as monotherapy, without a concomitant xanthine oxidase inhibitor.[9]

3.3.2.2 Cardiovascular safety

Due to the high rate of cardiovascular risk in patients with gout, the Applicant had an independent cardiovascular endpoints adjudication committee review all deaths and potential cardiovascular AEs to assess whether events met criteria for MACE or non-MACE. Although the gout population typically has increased comorbid conditions, increased risk of MACE events would be expected in all treatment groups, but was not.

There were a total of 17 MACE events (including 4 deaths) that occurred in 15 patients. However, 13 of the 15 patients with MACE events had multiple risk factors, and 9 had underlying chronic kidney disease. There were 3 subjects with 4 events in the placebo group, 4 subjects with 4 events in the lesinurad 200 mg group, and 8 subjects with 9 events in the lesinurad 400 mg group. In the lesinurad +XOI placebo-controlled treatment groups, there were 4 MACE deaths, and in the 6-month monotherapy study, there was one MACE death. The clinical reviewer could not conclude why there was an imbalance in MACE events observed in the lesinurad 400 mg +XOI group from the pooled, 12-month, lesinurad +XOI studies that is not observed in the lesinurad 400 mg group from the 6-month monotherapy study.[9] The incidence rates for the number of subjects with MACE events and the overall number of MACE events for both the placebo +XOI and the lesinurad 200 mg +XOI group were comparably low, however the risk for subjects with MACE events as well as the overall number of MACE events is nearly double for the LESU400 mg +XOI treatment group (0.71, 0.96, 1.94, respectively). The clinical reviewer notes that the small number of cases and overlapping confidence intervals makes it difficult to draw conclusions from the data.[9]

3.3.2.3 Treatment in CYP2C9 Poor Metabolizers (PMs)

Lesinurad is a cytochrome p450 2C9 (CYP2C9) substrate and metabolized by CYP2C9. Pharmacokinetics studies indicate that use of lesinurad in CYP2C9 PMs had an approximate 1.8-fold increase in exposure to lesinurad. This effect was also consistent with use in moderate

[9] Neuner R. Clinical DPARP. Clinical Review for Zurampic (lesinurad), dated September 17, 2015.

CYP2C9 inhibitors (i.e. fluconazole) which increased lesinurad exposure by 56%.[10] Although the sample size of CYP2C9 PMs was limited from patients in Study 202 (n=0 lesinurad 200 mg, n=2 lesinurad 400 mg, and n=4 lesinurad 600 mg), there is a potential safety concern due to the dose-dependent renal effects observed in the indicated population. Lesinurad, if approved, should be used with caution in patients who are CYP2C9 PMs or taking moderate inhibitors of CYP2C9, however no dose adjustment is needed.

4 RISK MANAGEMENT ACTIVITIES PROPOSED BY APPLICANT

4.1 APPLICANT PROPOSED LABELING

The labeling for lesinurad proposed by the Applicant, dated December 29, 2014, and updated most recently on August 31, 2015 and September 19, 2015, includes a contraindication for patients with tumor lysis syndrome, Lesch-Nyhan syndrome, severe renal impairment (CrCl <30 mL/min), end-stage renal disease, and patients on dialysis. The proposed Warnings and Precautions section for lesinurad includes the risk of renal events, which states that there was a higher incidence of sCr elevations and renal-related adverse events at twice the recommended dose (b) (4) with the highest incidence when lesinurad was given as monotherapy. The label also recommends monitoring patient's rental function at initiation and periodically, thereafter. The Applicant has also proposed inclusion of a Boxed Warning to warn prescribers of the increased risk of acute renal failure with monotherapy use and the importance of co-administration with an XOI.

4.2 REVIEW OF APPLICANT'S PROPOSED REMS

The REMS for lesinurad proposed by the Applicant was submitted on December 29, 2014, consisting of a MG and CP to mitigate the risk of renal toxicity. The CP proposed included a Dear Health Care Professional Letter, a Zurampic REMS Website, and letters to professional organizations. The goals of the proposed lesinurad REMS are: (b) (4)

.

Reviewer's Comment*: The goals of the Applicant's proposed REMS, as described in Section 4.2,* (b) (4)

The Applicant has proposed a MG as an element of the REMS, and states that a MG will be dispensed with each lesinurad prescription in accordance with 21 CFR 208.24 similar to what would be required if the MG was part of product labeling. DRISK recommends that the MG be part of labeling but does not recommend that the MG be an element of the REMS. In addition to including the MG with each lesinurad packaged product, the Applicant has proposed making the MG available through the product website www.ZURAMPIC.com upon request by calling the

[10] Chen J. Clinical Pharmacology Division II. Clinical Pharmacology Review for Zurampic (lesinurad), NDA 207988, dated September 3, 2015.

