



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for lesinurad

Proprietary Product Name: Zurampic

Sponsor: AstraZeneca Pty Ltd

**September 2016**

**TGA** Health Safety  
Regulation

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

## About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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## Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ACSOM	Advisory Committee on the Safety of Medicines
AE	adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AUC	area under the plasma drug concentration-time curve
AUC <sub>t1-t2</sub>	area under the plasma drug concentration-time curve from t1 to t2
CHMP	Committee for Medicinal Products for Human Use
C <sub>max</sub>	maximum serum concentration of drug
CMI	Consumer Medicines Information
ECG	electrocardiograph
EMA	European Medicines Agency
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IC <sub>50</sub>	inhibitory concentration 50%
ICH	International Conference on Harmonisation
HIV-1	human immunodeficiency virus type-1
MSU	monosodium urate
NMT	Not More Than
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NSAID	non-steroidal anti-inflammatory drug
OAT	organic anion transporter
OD	once daily

Abbreviation	Meaning
PD	pharmacodynamic(s)
PI	Product Information
PK	pharmacokinetic(s)
PO	per os (oral)
qd	quaque die (once daily)
RMP	Risk Management Plan
SAE	serious adverse event
sCr	serum creatinine
sUA	serum uric acid
$t_{1/2}$	elimination half life
Tmax	Time taken to reach the maximum concentration (Cmax)
ULT	urate lowering therapy
URAT1	uric acid transporter 1
XO	xanthine oxidase

## I. Introduction to product submission

### Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	16 May 2016
<i>Date of entry onto ARTG</i>	1 June 2016
<i>Active ingredient:</i>	Lesinurad
<i>Product name:</i>	Zurampic
<i>Sponsor's name and address:</i>	AstraZeneca Pty Ltd 66 Talavera Road Macquarie Park NSW 2113
<i>Dose form:</i>	Immediate release, film coated oral tablet
<i>Strength:</i>	200 mg
<i>Container:</i>	PVC/PCTFE – Al blister pack
<i>Pack size:</i>	Cartons containing 10 tablets (starter pack) and 30 tablets
<i>Approved therapeutic use:</i>	Zurampic is indicated in combination with a xanthine oxidase inhibitor for the treatment of hyperuricaemia associated with gout in patients who have not achieved target serum uric acid levels with an adequate dose of a xanthine oxidase inhibitor alone
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	200 mg once daily in the morning
<i>ARTG number:</i>	236961

### Product background

This AusPAR describes the application by AstraZeneca Pty Ltd to register lesinurad (trade name: Zurampic) as a new chemical entity. Lesinurad is a uricosuric agent. It is an inhibitor of uric acid transporter 1 (URAT1), which is a transporter protein located on the luminal membrane of the proximal tubule of the kidney. URAT1 is responsible for most of the renal reabsorption of urate from the urine.<sup>1</sup> The proposed indication is:

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<sup>1</sup> Bobulescu IA, Moe OW. Renal Transport of Uric Acid: Evolving Concepts and Uncertainties. *Adv Chronic Kidney Dis.* 19: 358-371 (2012).

*[F]or the treatment of hyperuricaemia associated with gout in combination with a xanthine oxidase inhibitor.*

The submission proposes registration of only one dosage form/strength: a 200 mg immediate release tablet. The proposed dosage regimen is one 200 mg tablet taken once daily in the morning with food and water.

Gout is monosodium urate deposition disease. It occurs when patients have had, at some time, urate concentrations sufficiently elevated (usually greater than 0.42 mmol/L) for the solubility coefficient of sodium urate to be exceeded long enough for crystals to form in tissues. The plasma urate concentration is the single most important determinant of the risk of developing gout, with the incident rate of gout increasing exponentially with plasma urate levels greater than 0.54 mmol/L.

The term gout is reserved for the clinical attack of joint pain and swelling, which may be acute, palindromic (a recurrent, transient form), acute-on-chronic or chronic. It usually begins in one joint (classically the first metatarsophalangeal joint), but may become polyarticular and cause diagnostic confusion. Chronic tophaceous gout is destructive and may, unless it is treated, leave the patient disabled. Gout may also affect the kidney with two major manifestations being nephrolithiasis and chronic urate nephropathy. Both conditions may result in chronic renal impairment. Prevention of these outcomes is by management of serum urate levels and symptomatic treatment of acute episodes.

Uric acid is the end product of purine metabolism in man. It is produced in the liver through conversion of xanthine by the enzyme xanthine oxidase (XO). In addition to life-style measures, current treatments for the long term prevention of hyperuricaemia/gout include XO inhibitors (allopurinol or febuxostat) and the uricosuric agent probenecid. XO inhibition results in decreased production of urate. Probenecid is thought to act through inhibition of urate reabsorption via URAT1 in the proximal tubule, resulting in increased urate excretion. Therapeutic Guidelines<sup>2</sup> states that probenecid is less effective than allopurinol in reducing plasma urate concentrations but may be added to allopurinol in those individuals unable to achieve target levels with monotherapy, or those with severe tophaceous gout. Lesinurad is a uricosuric agent. Like probenecid, it acts by inhibition of URAT1. URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. Lesinurad also inhibits OAT4, a uric acid transporter involved in diuretic induced hyperuricemia.

Lesinurad has been proposed as an adjunctive treatment for patients with inadequate control of serum urate with a XO inhibitor.

## **Regulatory status**

At the time of lodgement to TGA (May 2015), similar submissions had been lodged in the US (25 December 2014) and EU (7 January 2015). Approved indications were:

### ***United States***

*Zurampic is a URAT1 inhibitor indicated 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.*

### ***European Union***

*Zurampic, in combination with a xanthine oxidase inhibitor, is indicated in adults for the adjunctive treatment of hyperuricaemia in gout patients (with or without tophi)*

<sup>2</sup> Revised October 2010. ©Therapeutic Guidelines Ltd (etg46 November 2015).



*who have not achieved target serum uric acid levels with an adequate dose of a xanthine oxidase inhibitor alone.*

Submissions were also made in Switzerland (28 May 2015) and New Zealand (25 June 2015).

## Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## II. Quality findings

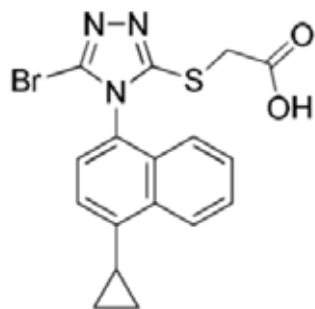
### Introduction

Packaging is proposed as Aclar blister packs of 10 and 30 tablets. The drug substance lesinurad is a new chemical entity for the Australian market. There are no European Pharmacopoeia (Ph. Eur.) or United States Pharmacopeia (USP) monographs for lesinurad drug substance or the product.

### Drug substance (active ingredient)

Lesinurad (Figure 1) is a white crystalline non hygroscopic powder. The drug substance exists as a racemic mixture (50:50) of two atropisomers (that is, atropisomer 1 and atropisomer 2). Studies to date suggest that the atropisomers do not readily interconvert, even under extreme conditions.

**Figure 1. Structure of lesinurad.**



Lesinurad has pH and temperature dependant solubility profiles. At above pH 6.2 at room temperature and pH 6.0 at 37 °C, a critical micelle concentration (CMC) is reached where lesinurad self-associates and forms an anionic micellar system.

Two known non solvated crystal forms (free acid polymorphs) exist; Form 1 (metastable) and Form 2 (thermodynamically stable). The proposed commercial manufacturing method of lesinurad drug substance yields only Form 2 (melting point 169-171°C). The polymorphic form does not change during stability storage and the FTIR identification (specification) test can distinguish between the two polymorphic forms. Both atropisomers for this drug substance have Form 2 crystal.

The particle size distribution of the drug substance used in this product is controlled by the acceptable specification limits. These specification limits have been justified based on batch analysis data which included batches used in clinical studies.

Chirality of the drug substance is controlled by the acceptable atropisomer ratio specification limit. Batch analysis and stability results provided suggest that there is no interconversion during storage.

The specification limits for specified impurities exceed the International Conference on Harmonisation (ICH) qualification threshold of 0.15%. The Toxicological Section had advised that the specification limits for these specified impurities have been adequately qualified and are acceptable. All specifications for residual solvents comply with the ICH guideline.

The manufacturing and quality control of the drug substance (including the drug substance specification) is acceptable.

## Drug product

The proposed drug product is a blue, oval, film coated tablet containing 200 mg of the active pharmaceutical ingredient as the free acid, and the conventional excipients hypromellose, microcrystalline cellulose, lactose, crospovidone and magnesium stearate. The tablets measure 5.7 x 12.9 mm and are debossed with "LES200" on one side and are blank on the other. The drug product is intended for oral administration.

The product is to be supplied in PVC/PCTFE-Al blisters and in cartons of 10 tablets (starter pack) and 30 tablets (commercial pack).

The quality of the product is controlled by acceptable specifications that include tests and limits for Appearance, Identification, Assay, Uniformity of Dosage Units, Degradation Products, and Dissolution.

The specification limit for one specified degradation product exceeds the ICH qualification threshold of 0.15%. The Toxicological Section had advised that this limit has been adequately qualified and is acceptable.

The manufacturing and quality control of the finished product is acceptable. However, the Good Manufacturing Practice (GMP) Clearance for the proposed finished product manufacturer will expire prior to the decision date and a renewed clearance has not been issued. This matter remains outstanding, but is expected to be resolved in due course.

The analytical methods used to analyse the product were adequately described and validated.

The stability data supplied supported a shelf life of 36 months for the unopened product (in PVC/PCTFE/Al blister) when it is stored below 30°C.

## Biopharmaceutics

A significant number of clinical studies have been conducted on lesinurad in humans. The absolute bioavailability and interaction studies were not fully evaluated by the Pharmaceutical Subcommittee (PSC), but are briefly summarised below. The food effect Study RDEA594-121 was fully evaluated by PSC.

- Absolute Bioavailability: Lesinurad has an absolute bioavailability of approximately 100%, as determined in Study RDEA594-131 (that is, Study 131).
- Dose Proportionality: Studies have shown that the maximum serum concentration of drug (C<sub>max</sub>) and area under the plasma drug concentration-time curve (AUC) increased proportionally with single doses of lesinurad from 5 to 600 mg under both fasted and fed conditions (Study 101) and from 200 to 1200 mg under fed condition (Study 117).

- **Comparative Bioavailability:** There are no formulation differences between the 200 mg Phase III formulation and the proposed commercial 200 mg formulation. In addition, the 400 mg tablet, used in a number of clinical studies, is proportionally similar to the 200 mg product proposed for registration with similar dissolution profiles. Therefore, comparative bio-studies were not required.
- **Drug-Drug Interaction:** Lesinurad is intended to be co-administered with a XO inhibitor, that is, allopurinol or febuxostat. Pharmacokinetic studies have been conducted to determine any drug-drug interactions with those agents.

#### *Febuxostat*

Study 105 compared the multiple dose pharmacokinetics (PK) of febuxostat in the absence versus presence co-administration of lesinurad and vice versa. This study concluded that:

- Plasma and urine PK of lesinurad at doses of 200 mg and 400 mg every day for 14 days were not affected by concomitant administration of febuxostat 40 mg every day (qd).
- The plasma PK of febuxostat 40 mg qd were unaffected by lesinurad 200 mg qd and showed exposure increases of approximately 25% to 30% with lesinurad 400 mg qd.

Study 111 evaluated (i) the multiple dose plasma PK of febuxostat alone and in combination with lesinurad, (ii) the multiple dose plasma PK and urinary excretion of lesinurad in combination with febuxostat, and (iii) the multiple dose plasma PK of colchicine alone and in combination with febuxostat or both febuxostat and lesinurad. The study found that:

- The plasma and urinary PK profiles of lesinurad were similar when administered with either 40 mg or 80 mg of febuxostat.
- Plasma exposure of febuxostat was increased by approximately 8% to 21% with co-administration of lesinurad.
- Colchicine plasma exposure was decreased by lesinurad, with less change in exposure at the lower 400 mg dose (colchicine AUC decreased by approximately 20%) than at the higher 600 mg dose (colchicine AUC decreased by approximately 30%).
- Febuxostat had no effect on the PK of colchicine.

#### *Allopurinol*

Study 110 assessed the multiple dose PK and PD drug-drug interaction (DDI) study of lesinurad in 21 male hyperuricemic subjects with gout. The primary objectives of the study were: (i) to evaluate the multiple dose plasma PK and urinary excretion of allopurinol and oxypurinol alone and in combination with lesinurad, (ii) to evaluate the multiple dose plasma PK and urinary excretion of lesinurad alone or in combination with allopurinol, and (iii) to evaluate the multiple dose plasma PK of colchicine alone and in combination with lesinurad, allopurinol, or both allopurinol and lesinurad. The PK findings were:

- The lesinurad plasma PK profile was unaffected when co-administered with allopurinol 300 mg qd in adult male subjects with gout.
- Allopurinol plasma exposures were minimally decreased by < 25% during co-administration of lesinurad 400 mg or 600 mg qd.
- Oxypurinol plasma exposures were reduced by approximately 25% to 35% when allopurinol was co-administered with lesinurad 400 mg or 600 mg qd. The

reduction of oxypurinol exposures occurred in conjunction with increased clearance (CLR) of oxypurinol.

- The pharmacologic effect of allopurinol was retained when lesinurad was added, as shown by only marginal decreases in 24 h urinary xanthine and hypoxanthine excretion in comparison to single agent allopurinol.

#### *Other interaction studies*

A number of other lesinurad DDI studies were conducted with a series of other pharmacological agents. No significant interactions were found to occur with naproxen, atorvastatin, repaglinide, tolbutamide, S-warfarin, or metformin. Lesinurad was found to be a weak to moderate inducer of CYP3A4, and as such some effect was found with substrates for this enzyme including colchicine, sildenafil, amlodipine and R-warfarin.

- Food Effect: in Study RDEA594-121, the effect of food on the bioavailability of lesinurad was evaluated in healthy adult male subjects. The study showed that:
  - C<sub>max</sub>: C<sub>max</sub> was decreased approximately 18% in the presence of food compared to the fasted state. The confidence interval of the geometric mean ratio (81.6%) for C<sub>max</sub> was 66.6% to 99.8%, which falls outside the standard equivalence limit for bioequivalence of 80% to 125%, indicating that there was a small but significant effect of food on the peak concentration of lesinurad.
  - AUC: There was an approximate 8% decrease in the overall exposures of lesinurad as determined by AUC<sub>last</sub> and AUC<sub>∞</sub>. The confidence intervals of the geometric mean ratios for both parameters were within the equivalence limit of 80% to 125%, indicating that the extent of absorption of lesinurad was not altered by food.
  - T<sub>max</sub>: A slight delay (0.5 h) in lesinurad absorption was observed under the fed condition, however this difference in T<sub>max</sub> values was not statistically significant (P = 0.9697).
  - Half-life: Terminal elimination half-life of lesinurad in plasma was approximately 17 to 18 h under both the fed and fasting conditions. This suggests that the elimination of lesinurad in plasma was not affected by food.
  - Urinary Excretion: Compared to the fasting condition, urine excretion was increased by approximately 33% with food, while renal clearance (CLR<sub>0-72</sub>) was increased by approximately 44%. These results indicate a significant food effect on the urinary excretion and elimination of lesinurad.

The results from the food effect study were brought to the attention of the Clinical Delegate for consideration whether this apparent effect of food is clinically relevant and whether the PI instruction that Zurampic *should be taken with food* is acceptable from a clinical perspective.

#### **Quality summary and conclusions**

- There is one outstanding issue in relation to the GMP clearance, but this issue is expected to be addressed in due course, prior to the decision date. All other issues raised in relation to the chemistry and quality aspects of the submission have been adequately resolved and these aspects are now acceptable.
- There were biopharmaceutics issues that were brought to the attention of the Clinical Delegate for consideration whether the food effect results are considered to be clinically relevant and whether the proposed dosage and administration on the PI for the tablet to be taken with food is appropriate from a clinical perspective.

- The application has not been considered by the PSC of the Advisory Committee on Prescription Medicines (ACPM) because no issues requiring their expertise were identified during the chemistry and quality evaluation.

### III. Nonclinical findings

#### Introduction

The submission was comprehensive and of high quality, consisting of GLP compliant studies that addressed the relevant ICH guidelines for nonclinical studies. The monkey was selected as the non-rodent species based on similarities between monkeys and humans with respect to the in vitro metabolic profile, and the absence of metabolite M4 in dogs. Submitted data included combination repeat dose toxicity studies (including toxicokinetic data) with allopurinol and febuxostat. Studies that were submitted but not evaluated are included. In comparison to humans, other mammals (including most primates) have considerably lower serum uric acid concentrations, as the enzyme uricase converts uric acid to allantoin. This enzyme has been functionally deleted in humans. In addition, there may be other interspecies differences in uric acid homeostasis. As a result, there are no adequate animal models for the assessment of the primary pharmacodynamic effect of lesinurad in vivo, and this may limit the relevance of the nonclinical data to a certain extent.

Throughout this assessment, relative exposures have been calculated based on mean plasma C<sub>max</sub> and AUC<sub>0-24</sub> values in normal males of 6.92 µg/mL and 28.0 µg.h/mL, respectively, and assuming 98.2% of the total plasma lesinurad concentration is bound to proteins in plasma. The concentration of unbound lesinurad in plasma is therefore estimated to be 125 ng/mL, or 0.308 µM. The mean urinary concentration of lesinurad in the first six hours after dosing was 20.1 µg/mL or 49.7 µM.

#### Pharmacology

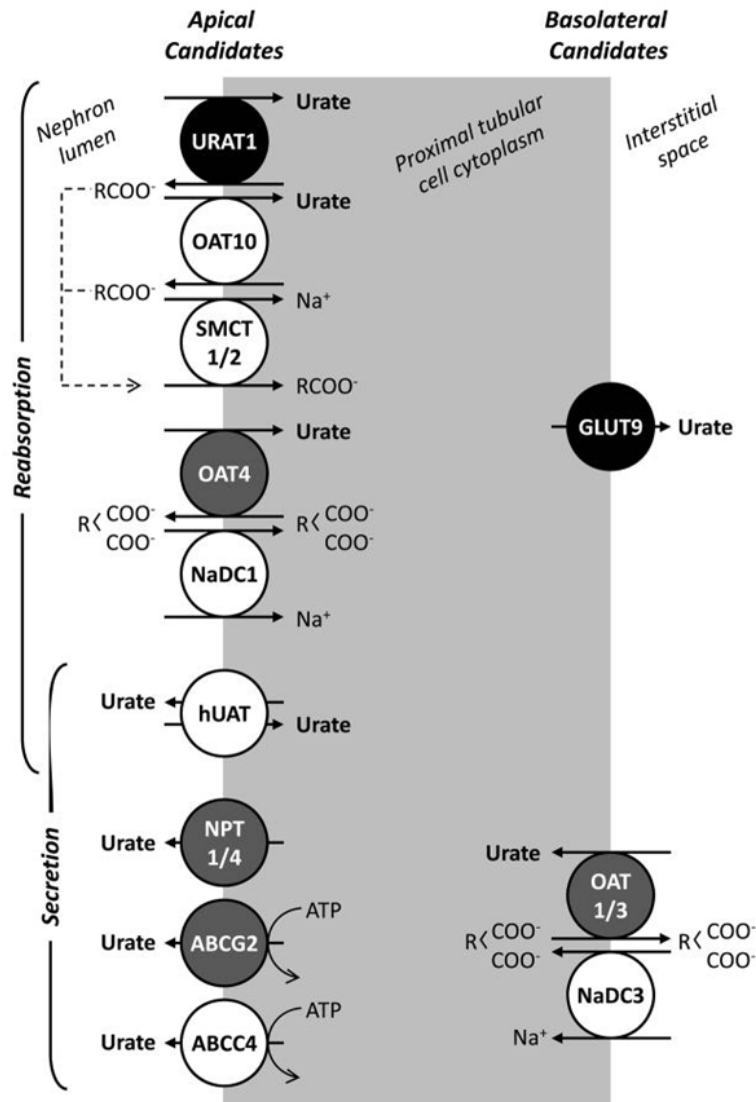
##### Primary pharmacology

Gout is an inflammatory arthritis characterised by elevated plasma levels of uric acid (hyperuricaemia), which results in the deposition of urate crystals in joints owing to its low solubility. Lesinurad was identified as a uricosuric metabolite of RDEA806, a compound that was under investigation for anti HIV1 activity. Investigations of the potential mechanism(s) underlying the uricosuric effect of lesinurad were centred around its effect on renal membrane transport proteins. The role of these proteins in uric acid homeostasis is briefly reviewed before the nonclinical primary pharmacology studies are discussed.

Uric acid homeostasis is a balance between production, intestinal secretion and renal excretion, with the latter accounting for the excretion of 60-70% of total body uric acid. At the same time, approximately 90% of filtered urate is reabsorbed by the kidney. The rate of uric acid absorption and excretion in humans is modulated by a number of different renal transport proteins (Figure 2). URAT1 (encoded by the SLC22A12 gene), a protein specifically localised to the brush border membrane of the proximal tubule, is thought to play a predominant role in the apical reabsorption of urate in humans, based on studies examining the association between serum urate levels and genetic polymorphisms in URAT1. Other apical entry pathways are also believed to be involved since some urate reabsorption remains in subjects with complete loss of URAT1 function. In addition to this apical pathway for urate reabsorption, the glucose co-transporter GLUT9 (SLC2A9 gene) is

believed to be the principal pathway of basolateral urate exit from the proximal tubule, with URAT1 and GLUT9 acting together to achieve transcellular urate transport (Bobulescu and Moe, 2012).

**Figure 2. Candidate transport proteins involved in urate handling in the human proximal tubule.**



Circles representing individual transporters are coloured according to the level of evidence for their role; black, grey and white circles represent strong, moderate and weak evidence, respectively. Reproduced from Bobulescu and Moe (2012).<sup>3</sup>

The organic anion transporter OAT4 is also proposed to play a role in apical urate reabsorption. Additional organic anion transporters that have been proposed to modulate the rate of urate absorption and excretion in humans include the ATP binding cassette subfamily G member 2 (ABCG2), multidrug resistance protein 4 (MRP4), sodium dependent phosphate co-transporter types 1 and 4 (NPT1 and NPT4) and the organic anion transporters OAT1 and OAT3. Evidence for a role of BCRP, NPT1 and NPT4 is based on the association between gout and hyperuricaemia with genetic polymorphisms of these transporters. In addition, studies in OAT1 and OAT3 knockout mice found an

<sup>3</sup> Bobulescu IO, Moe OW. Renal transport of uric acid: evolving concepts and uncertainties. *Advances in Chronic Kidney Disease* 19: 358-71 (2012).

approximately 30% decrease in the secretion of urate, suggesting that they contribute to uric acid homeostasis in this species.<sup>4</sup>

Inhibition of URAT1 is a primary mechanism of action of the uricosuric agents probenecid and benzbromarone, which were used as positive control substances in the pharmacodynamic studies (of these two agents only probenecid is registered in Australia). The sponsor is claiming that unlike probenecid, lesinurad is a 'selective' inhibitor of URAT1, and is therefore less prone to DDI; this issue is discussed below (see 'Pharmacokinetic Drug Interactions'). In addition, the angiotensin receptor inhibitor losartan has a uricosuric effect that is believed to be mediated by inhibition of URAT1.<sup>5</sup>

Lesinurad was shown to inhibit human URAT1 (hURAT1) in in vitro studies, with an IC<sub>50</sub> of 7.3 µM for inhibition of radiolabelled uric acid uptake into transfected human embryonic kidney (HEK) 293 cells. Lesinurad was not itself a substrate for URAT1, and demonstrated weak trans- as well as cis-inhibition of hURAT1 expressed in *Xenopus* oocytes (although the inhibition of cis-urate transport in oocytes was almost ten-fold relatively lower than its activity in the mammalian expression system). The dealkylated lesinurad metabolite M6 also exhibited comparable activity against hURAT1 expressed in HEK293 cells (IC<sub>50</sub> = 8.85 µM), but metabolites M2, M3 and M4 showed negligible inhibition. Formation of M6 represents a very minor metabolic pathway in humans (M6 exposures are approximately 0.3% that of the parent compound; see 'Pharmacokinetics'), so this metabolite is not expected to contribute to efficacy in clinical use.

An additional potential mechanism underlying the uricosuric effect of lesinurad is through inhibition of OAT4, also located on the apical membrane of the proximal tubule.<sup>6</sup> The IC<sub>50</sub> against human OAT4 in HEK293 cells was 3.7 µM, which was again comparable to the activity of probenecid and benzbromarone. Lesinurad metabolites M2 and M6 had almost one tenth as much activity against OAT4, with IC<sub>50</sub> values of 12.2 and 13.0 µM, respectively. Assuming that lesinurad is acting on these transporters at the apical surface of the proximal tubular cells, then the estimated urinary lesinurad concentration of approximately 50 µM is consistent with its uricosuric effect being mediated by inhibition of both URAT1 and OAT4.

OAT1, OAT2 and OAT3 at the basolateral membrane and BCRP, NPT1, NPT4 and MRP4 at the apical membrane are involved in renal secretory transport of uric acid. In particular, BCRP, NPT1 and NPT4 may make significant contributions to renal handling of uric acid because genetic polymorphisms of these transporters are associated with gout and/or hyperuricaemia. Lesinurad also inhibited the organic anion transporters OAT1 and OAT3 (IC<sub>50</sub> against hOAT1 expressed in HEK293 cells was 4.34 µM, while the IC<sub>50</sub> against hOAT3 expressed in *Xenopus* oocytes was 3.54 µM). Since these transporters are located on the basolateral membrane and the maximum unbound concentration of lesinurad in plasma is estimated to be 0.213 µM, the in vitro data suggest that their inhibition is unlikely to be of clinical significance. Weak inhibition of the sodium phosphate transporter (NPT1) or the breast cancer resistance protein (BCRP) is also not considered to be clinically relevant.

Evidence provided from in vitro studies indicated that lesinurad's uricosuric effect was not mediated by inhibition of GLUT9 (solute carriers SLC2A9 variants 1 and 2), XO or purine nucleoside phosphorylase.

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<sup>4</sup> Eraly SA, et al. Multiple organic anion transporters contribute to net renal excretion of uric acid. *Physiological Genomics* 33: 180-192 (2008).

<sup>5</sup> Hamada T, et al. Uricosuric action of losartan via the inhibition of urate transporter 1 (URAT1) in hypertensive patients. *American Journal of Hypertension* 21: 1157-62 (2008).