AstraZeneca toll-free product information line (1-800-236-9933) and to HCPs from the field representatives from AstraZeneca. The dispensing requirement for the MG in the Applicant's proposal would be the same for a MG that is part of labeling. DRISK does not have concerns with making the MG available via the aforementioned venues, which can occur outside of a REMS. Therefore, DRISK believes that it is not necessary to include the MG in a REMS, but does recommend including the MG as part of the product labeling.

The proposed product labeling for lesinurad will include a Box Warning indicating the risk of acute renal failure with lesinurad, that the risk was more common when lesinurad was given alone, and that lesinurad should be used in combination with a xanthine oxidase inhibitor. A limitation of use is also proposed which states that lesinurad should not be used as monotherapy. In addition, the Applicant has only proposed the 200 mg dose for approval, and the proposed Warning and Precautions section of the label addresses the higher incidence of renal events observed at the 400 mg dose. DRISK believes that the risk of renal toxicity can be communicated through labeling and a REMS is not necessary to ensure the benefits outweigh these risks with lesinurad.

4.3 SUMMARY OF APPLICANT'S PROPOSED RISK MANAGEMENT PLAN

The Applicant has proposed a targeted post launch healthcare professional follow-up questionnaire when renal related events are reported. The questionnaire includes details of:

- lesinurad therapy
- adverse event(s), including worsening of a pre-existing condition
- other drugs that might be causally related to the event, if applicable
- other concomitant drugs and illnesses
- laboratory values
- reporter details

This proposed risk management plan was not evaluated by DRISK.

5 DISCUSSION

Based on results of the clinical program, the clinical reviewer has concluded that lesinurad was found to be modestly efficacious with an acceptable safety profile for the treatment of hyperuricemia associated with gout, in combination with an XOI. The AESIs associated with lesinurad include renal toxicity, cardiovascular events, and use in CYP2C9 PMs.

Although lesinurad is associated with increases in sCr, elevations generally resolved without treatment interruption. However, at doses greater than the proposed dose of 200 mg in combination with an XOI, or if used as monotherapy, lesinurad is associated with an increased incidence of serious adverse events, including renal impairment and renal failure. Although lesinurad 200 mg was associated with a smaller increased risk of renal toxicity compared to lesinurad 400 mg, results suggest toxicity is dose-dependent. Serious events that did occur were confounded with concomitant medications and conditions that adversely affect renal function. However, in an effort to communicate the risk of renal toxicity and recommendations for appropriate monitoring, the Applicant has proposed a Boxed Warning and inclusion of these risks in the Warnings and Precautions section of the label.

Although cardiovascular events did occur with lesinurad use, a causal relationship has not been established. However, cardiovascular events have also been included in the Warnings and Precautions section of the proposed labeling. Use with CYP2C9 has also been included in the Drug Interactions section of proposed labeling. It is recommended that lesinurad be used with caution in CYP2C9 PMs as lesinurad exposure can be increased.

To future characterize the potential risks associated with lesinurad, the Applicant has also proposed post-marketing trials to look at cardiovascular events and renal safety.

Additionally, the Advisory Committee echoed concerns regarding labeling and recommended that it include specific recommendations for patient creatinine level monitoring and advising caution when using this product in patients with renal insufficiency, which has been addressed by the Sponsor.

Therefore, based on the currently available data, DRISK does not recommend a REMS as necessary to ensure the benefits of lesinurad 200 mg once daily in combination with a XOI for the treatment of hyperuricemia outweigh the risks. Gout is a chronic condition that affects approximately 8.3 million adults in the United States and has limited treatment options available. Lesinurad, if approved, would be the first product to treat inefficient excretion of uric acid in 60 years since the approval of probenecid; thereby, adding a potential treatment option for the condition. The proposed Boxed Warning and Warnings and Precautions section of the label for lesinurad includes monitoring renal function at initiation and during therapy with lesinurad and warnings related to an increase in renal events, including acute renal failure, specifically with lesinurad use as monotherapy and at twice the recommended dose. In addition there is a limitation of use that states that lesinurad should not be used as monotherapy.

6 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling are not warranted for lesinurad, at this time. Based on the currently available data, the benefit-risk profile for lesinurad is acceptable for the treatment of hyperuricemia associated with gout in combination with an XOI in patients who have not achieved target serum uric acid levels with an XOI alone.

Should DPARP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JASMINDER N KUMAR
12/20/2015

CYNTHIA L LACIVITA
12/20/2015
Concur