<sup>6</sup> Hagos Y, et al. Human renal organic anion transporter 4 operates as an asymmetric urate transporter. *Journal of the American Society for Nephrology* 18: 430-439 (2007).

There was very little evidence from in vivo studies to support the proposed therapeutic use, based on the lack of a suitable animal model. Rat and mouse URAT1 show only 75% and 73% protein sequence homology with human URAT1. Lesinurad showed very little inhibition against HEK293 transfected mouse or rat URAT1 in vitro, indicating that these species were not suitable for in vivo studies. The sensitivity of cynomolgus monkey URAT1 to lesinurad is unknown. In addition, there are very important species differences in the metabolism of uric acid. In most mammals, including old world monkeys (with the exception of the bush baby), the urinary excretion of nitrogenous waste involves the oxidation of uric acid by the enzyme uricase (urate oxidase) to 5-hydroxyisourate, followed by hydrolysis to the much more soluble allantoin, so that uric acid is avidly secreted by renal tubules. In these species endogenous plasma urate concentrations are very low (<3 µg/mL)<sup>7</sup> and liver uricase activity is high. Tubular reabsorption of uric acid appears to become relatively more important in New World monkeys. Humans, apes and the spider monkey appear to be the only primates that have lost the capacity to oxidise uric acid owing to mutations that have silenced the gene for uricase. As a result, circulating uric acid levels in these primates are 5 to 20 fold higher than in most other mammals.<sup>8</sup> Reference values for uric acid in humans are 25-80 µg/mL for males, and 19-75 µg/mL for females.<sup>9</sup>

A preliminary investigation of the uricosuric effects of lesinurad in a New World monkey species (*Cebus apella*; Study SR07-117) found substantial amounts of allantoin in plasma and urine, indicating the presence of uricase. Although lesinurad and benzbromarone increased the urinary excretion of uric acid and lesinurad, there were no changes in the plasma concentrations of either substance. The extent of homology between human and *Cebus apella* monkey URAT1 (or other uric acid transporters) is unknown. The sponsor has attempted to identify a suitable animal model for gout, and the lack of in vivo data is therefore justified. The uricosuric effect of lesinurad (as a metabolite of RDEA806) had already been demonstrated; a strong linear correlation was found between uric acid excretion and the urinary excretion of lesinurad (but not RDEA806 or its other metabolites; Study SR07-125).

In conclusion, inhibition of both URAT1 and OAT4 are likely to underlie the clinically observed uricosuric effect of lesinurad based on in vitro data. This mechanism of action is similar to that of probenecid, although inhibition of OATs 1 and 3 may also occur clinically with this agent. The lack of supporting in vivo data for the proposed indication is justified based on the lack of an appropriate animal model. Uricosuric agents such as probenecid pose an increased risk of urate precipitation in the renal tubule owing to the enhanced secretion of uric acid into the tubule for excretion, and require dose adjustment in renally impaired patients and in patients with a history of renal calculi. Based on a similar mechanism of action, urate precipitation may also be a risk for lesinurad during clinical use, but would not be anticipated in the nonclinical species.

### **Secondary pharmacodynamics and safety pharmacology**

Lesinurad was tested for potential secondary activity at 169 other receptors, ion channels and transporters. An IC<sub>50</sub> of approximately 5 µM was reported at the prostanoid thromboxane receptor, which is unlikely to be clinically relevant based on a maximum unbound lesinurad concentration in plasma of 0.3 µM. A lack of potential secondary activity was confirmed in functional assays, including assays for platelet aggregation,

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<sup>7</sup> Dan T, et al. Hypouricemic and uricosuric actions of AA-193 in a hyperuricemic rat model. *Metabolism* 43: 123-8 (1994).

<sup>8</sup> Bobulescu IO, Moe OW. Renal transport of uric acid: evolving concepts and uncertainties. *Advances in Chronic Kidney Disease* 19: 358-71 (2012).

<sup>9</sup> Williamson et al (2011). In: Wallach's Interpretation of Diagnostic Tests. 9th Edition. Philadelphia, Pa: Wolters/Kluwer/Lippincott Williams & Wilkins Health.



neuropeptide Y receptor function and anti HIV-1 activity, and a nuclear receptor cross reactivity screen. Lesinurad did not exhibit cytotoxic potential or toxicity against DNA polymerases in cell based assays, and lacked the mitochondrial toxicity exhibited by benzbromarone in an in vitro assay (thought to underlie its hepatotoxic effect). There was no evidence of myotoxicity potential in a rat muscle cell line, and the addition of lesinurad did not enhance the myotoxic effects of statins or colchicine.

Lesinurad showed some anti-inflammatory activity in the monosodium urate (MSU) crystal induced air pouch and MSU induced knee joint inflammation models in rats, reducing exudate volume, plasma extravasation and white blood cell (WBC) infiltration when administered orally (PO, per os) at 10 mg/kg, and reducing knee joint swelling at 60 mg/kg. Some inhibitory activity against the thromboxane A2 receptor and prostaglandin D2 was observed in vitro, but is unlikely to be clinically relevant. Neither lesinurad nor its M4 metabolite exhibited any activity against COX-1, COX-2 and/or prostaglandin E2 receptors EP2 and EP4.

A comprehensive GLP compliant safety package was submitted, examining the central nervous system (CNS), cardiovascular, respiratory, renal and gastrointestinal systems. With the exception of the CNS study the in vivo safety studies only used male animals. In the male rat, the renal route only accounts for approximately 10% of lesinurad excretion, while in female rats the renal and faecal routes were approximately equal, and in male humans approximately two thirds of lesinurad is excreted renally. Gender differences in the nonclinical pharmacokinetic studies are discussed in more detail below.

The results of the safety pharmacokinetic studies are summarised in Table 1. Lesinurad showed no adverse CNS effects in rats at oral doses corresponding to 24 times the clinical C<sub>max</sub>. The no-observed-effect level (NOEL) for cardiovascular and respiratory effects in telemetered monkeys was 21x and 38x based on C<sub>max</sub> and AUC<sub>0-24</sub>; therefore prolongation of QT intervals is not predicted based on in vitro data. A preliminary cardiovascular study in conscious rats found cardiac toxicity following IV administration of 150 mg/kg lesinurad, with a no-observed-adverse-effect level (NOAEL) corresponding to 67 times the clinical C<sub>max</sub>. The NOEL for the lesinurad induced reduction in intestinal motility of male rats corresponded to 24 times the clinical C<sub>max</sub>. In a comprehensive renal and urinary system safety study in male rats the only findings corresponded to the expected pharmacological activity of lesinurad. While the NOEL was 12 times the clinical C<sub>max</sub> this is not indicative of a possible lack of clinical efficacy owing to the species difference between rat and humans with respect to lesinurad's actions on URAT1.

In conclusion, the safety pharmacology studies were comprehensive and consistent with ICH guidelines,<sup>10</sup> and did not reveal any safety issues of clinical relevance.

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<sup>10</sup> European Medicines Agency, "ICH Topic S7A. Step 5. Note for guidance on safety pharmacology studies for human pharmaceuticals (CPMP/ICH/539/00)", June 2001; European Medicines Agency, "ICH Topic S7B. Note for guidance on the nonclinical evaluation of the potential for delayed ventricular repolarisation (QT interval prolongation) by human pharmaceuticals (CPMP/ICH/423/02)," November 2005.

**Table 1. Summary of findings in safety pharmacology studies.**

Study No.	Species/ test system	Study Type; Dose & Route	Activity	Estimated Exposure	Relative Exposure #
SR08-027	Rat	CNS activity, 30, 100, 300 mg/kg PO (both sexes)	NOEL = 300 mg/kg	Based on Study SR08-071; C <sub>max</sub> at NOEL = 165 µg/mL	24 X based on C <sub>max</sub>
SR08-021	hERG channel/ HEK293 cells	Up to 200µM	IC <sub>50</sub> = 198 µM	NA	643 X
SR08-158		Lesinurad M6: up to 300 µM	M6 IC <sub>50</sub> = 227 µM		737 X
SR08-054	Rabbit Purkinje fibres	Effects on action potential duration (APD) <i>in vitro</i>	Small increases in APD, and decrease in dV/dt at 200 µM	NA	649 X
SR08-085		As above, with human albumin	No effects at up to 158 µM		9.3 X
SR08-061	Rat (conscious, restrained ♂)	Exploratory cardiovascular assessment, 41, 82 & 150 mg/kg IV	Mortality at HD and AV block; hypotension at all doses; NOAEL = MD	C <sub>max</sub> at NOAEL = 464 µg/ml	67 X
SR08-020	Monkey (telemetered, ♂)	Cardiovascular and respiratory parameters, 30, 100 & 300 mg/kg PO	Vomiting; NOAEL for cardiovascular & respiratory effects = 300 mg/kg	Based on day 1 of Study SR08-094; C <sub>max</sub> at NOAEL = 146 µg/mL; AUC <sub>0-24</sub> = 1060 µg,h/mL	21 X and 38 X based on C <sub>max</sub> and AUC <sub>0-24</sub>
SR08-088	Rat, ♂	Renal and urinary system, 30, 100, 300 & 1000 mg/kg PO	Urinary and serum chemistry effects consistent with pharmacological activity; NOEL 100 mg/kg	Based on Study SR08-071 C <sub>max</sub> at NOEL = 83.7 µg/mL	12 X based on C <sub>max</sub>
SR08-033	Rat, ♂	Charcoal transit (intestinal motility) 30, 100, 300, 1000 mg/kg	Significant decrease (17%) in motility at 1000 mg/kg; NOEL = 300 mg/kg	Based on Study SR08-071; C <sub>max</sub> at NOEL = 165 µg/mL;	24 X based on C <sub>max</sub>

#Relative to clinical total C<sub>max</sub> of 6.92 µg/mL/17µM, unbound C<sub>max</sub> of 0.125 µg/mL/0.308 µM, or AUC<sub>0-24</sub> of 28 µg,h/mL

## Pharmacokinetics

Absorption was rapid following oral administration of single doses to rats, dogs and monkeys, with  $T_{max}$  ranging from 0.25 to 3 h, and the oral bioavailability in these species was 71-75%, 100% and 41%, respectively. The plasma clearance was low relative to liver blood flow, and the volume of distribution indicated that there was minimal distribution outside the vascular space. In multiple dose toxicokinetic studies (conducted in transgenic mice, rats and monkeys), exposures ( $C_{max}$  or AUC) generally increased with dose, although there was evidence of saturation with very high doses in transgenic mice. Female transgenic mice had higher exposure levels than males, but there was no apparent gender difference in rats and monkeys. Exposure levels tended to decrease with repeated dosing of rats at doses  $\geq 100$  mg/kg and monkeys at  $\geq 30$  mg/kg/day, which is suggestive of autoinduction. The basic characteristics of absorption and clearance in the nonclinical species are comparable to those observed in man.

A pharmacokinetic evaluation of lesinurad in plasma and urine of nephrectomised rats examined the potential impact of chronic renal impairment (Study SR12-042). There was an increase in systemic exposures based on  $AUC_{0-\infty}$  of 22% and 68% in renally impaired males and females, respectively. Fractional excretion and renal clearance of lesinurad were comparable in normal and renally impaired male rats, but in females, where renal clearance plays a greater role in elimination of lesinurad, the fractional excretion of lesinurad was 70% lower in renally impaired female rats compared with rats with normal renal function, and renal clearance was 84% lower. Renal excretion of lesinurad is relatively more important in humans compared with the nonclinical species (see below), and hence these data suggest that systemic exposures may be increased in patients who are renally compromised. This has been confirmed clinically and is described in the proposed PI document.

Lesinurad was highly bound to proteins in plasma from mouse, rat, dog, monkey and human, being approximately 98% bound in all species except the mouse (binding  $\geq 94\%$ ). There was no evidence that  $^{14}C$  lesinurad associated radioactivity distributed preferentially to the cellular component of blood in rats or monkeys. In tissue distribution studies in albino and pigmented rats the highest concentrations of radioactivity following oral administration were in the gastrointestinal tract, liver and kidney, with all other tissue to blood ratios being below zero (and with the lowest tissue to blood ratio being found in the brain and spinal cord). There was no indication of binding to pigmented tissues, and no evidence of retention.

Qualitatively, metabolism was essentially similar across the nonclinical species and humans, but with some notable quantitative differences. Microsomes or hepatocytes from mouse, rat, dog, monkey and human showed a low capacity to metabolise lesinurad, which was the predominant component circulating in the plasma of rats and humans after single or multiple doses. However, lesinurad was the major drug related component in monkey plasma after a single dose of lesinurad, with formation of the S-dealkylated metabolite M6 becoming increasingly important with repeated dosing such that after 3 to 12 months of repeated dosing its concentration in plasma was 2 to 6 times that of the parent compound. Although M6 was formed in humans in vitro, metabolism of lesinurad by this pathway was negligible in vivo, with median molar ratios for lesinurad to M6  $C_{max}$  and AUC values being less than 0.3% after repeated dosing (Study RDEA202). The molar ratios did not increase with time, indicating no accumulation of this metabolite in humans.

In addition to S-dealkylation, biotransformation pathways included:

- oxidation (yielding M3);
- glucuronidation (to form M1, a major component of bile in rats and monkeys, or glucuronides of other primary metabolites);

- debromination by intestinal microflora (M2);
- cysteine adduction of an oxidative metabolite to form M9, which was the second most abundant metabolite in the bile of monkeys, and was also formed in human liver in vitro;
- Various combinations of these pathways (for example, M5, an important metabolite in the rat, was the product of both oxidation and debromination).

A major and toxicologically important difference between the metabolic pathway for lesinurad in humans and the nonclinical species concerns the ultimate fate of the oxidative metabolite, M3. This metabolite was detected in human plasma and was the major urinary metabolite in the rat, and a relatively abundant human metabolite (comprising 18.9% of urinary drug related radioactivity). M3 formation in humans is predominantly catalysed by CYP2C9, with a lesser contribution from CYP1A1, CYP2C19 and CYP3A4. In vitro studies using recombinant CYP2C9 and microsomes or hepatocytes indicated that epoxide intermediate M3c is formed by CYP2C9. In human liver microsomes, M3c is subsequently hydrolysed to the dihydrodiol metabolite M4 by microsomal epoxide hydrolase. The epoxide intermediate was not detected in human plasma, urine or faeces samples, and is likely to be rapidly hydrolysed in vivo.<sup>11</sup> M4 was the major urinary metabolite in humans, comprising 25% of lesinurad associated radioactivity. This is an important point of difference between humans and the nonclinical species. Although M3 comprised 54% of urinary radioactivity in male rats, and 18% in females, M4 was only detected in one study in this species, where it accounted for 0.6% of urinary radioactivity in bile duct cannulated male rats (0.13% of dose). In the monkey, both M3 and M4 were minor metabolites, accounting for only 0.9% and 0.5% of urinary radioactivity, respectively after oral administration of lesinurad. It is proposed that in the monkey the epoxide intermediate, M3c, reacts with cysteine to form the cysteine adduct M9, which is a significant metabolite in this species. Trace amounts only of M4 were detected in the urine of TgHras2 mice.

M4 was not detected in plasma from rats or monkeys, but was present in plasma from humans. Study RDEA594-105-MET-M4 examined the concentration of M4 in human plasma samples from Study RDEA594-105, in which 9 healthy subjects received lesinurad at a dose of 400 mg. The mean C<sub>max</sub> and AUC<sub>0-24h</sub> in 6 subjects were 385 ng/mL and 1870 ng.h/mL, and the mean M4:lesinurad molar ratios for C<sub>max</sub> and AUC<sub>0-24h</sub> were 2.63% and 3.04%, respectively.

Nonclinical characterisation of human metabolites is warranted when that they are observed at exposures greater than 10% of the total drug related exposure and at significantly greater levels in humans than the maximum exposure seen in the toxicity studies.<sup>12</sup> M4 is therefore considered to be a disproportionate metabolite in humans.<sup>13</sup> The consideration of whether M4 (and its immediate precursor, the epoxide M3c) are adequately qualified in the repeat dose toxicity studies is discussed below (see 'Repeat Dose Toxicity').

There were some interspecies differences in the CYP isozymes responsible for lesinurad biotransformation. Formation of M3 in humans appears to be predominantly catalysed by CYP2C9, with a lesser contribution from CYP1A1, CYP2C19 and CYP3A4. In the rat, CYP2C11 catalysed the formation of M3 (with minor contributions from CYP1A1 and CYP3A2), whereas CYP2C75 was important for M3 formation in the monkey. Dealkylation

<sup>11</sup> European Medicines Agency, "ICH guideline M3(R2) – questions and answers. Step 5 (EMA/CHMP/ICH/507008/2011)", May 2012.

<sup>12</sup> European Medicines Agency, "ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. Step 5 (EMA/CPMP/ICH/286/1995)", December 2009.

<sup>13</sup> European Medicines Agency, "ICH guideline M3(R2) – questions and answers. Step 5 (EMA/CHMP/ICH/507008/2011), May 2012.

of M6 to form M6 was catalysed by CYP3A4 humans and by CYP3A8 in the monkey. Glucuronidation of lesinurad in human liver microsomes was predominantly catalysed by UGT1A1 and UGT2B7, with a lesser role played by UGT1A3.

Despite these considerable quantitative differences, all of the human metabolites were formed in the nonclinical species, making them qualitatively adequate models for the purposes of toxicological assessment. The oxidative metabolites M3 and M4 were the major human plasma and urinary metabolites, with the debrominated metabolites M2 and M5 being the most important faecal metabolites.

The relative importance of the renal route for excretion of lesinurad and its metabolites showed both species and (where studied) gender specific effects. In male subjects (Study RDEA594-112) 63% of the administered dose was excreted in the urine. Urinary excretion accounted for 36% and 33% of an oral dose administered to female rats and male monkeys, respectively, but only 12% in male rats. In TgHras2 mice, the renal route accounted for 14% and 17% of the dose in males and females, respectively. A study in bile duct-cannulated rats indicated that approximately 50% of intraduodenally administered radioactivity was reabsorbed through enterohepatic recycling.

In conclusion, the pharmacokinetic data provide support for the selection of the nonclinical species used in the repeat dose toxicity studies, but draw attention to some limitations. The nonclinical species showed the same basic characteristics of absorption and clearance as humans, and the extent of binding to proteins in plasma was comparable between species. However, although there were no unique human metabolites, M4 is considered to be a disproportionate metabolite, and a comparisons of relative exposure levels in the repeat dose toxicity studies are an important component of the toxicological assessment (see 'Repeat-Dose Toxicity').

### Pharmacokinetic drug interactions

As already mentioned, lesinurad is a substrate of CYP2C9, UGT1A1 and UGT2B7. Approximately half of an oral dose of lesinurad is cleared via CYP2C9 metabolism, and in clinical studies co-administration with the CYP2C9 inhibitor fluconazole increased the lesinurad AUC by 56%. Higher lesinurad exposures were also observed in subjects who were genotypically classified as being moderate or poor CYP2C9 metabolisers, compared with extensive metabolisers. Co-administration with rifampin, a moderate CYP2C9 inducer, decreased lesinurad AUC by 38%, and decreased the maximal lowering of serum uric acid from 39% to 30%. In vitro studies found evidence of lesinurad inhibition of CYP2C8 and CYP2C9, but this does not appear to be clinically relevant. Induction of CYP3A4 activity by lesinurad in vitro may be of clinical relevance, as exposures of the CYP3A substrates sildenafil and amlodipine were reduced, although atorvastatin and colchicine exposures were unaffected. Induction of CYP2C8 and CYP2C9 was observed in vitro, but appears not to be clinically relevant.

The formation of M4 in human liver microsomal preparations in vitro is mediated by microsomal epoxide hydrolase (mEH). Based on studies with human liver microsomes, known inhibitors of mEH (such as sodium valproate) may interfere with the metabolism of lesinurad, and lead to accumulation of the epoxide intermediate M3c.

A comprehensive series of studies examined the potential for interactions based on lesinurad being either a substrate or inhibitor of a wide range of membrane transporter proteins. Lesinurad was a substrate of organic anion transporting polypeptide (OATP)1B1, the organic cation transporter OCT1 and the kidney transporters OAT1 and OAT3. Co-administration of lesinurad with the OAT3 inhibitor cimetidine did not affect the renal excretion of lesinurad in rats, but co-administration with probenecid (which inhibits OAT1, OAT2, OAT3 and OAT4) reduced lesinurad excretion by 44%. Therefore, clinical

interactions between lesinurad and inhibitors of organic anion transport should be considered.

Lesinurad itself showed potential to inhibit OAT1 and OAT3, OATP1B1 and OCT1 in vitro, with the most potent inhibition being against OATs 1 and 3. Based on the IC<sub>50</sub> for lesinurad inhibition of these transporters and assuming a maximum unbound concentration of lesinurad in plasma of 0.213 µM, the in vitro data suggest that their inhibition is unlikely to be of clinical significance. This was supported by lesinurad's lack of effect on the mean urinary excretion of the OAT1/3 substrates zidovudine and tenofovir in rats. In addition, there was no effect of lesinurad on metformin exposure in clinical studies.

Lesinurad is proposed to be used in combination with a XO inhibitor (allopurinol or febuxostat) when additional therapy is warranted. Potential pharmacokinetic interactions were investigated in repeat dose toxicity studies with lesinurad in combination with both of these agents. Allopurinol did not affect the pharmacokinetics of lesinurad, although there was a tendency for allopurinol exposures to increase. Lesinurad did not affect the pharmacokinetics of febuxostat, although lesinurad exposures tended to increase. None of these effects were remarkable, and no interactions were found clinically.

## **Toxicology**

### **Acute toxicity**

Acute toxicity studies were not submitted, but the acute oral toxicity was low based on the maximum non-lethal acute doses in the 6 and 12 month repeat dose toxicity studies in rats and monkeys (300 and 600 mg/kg/day respectively, corresponding to relative exposures of 23 and 37 based on C<sub>max</sub>). The cause of death for rats dosed at 600 mg/kg in the 6 month repeat dose study (relative exposure 28) was kidney tubular degeneration intestinal epithelial cell necrosis. In monkeys, deaths were attributed to severe diarrhoea, emesis and decreased food consumption associated with gastrointestinal toxicity.

### **Repeat dose toxicity**

Consistent with the relevant ICH guidelines,<sup>14</sup> GLP compliant studies of up to 6 months duration were conducted in rats and 12 months in monkeys, using the clinical route and dosing frequency, and with appropriate recovery groups. The study design and conduct were appropriate, and the doses selected were adequate for toxicological assessment. The selection of the monkey as the non-rodent species was based on the absence of metabolite M4 in dogs. The toxicology program included genotoxicity, carcinogenicity and developmental and reproductive toxicity studies, as well as combination repeat dose toxicity studies with allopurinol and febuxostat. No independent immunotoxicity or antigenicity studies were conducted based on the absence of any histological or haematological effects on immune parameters.

### **Relative exposure**

Exposure ratios have been calculated based on animal: human plasma AUC<sub>0-24h</sub>. Human reference values are from Phase I Clinical Study RDEA594-105 in healthy subjects. The AUC data used for animals is the mean of male and female values on the last sampling

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<sup>14</sup> European Medicines Agency, "ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (EMA/CPMP/ICH/286/1995)", December 2009; European Medicines Agency, "Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1)", 18 March 2010; European Medicines Agency, "ICH harmonised tripartite guideline S4, Step 5: Duration of Chronic Toxicity testing in Animals (Rodent and Non Rodent Toxicity Testing) (CPMP/ICH/300/95)", May 1999.

occasion. The sponsor has cited slightly higher values for relative exposure based on the mean of the AUC data throughout the study. Using the last sampling period provides a more conservative estimate of relative exposure as AUC values declined with repeated dosing (probably indicative of minor auto induction). Despite this, the relative exposures achieved in the mouse and rat studies were high, while those in the monkey studies were adequate.

**Table 2. Relative exposure in repeat-dose toxicity and carcinogenicity studies.**

Species	Study duration	Dose (mg/kg/day)		AUC <sub>0-24h</sub> (µg·h/mL)	Exposure ratio <sup>#</sup>
<b>Mouse</b> (TgRash2)	4 weeks	60		528	19
		125		954	34
		250		1730	62
	6 months [carcinogenicity]	♂	15	89.8	3.2
		♀	30	232	8.3
		♂	45	260	9.3
		♀	90	724	26
♂		125	926	33	
♀	250	1760	63		
<b>Rat</b> (SD)	28 days	10		23.1	0.82
		30		87.1	3.1
		100		425	15
		300		1093	39
	6 months	10		26	0.93
		30		97	3.5
		100		672	24
		300		1017	36
		600 <sup>a</sup>		3520	126
	2 years [carcinogenicity]	25		114	4.1
		75		555	20
		200		975	35
	<b>Monkey</b> (Cynomolgus)	12 months	30		32.5
100			83	2.9	
300			138	4.9	
600			321	11	
<b>Human</b> (healthy volunteers, male)	steady state	200 mg		28.0	-

<sup>#</sup> = animal: human plasma AUC<sub>0-24h</sub>; <sup>a</sup> Day 22 value;

### Major toxicities

The major target organs for lesinurad were the kidney and intestines, with some effects also observed on the liver and thyroid in rats, and the bile duct in rats and monkeys.

Renal toxicity is not unexpected since the kidney is the target organ for lesinurad pharmacodynamic activity. Renal tissues had the highest concentrations of radioactivity following administration of <sup>14</sup>C lesinurad to rats, and the kidney is the predominant excretory organ for the unchanged drug. In the renal function safety pharmacology study in rats evidence of pharmacodynamic activity included increased urinary excretion of uric acid, protein, calcium, phosphorous and electrolytes, and decreased creatinine clearance, following administration of single doses ≥ 300 mg/kg (NOEL 100 mg/kg, corresponding to 12 times the clinical C<sub>max</sub>). This is not unexpected given the relative low level of activity for lesinurad against rodent URAT1 in vitro compared with the human transporter. There was some variability in the NOEL for renal histopathological findings in the repeat dose

toxicity studies in rats. Renal tubular epithelial degeneration, associated with increased serum BUN and creatinine, was observed in the 14 day study from 100 mg/kg in males, and 300 mg/kg/day in females. In the 28 day study, minimal to mild kidney tubular degeneration was seen in the interim necropsy on day 15, but no renal histopathological findings were reported in the terminal necropsy at doses  $\leq$  300 mg/kg/day, nor in the 6 month repeat dose study at this dose. However, mortality due to renal toxicity was reported at 600 mg/kg/day in this study. The time dependence of renal toxicity findings in the repeat dose toxicity studies in rats is suggestive of a possible adaptive response. However, in contrast to the longer duration repeat dose toxicity studies, renal toxicity was reported in the carcinogenicity study in which rats were dosed for 2 years. The renal effects observed in this study consisted of tubular epithelial degeneration, vacuolation and dilatation, accompanied by interstitial inflammation. They were most severe in animals exhibiting papillary necrosis or loss. The treatment related cortical pathology was mostly restricted to the HD level of 200 mg/kg/day, and was considered to be an adverse effect of treatment with lesinurad in this study. However, rats are more susceptible to papillary necrosis than humans, as they do not have multi-papillary kidneys.<sup>15</sup> The NOAEL for renal toxicity in this study of 75 mg/kg represents a relative exposure of 20 times the clinical exposure at the MRHD.

Renal toxicity was also observed in transgenic mice in the 4-week repeat dose study. Increased renal weight was associated with cortical tubular regeneration and degeneration or necrosis, predominantly in males dosed at 500 mg/kg/day, with a NOEL of 250 mg/kg/day, corresponding to a relative exposure of 62. No renal toxicity was reported in the 6 month carcinogenicity study in transgenic mice, where the HD levels were 125 and 250 mg/kg/day in males and females respectively (relative exposures of 33 and 63, respectively). In addition, no renal toxicity was reported in repeat dose toxicity studies in monkeys, other than an increase in renal weight, which is not considered to be adverse. Like the rat, this species also has a unipapillate kidney (Frazier, 2013). It should be noted however that the relative exposure levels achieved in this species were lower than those achieved in rats, with a maximum relative exposure of 11 in the 12 month repeat dose study.

It is accepted that the renal toxicity observed in rats may represent a species-specific effect. However, in view of the concerns for the appropriateness of the nonclinical species with lesinurad (based on a relative lack of activity for lesinurad against the pharmacological target protein URAT1 in rodents, as well as other interspecies differences in uric acid homeostasis) a conservative approach may be justified. This is also based on the kidney being the pharmacological target and organ of lesinurad excretion. Considering the dataset as a whole, the NOAEL for renal toxicity in the most sensitive species is 75 mg/kg/day in the 2 year carcinogenicity study, corresponding to a relative exposure of 20 times the clinical exposure at the Maximum Recommended Human Dose (MRHD).

Gastrointestinal toxicity was observed in all species, and was a dose limiting toxicity in rats and monkeys. As already discussed, in the safety pharmacology study, administration of single oral doses of lesinurad reduced gastrointestinal motility of rats. The mechanism underlying this effect is not known, as no secondary pharmacological activity was found in an extensive screen. In the repeat-dose toxicity studies in monkeys a dose related incidence of emesis, soft stool and diarrhoea was reported at  $\geq$  300 mg/kg/day, and mortalities at higher doses were preceded by decreased food consumption and body weight. Dose limiting gastrointestinal toxicity in rats consisted of enteropathy, characterised by single cell necrosis of the crypt epithelium of the duodenum, jejunum, ileum, caecum and/or colon. In the 6 month repeat dose study gastric erosions or haemorrhage and congestion were observed with doses  $\geq$  100 mg/kg at the 3 month

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<sup>15</sup> Frazier KS. (2013). Urinary System. In: Toxicologic Pathology: Nonclinical Safety Assessment, Ed Sahota, P.S. CRC Press, Boca Raton.



interim sacrifice, but not after 6 months of treatment, suggestive of a possible adaptive response. Single cell necrosis of the small or large intestine was observed at a low frequency in the 2 year carcinogenicity study at  $\geq 75$  mg/kg. In the carcinogenicity study in transgenic mice inflammation in the glandular stomach, fundal epithelial hyperplasia, and increased prominence of mucous cells in the foveolar glands was observed at  $\geq 30$  mg/kg/day (corresponding to 8 times the clinical exposure at the MRHD). The NOAELs in the rat and monkey were 25 mg/kg/day (based on the carcinogenicity study) and 300 mg/kg/day, respectively, which represent relative exposures of 4 and 5, respectively.

#### *Liver and bile duct*

Increased hepatic weight was observed in all species, and was associated in rodents with centrilobular hepatocyte hypertrophy. This effect is commonly seen in rodents in response to xenobiotic administration, and is an adaptive response associated with CYP enzyme induction. Additional hepatotoxic effects seen in transgenic mice in the 6 month carcinogenicity study included hepatocyte necrosis at doses  $\geq 45$  mg/kg/day in males and 90 mg/kg/day in females (relative exposures of 9 and 26 based on AUC), with hepatocyte mineralisation observed at higher exposure levels. In rats similar pathological findings were associated with increases in serum transaminases and total bilirubin in the 14 day study at doses of 1000 mg/kg. The NOELs for hepatic effects in the carcinogenicity studies were 15 and 45 mg/kg in male and female mice, respectively (relative exposures of 3 and 26), and 25 mg/kg in rats (relative exposure 4).

In addition, an increase in bile duct hyperplasia was seen in the carcinogenicity study at  $\geq 75$  mg/kg/day, and in the combination toxicity study with allopurinol, associated with lesinurad doses  $\geq 100$  mg/kg/day. The increased hepatic weight in monkeys was not associated with any clinical chemistry findings or microscopic changes, but bile duct hyperplasia was seen in the 12 month study after 6 months of dosing at  $\geq 300$  mg/kg in males and 600 mg/kg in females (relative exposures 5 and 11, respectively, based on AUC). The sponsor has speculated that the development of bile duct hyperplasia in this species may be associated with the increase in formation of M6 and M8 with repeated dosing in this species. M6 is mainly eliminated in the bile, and the glucuronidated forms (collectively termed M8) are excreted in bile or urine. This suggestion is possible, but has not been proven.

Thyroid follicular epithelial hypertrophy was observed in rats at 100 mg/kg/day in the 6 month study. This is a common finding in rats in association with hepatocellular hypertrophy and CYP enzyme induction, and is not thought to be relevant in humans.<sup>16</sup>

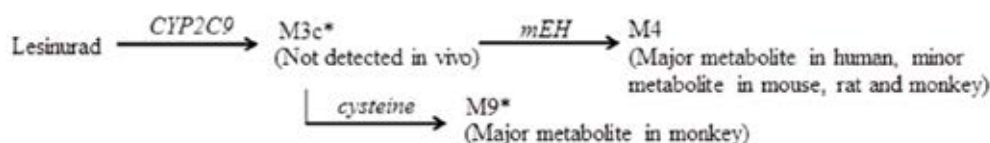
In Combination Toxicity studies in rats with the XO inhibitors allopurinol and febuxostat there was minimal evidence of renal toxicity when lesinurad was dosed alone at up to 300 mg/kg/day for 13 weeks. Lesinurad associated increases in serum creatinine and BUN were seen in the allopurinol combination study only. The kidney was the principal target organ for both allopurinol and febuxostat related toxicity, but there was no evidence of synergistic renal toxicity when lesinurad was co-administered with either of the XO inhibitors. There was evidence that co-administration of lesinurad attenuated febuxostat mediated renal toxicity, but the potential mechanism underlying this is unclear. Since the kidney was also a target organ for lesinurad toxicity in the repeat-dose studies it is reassuring that no exacerbation of renal toxicity was seen in these combination studies. However, the duration of these studies was only 13 weeks. In addition, the sponsor notes that the systemic exposure for oxypurinol in rats, the active metabolite of allopurinol and main circulating entity in humans, was lower than the human exposure in the clinical study at the most commonly used dose of 300 mg/day. No other toxicological finding showed any evidence of synergistic or additive effects, and no new toxicities emerged.

<sup>16</sup> Capen CC. Mechanistic data and risk assessment of selected toxic endpoints of the thyroid gland. *Toxicologic Pathology* 25: 39-48 (1997).

### Metabolite assessment

As discussed in the 'Pharmacokinetics' section of this assessment, metabolites M4 and the epoxide intermediate M3c are considered to be disproportionate metabolites in humans, and need to be assessed in the repeat dose toxicity studies (M3c and M4 could not be tested individually owing to the inherent instability of M3c and the lack of sufficient material for testing).<sup>17</sup> M3c is formed from lesinurad by the action (in humans) of CYP2C9, and is then rapidly hydrolysed by microsomal epoxide hydrolase to M4. Together M3 and M4 are the major urinary metabolites in humans. M3 was the major urinary metabolite in rats, but constituted only 1.9% of drug related material in the urine of monkeys. M4 was present at much lower levels in the urine of rats and monkeys compared with humans. In the monkey, M3c detoxification is mainly due to cysteine adduction to form M9, a major component of bile in this species. A diagrammatic summary of the elimination pathways for the epoxide intermediate M3c in rats, monkeys and humans is shown below (Figure 2). M3c could not be detected in plasma, urine or bile in any species owing to its very short biological half-life, but can be calculated based on M4 and M9 levels in each species.

**Figure 3. In vivo elimination of Epoxide Intermediate M3c.**



An interspecies comparison of relative exposure for the calculated amount of epoxide M3c is presented in the following table. As previously discussed, M4 was not detected in the plasma of rats or monkeys, and so exposure comparisons were made based on urinary data. The human data were calculated from Studies 112 CSR and 105 CSR, where the amount of epoxide formation was estimated from the amounts of M4 in urine and faeces following oral administration of 600 mg <sup>14</sup>C lesinurad in a liquid formulation (adjusted to a 200 mg oral capsule dose using a correction factor of 4.39). Relative exposure has been calculated as animal: human amount of epoxide on a mg/kg body weight basis, and also based on mg per g of liver, since M3c will be formed in this organ. This calculation is preferred, since metabolism of M3 to M4 (or M9), via M3c, will be occurring in the liver.

**Table 3. Relative exposure comparison for calculated Epoxide Intermediate M3c.**

Species	Dose	Calculated Epoxide Amount (0-24 h)			Relative Exposure	
		Total (mg)	Per Kg BW	mg per g liver wt	mg/kg BW	mg/g liver wt
Mouse	100 mg/kg	Trace	NC	NC	NC	
Rat	200 mg/kg	0.074	0.27	0.006	0.79	0.43
Monkey	300 mg/kg/day	63.5	25	1.1	74	88
Human	200 mg	29.5	0.34	0.014	NA	

NA = not applicable; NC = not calculable;

The relative exposure could not be calculated for the transgenic mouse, since only trace amounts of M4 were obtained in the metabolite study (Study SR11-037). The rat data are based on Study SR12-032, calculating the amount of epoxide based on metabolite M4 in urine comprising 0.13% of the administered dose. Liver weight for rats is assumed to be 45 g/kg body weight. For the monkey, data from Study SR10-029 were used to calculate the amount of epoxide formed, based on the sum of M4 and M9 detected in urine, bile,

<sup>17</sup> European Medicines Agency, "ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. Step 5 (EMA/CPMP/ICH/286/1995)", December 2009; European Medicines Agency, "ICH guideline M3(R2) – questions and answers. Step 5 (EMA/CHMP/ICH/507008/2011)", May 2012.

faeces and liver. The sponsor claims that based on a relative exposure of 0.79 in the rat in the carcinogenicity study at the NOEL and 82 in the 12 month monkey study at the NOAEL the epoxide M3c has been qualified. As already mentioned, comparisons based on liver exposure are preferred, since this is the site of epoxide formation and detoxification. The relative exposure in the rat carcinogenicity study based on the calculated liver concentrations is only 0.4, and therefore it is considered that M3c has not been adequately assessed in a carcinogenicity study. However, the level of M3c exposure in the rat micronucleus assay is expected to be approximately 4.6 times higher, indicating that M3c is likely to have been adequately assessed in the in vivo genotoxicity assay (see below). Only trace levels of M4 were detected in mice, so M3c was not adequately assessed in the carcinogenicity study in transgenic mice. However, the calculated relative exposure in the 12 month repeat dose toxicity study in monkeys provides a high safety margin.

Relative exposures have also been calculated for metabolite M4, as shown in the following table. In the rat, M3 was the predominant urinary metabolite, accounting for 27.7% of urinary radioactivity (5.87% of dose, with a further 2.99% of the dose excreted in bile). M4 was not detected in bile, and accounted for only 0.6% of urinary radioactivity (accounting for 0.13% of the administered dose). This is in contrast with the data from humans, where M3 and M4 accounted for 18.9% and 24.8% of urinary radioactivity, respectively. These data suggest that clearance of M3 and M4 in the rat is likely to be more efficient than in humans, and the urinary data probably overestimate systemic exposure in rats. Thus the relative exposures of 0.78 in the rat (or 0.4 based on estimated liver exposure) may be over-estimated. M4 has not been adequately assessed in the mouse and rat carcinogenicity studies, although its genotoxicity is considered to have been adequately assessed in the rat micronucleus assay. The estimated exposure data in the monkey represents a low multiple of the human exposure at the MRHD.

**Table 3. Relative exposure comparison for Metabolite M4.**

Species	Dose	Calculated M4 Amount (0-24 h)			Relative Exposure	
		Total (mg)	per Kg BW	mg per g liver wt	mg/kg BW	mg/g liver wt
Mouse	100 mg/kg	Trace	NC	NC	NC	
Rat	200 mg/kg	0.077	0.28	0.006	0.78	0.43
Monkey	300 mg/kg/day	2.7	1.19	0.05	3.1	3.6
Human	200 mg	30.7	0.36	0.014	NA	

NA = not applicable; NC = not calculable

### Genotoxicity

The genotoxicity of lesinurad was assessed in a bacterial reverse mutation assay, a chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells in vitro and a rat micronucleus assay in vivo. The range of studies and their design and conduct complied with the ICH guideline.<sup>18</sup> Lesinurad was negative in the Ames test, and did not produce a biologically relevant increase in chromosomal aberrations in vitro, or any biologically relevant increases in micronuclei in vivo. Systemic exposures at the highest dose tested in the micronucleus assay were 45 and 159 times the clinical exposure at the MRHD based on Cmax and AUC, respectively.

The genotoxicity of M4 was not tested directly since it could not be synthesised or isolated in sufficient quantities, but it does not possess any structural alert. Similarly, M3c could not be tested directly for genotoxicity as it is inherently unstable. The estimated systemic

<sup>18</sup> European Medicines Agency, "ICH guideline S2(R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use (EMA/CHMP/ICH/126642/2008)", March 2008.

exposure for M3c and M4 at the high dose (HD) level in the micronucleus assay would be approximately 4.6 times that of the HD level in the rat carcinogenicity assay, based on the ratios of exposure at the HD levels in the micronucleus and carcinogenicity assays. As discussed above, M4 and its precursor M3c were not adequately assessed in the rat carcinogenicity assay based on calculated relative liver exposure data, but acceptable levels of M4 and M3c exposure are likely to have been achieved in the micronucleus assay. Therefore, the lack of genotoxicity data with M4 and M3c is not considered to be a deficiency. Metabolite M6 was tested in the Ames test, and was non genotoxic.

### **Carcinogenicity**

Carcinogenicity was assessed in a 6 month TgrasH2 transgenic mouse model as well as a standard 2 year rat assay. The transgenic mouse model is accepted as a suitable alternative to a second 2 year rodent bioassay. The design and conduct of both studies complied with their respective ICH guidelines.<sup>19</sup> The dose levels selected in both models were based on the results of short term toxicity tests, and are considered to be adequate. In addition, the metabolism of lesinurad was investigated in both species, including an assessment of changes in metabolic profile with long term dosing in rats.<sup>20</sup> In the transgenic mouse study there was no significant effect of lesinurad treatment on survival, and no evidence of neoplasia. The positive control group showed the expected decrease in survival, which was primarily due to the development of neoplasms including lymphosarcoma, haemangiosarcoma and squamous cell carcinoma. The NOEL for carcinogenicity in the transgenic mouse model corresponds to relative exposures of 33 and 63 in males and females, respectively. Lesinurad treatment was not associated with increased neoplasia in the 2 year rat carcinogenicity assay, and the NOEL of 200 mg/kg/day corresponds to a relative exposure of 35. As discussed above, owing to the relative lack of M4 formation in the transgenic mouse and a low level in rats, the epoxide metabolite M3c and metabolite M4 are considered not to have been adequately assessed in the rat carcinogenicity studies. However, M3c and M4 are considered to be non-genotoxic based on the rat micronucleus assay.

### **Reproductive toxicity**

Reproductive toxicity studies included a fertility study in male and female rats, embryofoetal development studies in rats and rabbits and a rat postnatal development assay. The design and conduct of these studies complied with ICH guidelines.<sup>21</sup> Relative exposure data are provided below. The exposures achieved in the repeat dose toxicity studies are high multiples of the human exposure at the MRHD. Placental transfer of lesinurad and its metabolites was not investigated. Lactational transfer of lesinurad and its metabolites was demonstrated in rats, with radioactivity levels in milk being comparable to those in plasma.

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<sup>19</sup> European Medicines Agency, "CHMP conclusions and recommendations on the use of genetically modified animal models for carcinogenicity assessment (CPMP/SWP/2592/02 Rev 1)", 23 June 2004; European Medicines Agency, "Note for guidance on carcinogenic potential (CPMP/SWP/2877/00)", 25 July 2002; European Medicines Agency, "ICH Topic S1B. Carcinogenicity Testing: Testing for carcinogenicity of pharmaceuticals (CPMP/ICH/299/95)", March 1998.

<sup>20</sup> European Medicines Agency, "ICH Topic S1C(R2). Dose selection for carcinogenicity studies of pharmaceuticals (EMA/CHMP/ICH/383/1995)", October 2008.

<sup>21</sup> European Medicines Agency, "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005)", 24 July 2008; European Medicines Agency, "ICH Topic S5 (R2). Detection of toxicity to reproduction for medicinal products and toxicity to male fertility (CPMP/ICH/386/95)", March 1994.

**Relative exposure**

See Table 4.

**Table 4. Relative exposure comparison for Metabolite M4.**

Species	Study	Dose (mg/kg/day)	AUC <sub>0-24h</sub> (µg·h/mL)*	Exposure ratio <sup>#</sup>
Rat (SD)	Fertility and early embryonic development	75	<sup>a</sup> 277	10
		150	<sup>a</sup> 702	25
		300	<sup>b</sup> 1017	36
Rat (SD)	Embryofoetal development	75	277	10
		150	702	25
		300	1370	49
Rabbit (NZW)	Embryofoetal development	25	113	4.0
		75	357	13
		125	1775	63
Rat (SD)	Peri- and postnatal	100	<sup>c</sup> 497	18
		200	-	-
		300	<sup>c</sup> 1370	49
Human (healthy volunteers)	steady state	200 mg	28	-

# = animal: human plasma AUC<sub>0-24h</sub>; \* mean of Gestational Day (GD) 6 & GD17 in rat, and mean of GD7 & GD20 in rabbit

a. Toxicokinetic data are taken from the embryofoetal toxicity study, noting that these data are from pregnant rats

b. Toxicokinetic data taken from 6 month repeat dose study (SR08-095)

c. AUC exposure taken from the dose range finding study SR09-068.

Administration of lesinurad to male and female rats at doses of 300 mg/kg/day (exposures 36 times the clinical exposure at the MRHD) was associated with mortality in females during the pre-mating phase and toxicity during gestation. However, this dose had no adverse effects on male or female fertility or reproductive performance. Maternal mortalities and toxicity were also observed for dams dosed at  $\geq 300$  mg/kg/day in the embryofoetal toxicity studies in rats. Embryofoetal viability was reduced, but this was most likely secondary to maternal toxicity. Maternal treatment with lesinurad at up to 300 mg/kg/day (relative exposure of 49) had no effects on foetal growth, and there were no treatment related malformations. Mortalities and severe maternal toxicity were observed in the rabbit embryofoetal toxicity, and the NOAEL for maternal toxicity was  $<25$  mg/kg/day (4 times the clinical exposure at the MRHD). The HD level of 125 mg/kg/day was terminated early because of the maternal toxicity. Owing to the high maternal toxicity and also a high incidence of non-pregnant animals and accidental deaths only 15 litters were available for evaluation at the middle dose (MD) level of 75 mg/kg/day, which is below the recommended litter number of 16-25.<sup>22</sup> Reduced foetal viability was evident at the MD level, but there was no treatment related effect on foetal external, soft tissue or skeletal malformations at  $\leq 75$  mg/kg/day. The NOEL for embryofoetal toxicity was 25 mg/kg/day, which corresponds to a relative exposure of 4.

Maternal toxicity was evident at doses  $\geq 200$  mg/kg/day in the peri and postnatal reproductive toxicity study in rats (NOAEL 100 mg/kg/day, corresponding to 18 times the clinical AUC). Consequently, treatment with lesinurad at these dose levels was associated with reduced gestation index and live born pups, increased still births and neonatal deaths and absence of suckling. Body weight and body weight gains through to postnatal day

<sup>22</sup> European Medicines Agency, "ICH Topic S 5 (R2) Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility, Step 5: (CPMP/ICH/386/95)", March 1994.

(PND) 50 were reduced, and pups from these groups showed delayed sexual maturation. These effects did not have any consequences for subsequent performance in behavioural and reproductive function. The NOAEL for growth and development is 100 mg/kg/day (relative exposure 18).

### ***Pregnancy classification***

The sponsor has proposed Pregnancy Category B1.<sup>23</sup> This is acceptable since adverse foetal effects are considered to be secondary to maternal toxicity, which was only evident at high relative exposures. The rabbit was the more sensitive species, and the NOAEL for maternal and foetal toxicity was 4. Despite this maternal toxicity, there was no evidence of foetal malformations in rats or rabbits at relative exposures of up to 49 and 13, respectively.

### **Phototoxicity**

Lesinurad has its peak absorbance in the UVB range and shows good photostability under UV and visible light. A study in albino and pigmented rats shows low distribution to light exposed tissues and a short elimination half-life. The phototoxic potential is considered to be low, and additional phototoxicity testing is not warranted.<sup>24</sup>

### **Impurities**

The proposed specifications for impurities and degradants in the drug substance or product have been adequately qualified.

### **Paediatric use**

Lesinurad is not proposed for paediatric use and no specific studies in juvenile animals were submitted. This is acceptable.

## **Nonclinical summary and conclusions**

### **Summary**

- The submission was comprehensive and of high quality, consisting of GLP compliant studies that addressed the relevant ICH guidelines for nonclinical studies. Humans differ considerably from other mammals (including most primates) in their uric acid homeostasis, as they lack the enzyme uricase. As a result, the nonclinical species have some limitations in their suitability as models for human pharmacodynamic effects, and possibly also for assessment of toxicity.
- Lesinurad acts on URAT1, the predominant renal tubular apical membrane transporter responsible for uric acid reabsorption. Lesinurad inhibited hURAT1 in vitro (IC<sub>50</sub> = 7.3 µM). Inhibition of the human renal organic anion transporter OAT4 (IC<sub>50</sub> = 3.7 µM) may also contribute to the pharmacodynamic action of lesinurad. These activities are likely to be relevant based on urinary lesinurad concentrations of approximately 50 µM. In vitro data indicate that lesinurad's uricosuric effect is not mediated by inhibition of GLUT9 (the predominant pathway for uric acid exit at the

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<sup>23</sup> Category B1: "Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage."

<sup>24</sup> European Medicines Agency, "ICH Guidance S10 on photosafety evaluation of pharmaceuticals (EMA/CHMP/ICH/752211/2012)", 25 August 2015.

basolateral membrane), XO or purine nucleoside phosphorylase. Lesinurad's major metabolites and the disproportionate human metabolite M4 are unlikely to contribute to its pharmacodynamic activity.

- Lesinurad had minimal activity against mouse or rat URAT1, which share only 75% and 73% protein sequence homology with hURAT1. Activity against monkey URAT1 was not investigated. A preliminary investigation in a New World monkey species, *Cebus apella*, indicated that it was not a suitable model to study the uricosuric effects of lesinurad. However, the uricosuric effect of lesinurad (as a metabolite of RDEA806) had already been demonstrated in clinical studies; a strong linear correlation was found between uric acid excretion and the urinary excretion of lesinurad, confirming that lesinurad was responsible for the uricosuric effect of RDEA806. Thus the nonclinical data provide information on the likely mechanism of action of lesinurad as a uricosuric agent in humans, but there are no supporting animal data in vivo owing to the lack of a suitable animal model.
- No clinically relevant secondary pharmacodynamic activity was identified in an extensive screen of receptors, ion channels and transporters, which was supported by functional assays as required.
- Safety pharmacology studies examining the CNS, cardiovascular, respiratory, renal and gastrointestinal systems did not reveal any safety issues of clinical relevance. The NOEL for reduced gastrointestinal motility corresponded to 24 times the C<sub>max</sub>. Increased urinary excretion of uric acid, protein, calcium, phosphorous and electrolytes, and decreased creatinine clearance was observed in the safety pharmacology study in male rats at 12 times the clinical C<sub>max</sub>.
- The basic characteristics of absorption and clearance in the nonclinical species are comparable to those observed in man. Exposures increased approximately in proportion to dose, and there were no notable gender differences. Mild autoinduction was evident in rats and monkeys based on reduced exposure levels after repeated dosing. The relative importance of the renal route for excretion of lesinurad and its metabolites showed both species and gender specific effects. In a clinical study in male subjects, 63% of the dose was excreted in the urine of male subjects, compared with 36% and 33% in female rats and male monkeys, respectively, and only 12% in male rats. Evidence of enterohepatic recycling was obtained in bile duct cannulated rats. A study in male and female nephrectomy rats indicated that lesinurad systemic exposures may be increased in increased in patients who are renally compromised.
- Metabolism in the nonclinical species was qualitatively similar to humans, involving oxidation and S-dealkylation by CYP isozymes, debromination by intestinal microflora, hydrolysis of an epoxide intermediate, M3c, by microsomal epoxide hydrolase (mEH) (or cysteine adduction in monkeys) and glucuronidation. Quantitatively, however, there are substantial interspecies differences in lesinurad metabolism. The dealkylation product M6 increased with repeated dosing in the monkey (and to a much lesser extent in the rat) to become the predominant moiety circulating in monkey plasma, whereas this pathway was relatively minor in humans.
- M4 (the product of M3 hydrolysis) was a disproportionate metabolite in humans. Estimated relative exposures for both M3c and M4 (based on mg/kg of body weight) were 0.8 in the rat carcinogenicity study at the NOEL, or 0.4 based on mg per g of liver. A relative exposure of 4.6 in the rat micronucleus assay suggests that M3c genotoxicity is likely to have been adequately assessed in vivo. In the monkey, relative exposures for M3c and M4 were 3.3 and 82, respectively on a mg/kg basis, with relative exposures in liver of 3.6 and 88, respectively. Only trace amounts of M4 could be detected in mice.

- Lesinurad was bound extensively to proteins in plasma from mouse, rat, dog, monkey and human, being approximately 98% bound in all species except the mouse ( $\geq 94\%$ ). Tissue distribution was mainly limited to the gastrointestinal tract, liver and kidney following oral administration of  $^{14}\text{C}$  lesinurad to albino and pigmented rats, with no indication of CNS penetration, no binding to pigmented tissues, and no evidence of retention.
- Lesinurad is a substrate of human CYP2C9, UGT1A1 and UGT2B7. Inhibitors of microsomal epoxide hydrolase may interfere with the metabolism of lesinurad, and lead to accumulation of the epoxide intermediate M3c. Lesinurad was a substrate of organic anion transporting polypeptide (OATP)1B1, the organic cation transporter OCT1 and the kidney transporters OAT1 and OAT3, and its excretion in rats was reduced when co-administered with probenecid, indicating that clinical interactions between lesinurad and inhibitors of organic anion transport are possible.
- Lesinurad itself showed potential to induce the activity of CYP3A4, but neither inhibition nor induction of CYP2C8 and CYP2C9 appeared to be clinically relevant. Similarly, inhibition of the human organic anion transporters OAT1 and OAT3 is unlikely to occur with therapeutic use. There were no notable pharmacokinetic interactions between lesinurad and the XO inhibitors allopurinol and febuxostat.
- The acute oral toxicity was low based on the maximum non-lethal acute doses in repeat dose toxicity studies in rats and monkeys. The cause of death for rats dosed at 600 mg/kg (relative exposure 28) in the 6 month repeat dose study was kidney tubular degeneration and intestinal epithelial cell necrosis of the crypt epithelium of the duodenum, jejunum, ileum, caecum and/or colon. In monkeys, deaths were attributed to severe diarrhoea, emesis and decreased food consumption associated with gastrointestinal toxicity.
- Renal toxicity in mice and rats included tubular vacuolation, dilatation or epithelial degeneration/papillary necrosis, associated with increased serum BUN and creatinine. There was considerable variability in the NOEL for renal histopathological findings in the repeat dose toxicity studies in rats, but considering the dataset as a whole, the NOAEL for renal toxicity in the most sensitive species was 75 mg/kg/day in the 2 year carcinogenicity study, corresponding to a relative exposure of 20 times the clinical exposure at the MRHD. No renal toxicity was reported in the 12 month monkey study at relative exposures of up to 11, or in the 6 month carcinogenicity study in transgenic mice (relative exposures of 33 and 63 in males and females, respectively).
- Gastrointestinal toxicity was observed in all species. In mice inflammation in the glandular stomach, fundal epithelial hyperplasia, and increased prominence of mucous cells in the foveolar glands was observed in the 6 month carcinogenicity study at relative exposure of 8. In rats, gastric erosions or haemorrhage and congestion were observed at the 3 month interim sacrifice, but not after 6 months of treatment, suggestive of a possible adaptive response. Single cell necrosis of the small or large intestine was observed at a low frequency in the 2 year carcinogenicity study at  $\geq 75$  mg/kg. The NOELs for gastric toxicity in the rat and monkey corresponded to relative exposures of 4 and 5, respectively.
- Increased hepatic weight was observed in all species, and was associated in rodents with centrilobular hepatocyte hypertrophy. Hepatocyte necrosis was observed in the mouse carcinogenicity study, with hepatocyte mineralisation observed at higher exposure levels. In rats similar pathological findings were associated with increases in serum transaminases and total bilirubin. The NOEL for liver effects in carcinogenicity studies corresponded to 3 and 26 in male and female mice, respectively, and 4 in rats. Thyroid follicular hypertrophy, commonly associated with hepatocellular hypertrophy



and CYP enzyme induction in rats (and not thought to be of relevance to humans), was seen in the 6 month study in this species.

- Combination toxicity studies in rats with the XO inhibitors allopurinol and febuxostat showed no evidence of synergistic or additive effects, and no new toxicities emerged. However, the kidney was the principal target organ for both allopurinol and febuxostat related toxicity, and as described above is also a target for lesinurad toxicity.
- Lesinurad does not show genotoxic potential based on the results of a bacterial reverse mutation assay, a chromosomal aberration assay and a rat micronucleus assay in vivo. Systemic exposures at the highest dose tested in the micronucleus assay were 45 and 159 times the clinical exposure at the MRHD based on Cmax and AUC, respectively. Metabolite M6 was non genotoxic in the Ames test.
- No lesinurad-associated neoplasia was observed in the 6 month transgenic mouse model and standard 2 year rat carcinogenicity assays. The NOELs corresponded to relative exposures of 33 and 63 in male and female mice, respectively, and 35 in the rat. Owing to the relative lack of M4 formation in the transgenic mouse and a low level in rats, the epoxide metabolite M3c and metabolite M4 are considered not to have been adequately assessed in the carcinogenicity studies. However, M3c is considered to be non-genotoxic based on the results of the rat micronucleus assay.
- Lesinurad did not affect male or female fertility or reproductive performance in rats (relative exposure of 36, which was associated with mortality in females during the pre-mating phase and toxicity during gestation). There was no evidence of teratogenicity or direct embryofetal toxicity in rats or rabbits following maternal dosing during the period of organogenesis at oral doses of up to 300 and 75 mg/kg per day (corresponding to approximately 49 and 13 times the human plasma exposure, respectively). Decreased embryofetal survival occurred only in association with maternal toxicity. Placental transfer of lesinurad and its metabolites was not investigated.
- Lactational transfer of lesinurad and its metabolites was demonstrated in rats, with radioactivity levels in milk being comparable to those in plasma. Maternal toxicity in the peri- and postnatal reproductive toxicity study in rats was associated with reduced adverse outcomes for the offspring, including reduced gestation index and live born pups, increased still births and neonatal deaths and absence of suckling, and although pups from these groups showed delayed sexual maturation there were no consequences for subsequent performance in behavioural and reproductive function. The NOEL for adverse effects on growth and development was 100 mg/kg/day (relative exposure 18).
- The phototoxic potential of lesinurad is considered to be low.

### Conclusions and recommendation

- The submission was comprehensive and of high quality, and the sponsor has considered all toxicological concerns. However, the validity of the nonclinical species for assessing the pharmacodynamic activity and toxicity of lesinurad in humans may be limited, as discussed below.
- The nonclinical data provide evidence that lesinurad's uricosuric effects in humans are likely to be mediated by inhibition of apical uric acid reabsorption through an effect on the human URAT1 transporter, with a possible additional effect mediated through inhibition of the organic anion transporter OAT4. No suitable in vivo animal model was found to investigate lesinurad as a potential treatment of hyperuricaemia in gout.

- Lesinurad has minimal activity against rodent URAT1, and the sensitivity of monkey URAT1 is unknown. In addition, serum uric acid concentrations are considerably lower in the nonclinical species compared with humans. Thus, rodents (and possibly also monkeys) are unlikely to be prone to renal tubular uric acid precipitation following administration of lesinurad, as occurs with other inhibitors of uric acid reabsorption in clinical use (for example, probenecid).
- Secondary pharmacodynamics and safety pharmacology studies did not identify any clinically relevant hazards.
- M4 was a disproportionate metabolite in humans, and is formed via an epoxide intermediate, M3c. Estimated relative exposures for both M3c and M4 based on mg/kg of body weight or mg per g of liver were subclinical at the NOEL in the rat carcinogenicity study (0.4-0.8). In the monkey, relative exposures for M3c and M4 were 3.3 and 82, respectively on a mg/kg basis, with relative exposures in liver of 3.6 and 88, respectively. Only trace amounts of M4 could be detected in mice, indicating that M3c and M4 were probably not adequately assessed in the carcinogenicity assay in that species.
- The target organs for lesinurad mediated toxicity were the kidney, gastrointestinal tract, liver, bile duct and thyroid. These effects are not anticipated clinically based on relative exposure levels at the NOEL being adequate multiples of human exposure at the MRHD.
- Lesinurad is not considered to pose a genotoxic or carcinogenic hazard. A relative exposure of 4.6 in the rat micronucleus assay suggests that M3c genotoxicity is likely to have been adequately assessed in vivo.
- There are no nonclinical objections to the registration of lesinurad, although the predictive value of the nonclinical data has limitations, mainly based on the lack of sensitivity of the pharmacological target to lesinurad in animals, and also to interspecies differences in uric acid homeostasis.

## IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

### Introduction

#### Clinical rationale

Uric acid is the end product of purine metabolism in man. It is produced in the liver through conversion of xanthine by the enzyme XO. Urate is poorly soluble and excessive accumulation in the body (hyperuricaemia) results in precipitation of urate crystals in tissues, typically in joints (gout).

Current treatments for the long-term prevention of hyperuricaemia/gout include XO inhibitors (allopurinol or febuxostat) and the uricosuric agent probenecid. XO inhibition results decreased production of urate. Probenecid is also thought to act through inhibition of urate reabsorption via URAT1 in the proximal tubule,<sup>25</sup> resulting in increased urate excretion.

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<sup>25</sup> Bach MH, Simkin PA. Uricosuric drugs: the once and future therapy for hyperuricaemia? *Curr Opin Rheumatol.* 26: 169-75 (2014).

The clinical rationale given by the sponsor is that combination of lesinurad with an XO inhibitor will result in both increased excretion and decreased production of urate, and will therefore enable a greater proportion of patients to achieve disease control, when compared to XO inhibitor monotherapy.

*Comment: The clinical rationale for lesinurad does not represent a novel approach to the treatment of hyperuricaemia with gout. Existing uricosuric agents such as probenecid have the same mechanism of action (URAT1 inhibition). Current clinical guidelines<sup>26</sup> recommend the combined use of a uricosuric agent and an XO inhibitor in subjects who cannot be managed with an XO inhibitor alone.*

Lesinurad was discovered as a metabolite of another agent, RDEA806, a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Treatment with RDEA806 was noted to be associated with reductions in serum urate concentrations.

### **Contents of the clinical dossier**

The submission contained the following clinical information:

- 32 clinical pharmacology studies, including 30 that provided predominantly pharmacokinetic data and 2 that provided predominantly pharmacodynamic data.
- 1 report analysing the effects of CYP2C9 polymorphism across various studies.
- 1 population pharmacokinetic analysis.
- 1 population PK/PD analysis.
- 1 population PK/safety analysis.
- 3 pivotal phase III efficacy/safety studies (301, 302 and 304).
- 2 Phase III open extension studies (306 and 307).
- 2 Phase II studies (202 and 203).
- 1 Phase III efficacy/safety study (303) that examined lesinurad monotherapy, an indication that is not being proposed with this application.
- 1 Phase III open extension study of lesinurad monotherapy (305).
- An Integrated Analysis of Efficacy and an Integrated Analysis of Safety, which contained tabulations of data to supplement those in the Summary of Clinical Efficacy and Summary of Clinical Safety.
- 2 reports analysing safety issues (renal toxicity and cardiovascular toxicity);
- Literature references.

### **Paediatric data**

The submission did not include paediatric data. The sponsor had obtained a waiver from the EMA on the grounds that the drug is “likely to be unsafe in this patient population”. According to the sponsor, the FDA had also agreed in principle that a full waiver was appropriate. Further details of these waivers were not provided.

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<sup>26</sup> Khanna D, et al. American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res.* 64: 1431-46 (2012); Richette P, et al. Updated EULAR Evidence-Based Recommendations for the Management of Gout. *Ann Rheum Dis.* 73 (Suppl 2): 783 (2014).

## Good clinical practice

All study reports included in the submission contained an assurance that each trial was conducted in accordance with the relevant articles of the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice (ICH GCP) consolidated guidelines.

## Guidance

The following EMA guidelines, which have been adopted by the TGA, are considered relevant to the current evaluation:

- Guideline on pharmacokinetic studies in man;<sup>27</sup>
- Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function;<sup>28</sup>
- Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function;<sup>29</sup>
- Guideline on the investigation of drug interactions;<sup>30</sup>
- Guideline on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.<sup>31</sup>

Compliance with these guidelines will be considered in the relevant sections of this report.

## Pharmacokinetics

### Studies providing pharmacokinetic data

Table 5 shows the studies relating to each pharmacokinetic topic.

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<sup>27</sup> European Medicines Agency, "Pharmacokinetic studies in man (Directive 75/318/EEC)", February 1987.

<sup>28</sup> European Medicines Agency, "Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function (CHMP/EWP/225/02)"; 23 June 2004.

<sup>29</sup> European Medicines Agency, "Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function (CPMP/EWP/2339/02)", 17 February 2005.

<sup>30</sup> European Medicines Agency, "Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2)", 21 June 2012.

<sup>31</sup> European Medicines Agency, "Guideline on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (CHMP/ICH/2/04)", November 2005.

**Table 5. Submitted pharmacokinetic studies.**

PK topic	Subtopic	Study ID	*
<b>PK in healthy adults</b>	General PK - Single dose	RDEA594-101	*
	- Multi-dose	RDEA594-102	*
	- Mass balance	RDEA594-112	*
	- Absolute bioavailability	RDEA594-131	*
	Bioequivalence† - Single dose	RDEA594-109	*
		RDEA594-129	*
		RDEA594-132	*
	Food effect	RDEA594-121	*
<b>PK in special populations</b>	Hepatic impairment	RDEA594-118	*
	Renal impairment	RDEA594-104	*
		RDEA594-120	*
	Japanese subjects	RDEA594-125	*
<b>Genetic/gender related PK</b>	Males vs. females	RDEA594-117	
	CYP 2C9 polymorphism	SR13-015	*
<b>PK interactions</b>	Allopurinol/colchicine	RDEA594-110	*
	Febuxostat	RDEA594-105	*
	Febuxostat/colchicine	RDEA594-111	*
	Naproxen/indomethacin	RDEA594-126	*
	Sildenafil	RDEA594-108	*
	Atorvastatin	RDEA594-113	*
	Amlodipine	RDEA594-114	*
	Fluconazole and rifampicin	RDEA594-122	*
	Tolbutamide	RDEA594-115	*
	Warfarin	RDEA594-123	*
	Repaglinide	RDEA594-116	*
	Frusemide and metformin	RDEA594-128	*

PK topic	Subtopic	Study ID	*
	Ranitidine	RDEA594-127	*
	Antacids	RDEA594-130	*
<b>Population PK and PK/PD analyses</b>	Population PK	n/a	*
	Population PK/PD for serum urate	n/a	*
	Population PK/PD for serum creatinine	n/a	*

\* Indicates the primary aim of the study.

† Bioequivalence of different formulations.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

A number of other PK studies were included in the submission, but have not been reviewed in this report as they were not considered relevant. Three Phase I comparative bioavailability studies compared the initial immediate capsule formulations (FN01 or FN07) with experimental formulations (various extended release formulations, a gastro-retentive formulation and an alternative tablet formulation). None of these experimental formulations were studied further and hence the data from these studies are not considered relevant to the current application. The sponsor closed another Phase II study due to slow enrolment.

The studies that were submitted but not reviewed in this report are listed in Table 6.

**Table 6. Pharmacokinetic studies not reviewed in this report.**

Study ID	Subtopic(s)	Reason
RDEA594-103	Comparative Bioavailability (in healthy volunteers)	Comparison of early 50 mg immediate release capsule formulation (FN01) with various extended release tablet formulations that were not developed further.
RDEA594-106	Comparative Bioavailability (in healthy volunteers)	Comparison of early 50 mg immediate release capsule formulation (FN01) with a gastro-retentive tablet formulation that was not developed further.
RDEA594-107	Comparative Bioavailability (in healthy volunteers)	Comparison of early 100 mg immediate release capsule formulation (FN07) with an alternative (sodium salt) tablet formulation that was not developed further.
RDEA594-204	PK in renal impairment; Interaction with allopurinol and colchicine.  (in subjects with gout)	Study closed due to slow enrolment. Only 4 of a planned 24 subjects enrolled. 3 of the 4 subjects received the wrong dose.

### Evaluator's conclusions on pharmacokinetics

The pharmacokinetics of lesinurad have been adequately defined. The submitted studies generally complied with the relevant EMA guidelines adopted by the TGA. Issues of potential concern are the following:

- Use of lesinurad in subjects with pre-existing moderate or severe renal impairment. On the available PK evidence it is possible that these subjects will have approximately twice the systemic exposure to lesinurad as other subjects. Lesinurad itself is nephrotoxic. If lesinurad dose reduction is not practical, it may be appropriate to avoid use of the drug altogether in these subjects.
- The effect of severe hepatic impairment on the PK of lesinurad has not been defined.
- Lesinurad causes mild induction of CYP3A4. This may be clinically significant in subjects receiving CYP3A4 substrates that have a narrow therapeutic window.
- Lesinurad results in some increased systemic exposure to indomethacin, a drug that is likely to use in subjects with gout. Although the clinical consequences of this interaction are unclear it would be appropriate to at least describe it in the PI.

### Pharmacodynamics

#### Studies providing pharmacodynamic data

Table 7 shows the studies relating to each pharmacodynamic topic.

**Table 7. Pharmacokinetic studies not reviewed in this report.**

PD Topic	Subtopic	Study ID	*
<b>Primary Pharmacology</b>	Effect on serum urate		
	- gout subjects	RDEA594-201	*
	- healthy volunteers	Various PK studies	
	Effect on urinary urate		
	- gout subjects	RDEA594-201	
	- healthy volunteers	Various PK studies	
<b>Secondary Pharmacology</b>	Effect on ECG/QT interval	RDEA594-117	*

\* Indicates the primary aim of the study.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

### Evaluator's conclusions on pharmacodynamics

The PD data are consistent with the stated mechanism of action for lesinurad. The data do not raise any specific issues of concern.

## Dosage selection for the pivotal studies

In Study 101, doses below 200 mg did not have a sustained effect on serum urate. Doses of 200, 400 and 600 mg were studied in gout patients in Phase I study and Phase II studies. Doses of 600 mg were only marginally more effective than 400 mg. Therefore, doses of 200 and 400 mg were chosen for the pivotal studies.

## Efficacy

### Studies providing efficacy data

#### *Studies RDEA594-301 (CLEAR 1) and RDEA594-302 (CLEAR 2)*

The studies were both randomised, double blind, placebo-controlled trials with three parallel groups. Subjects were randomised to receive lesinurad (200 or 400 mg) or placebo once daily for 12 months in combination with a stable dose of allopurinol.

The primary objective was to determine the efficacy of lesinurad by Month 6 when used in combination with allopurinol compared to allopurinol monotherapy.

The secondary objectives were to:

- Determine the efficacy of lesinurad by Month 12 when used in combination with allopurinol compared to allopurinol monotherapy;
- Determine the safety of lesinurad over 6 months and 12 months when used in combination with allopurinol;
- Investigate by a population analysis approach the influence of intrinsic factors (age, sex, race, body weight, renal function, concomitant medication use) on oral clearance of lesinurad;
- Determine the effect of lesinurad when used in combination with allopurinol on Health Related Quality of Life and physical function.

Study 301 was conducted at 181 sites in the USA between February 2012 and July 2014. The study report was dated 20 November 2014. Study 302 was conducted at 185 sites in 12 countries (USA, Canada, Spain, France, Belgium, Germany, Poland, Switzerland, the Ukraine, South Africa, Australia, and New Zealand) between December 2011 and July 2014. The study report was dated 21 November 2014.

#### *Study RDEA594 - 304 (CRYSTAL)*

Study 304 was a randomised, double blind, placebo controlled trial with three parallel groups. Subjects were randomised to receive lesinurad (200 or 400 mg) or placebo once daily for 12 months in combination with febuxostat.

The primary objective was to determine the efficacy of lesinurad by Month 6 when used in combination with febuxostat compared to febuxostat monotherapy.

The secondary objectives were to:

- Determine the efficacy of lesinurad by Month 12 when used in combination with febuxostat compared to febuxostat monotherapy;
- Determine the safety of lesinurad over 6 months and 12 months when used in combination with febuxostat;
- Investigate by a population analysis approach the influence of intrinsic factors (age, sex, race, body weight, renal function, concomitant medication use) on oral clearance of lesinurad;



- Determine the effect of lesinurad when used in combination with febuxostat on Health Related Quality of Life and physical function.

Study 304 was conducted at 141 sites in 6 countries (US, Canada, Poland, Switzerland, Australia, and New Zealand) between February 2012 and April 2014. The study report was dated 17 November 2014.

#### **Study RDEA594-303**

Study 303 was a randomised, double blind, placebo controlled trial with two parallel groups. The primary objective was to examine the efficacy of lesinurad *monotherapy* compared to placebo. The trial enrolled gout subjects who had a history of intolerance to, or a contraindication for, either allopurinol or febuxostat. Subjects were also to have a serum uric acid (sUA) level of  $\geq 6.5$  mg/dL at screening. Subjects were randomised (1:1) to receive either lesinurad 400 mg OD or placebo for 6 months. The primary endpoint was the proportion of subjects with a sUA level  $< 6.0$  mg/dL (360  $\mu$ mol/L) at Month 6.

A total of 214 subjects were randomised and received treatment, 107 in each group. Lesinurad 400 mg was significantly more effective than placebo. The proportion of subjects with a sUA level  $< 6.0$  mg/dL at Month 6 was **29.9%** with lesinurad and **1.9%** with placebo ( $p < 0.0001$ ).

Subjects completing study 303 could enrol in an extension study (Study 305) in which all subjects received lesinurad 400 mg once daily for up to 18 months. Efficacy was maintained over this period.

*Comment: The efficacy findings of this study are not relevant to the current application. This study examined monotherapy, whereas the application only seeks approval for use in combination with a XO inhibitor. The 400 mg dose used is also higher than that proposed for registration.*

#### **Study RDEA594-306**

Study 306 was an extension study for those subjects who had completed Study 301 or 302. Subjects who had received lesinurad 200 mg or 400 mg in the pivotal studies were maintained on the same dose. Subjects who had received placebo in the pivotal studies were randomised (1:1) to receive either lesinurad 200 mg or lesinurad 400 mg. All subjects continued to receive allopurinol. The first subject enrolled in February 2013 and the study was ongoing at the time of data cut-off (June 2014) for the study report, at which time a total of 714 subjects had been enrolled. The study report was an interim report and no efficacy data were presented.

#### **Study RDEA594-307**

Study 307 was an extension study for those subjects who had completed study 304. Subjects who had received lesinurad 200 mg or 400 mg in the pivotal studies were maintained on the same dose. Subjects who had received placebo in the pivotal studies were randomised (1:1) to receive either lesinurad 200 mg or lesinurad 400 mg. All subjects continued to receive febuxostat. The first subject enrolled in March 2013 and the study was ongoing at the time of data cut-off (June 2014) for the study report, at which time a total of 196 subjects had been enrolled. The study report was an interim report and no efficacy data were presented.

#### **Phase II studies**

Prior to the Phase III studies, the sponsor conducted three Phase II studies. The first of these was RDEA594-201, which was described as a Phase IIa, pilot pharmacodynamic study. The remaining Phase II studies are reviewed in this section.

*Study RDEA594-202*

This was a Phase II, randomised double blind placebo controlled, dose response study with four parallel groups. The primary objective was to compare the proportion of subjects whose sUA level was < 6.0 mg/dL after 4 weeks of treatment. It was conducted at 30 centres in Europe and North America in 2009-10.

The trial enrolled gout subjects with sUA  $\geq$  8.0 mg/dL (after a 2 week washout of any existing ULTs). Subjects were randomised (1:1:1:1) to one of four treatment groups:

- Group 1: Lesinurad 200 mg OD for 28 days;
- Group 2: Lesinurad 200 mg OD for 7 days, then 400 mg for 21 days;
- Group 3: Lesinurad 200 mg OD for 7 days, then 400 mg for 7 days; then 600 mg for 14 days;
- Group 4: Placebo.

Lesinurad was supplied as 100 mg immediate release capsules (FN07). Subjects were not permitted to take concurrent XO inhibitors (that is, allopurinol or febuxostat). All subjects were treated with colchicine prophylaxis beginning 7-14 days prior to randomised treatment, and continuing for 1 week afterwards.

A total of 123 subjects were enrolled and treated: 31 in group 1, 33 in group 2, 32 in group 3, and 27 in group 4. 108 subjects completed the study. The four groups were reasonably well balanced with respect to balance characteristics.

Lesinurad monotherapy (at 400 or 600 mg per day) was superior to placebo in reducing sUA levels to < 6.0 mg/dL. The 200 mg dose was no more effective than placebo.

On completion of the study, 50 subjects entered an open label extension phase, in which all subjects were treated with lesinurad 200-600 mg daily for up to 68 weeks. The sUA response (<6.0 mg/dL) was maintained in the majority of subjects who received 400 or 600 mg.

*Study RDEA594-203*

This trial was a Phase II, randomised double blind placebo controlled study. The primary objective was to assess the per cent reduction from baseline in sUA levels following 4 weeks of continuous treatment with lesinurad in combination with allopurinol compared to allopurinol alone (the placebo group) in patients with documented inadequate response with standard doses of allopurinol. The study was conducted at 53 centres in 7 countries in Europe and North America between 2009 and 2011.

The trial enrolled gout subjects who had been receiving allopurinol as sole ULT for at least 6 weeks, at a dose between 200 and 600 mg per day, without an adequate response (that is, sUA remained > 6.0 mg/dL at screening).

There were several cohorts in the study. Within each cohort subjects were randomised (2:1) to receive lesinurad or placebo. The lesinurad dose for each cohort was as follows:

- Cohorts 1A, 1B, 4: Lesinurad 200 mg OD for 28 days;
- Cohort 2: Lesinurad 200 mg OD for 7 days, then 400 mg OD for 21 days;
- Cohort 3: Lesinurad 200 mg OD for 7 days, then 400 mg for 7 days; then 600 mg for 14 days.

All subjects continued treatment with allopurinol 200-600 mg per day, and were also treated with colchicine prophylaxis beginning 14 days prior to randomised treatment, and continuing for 1 week afterwards.

A total of 208 subjects were enrolled and treated, as follows:

- 20 (13 lesinurad, 7 placebo) in Cohort 1A (200 mg)
- 20 (14 lesinurad, 6 placebo) in Cohort 1B (200 mg)
- 65 (42 lesinurad, 23 placebo) in Cohort 2 (400 mg)
- 75 (48 lesinurad, 27 placebo) in Cohort 3 (600 mg)
- 28 (19 lesinurad, 9 placebo) in Cohort 4 (200 mg)

The various treatment groups were reasonably well balanced with respect to baseline factors.

For all lesinurad dosages, the per cent reduction from baseline in sUA levels was significantly greater than placebo. Reductions were dose related.

#### *Double blind extension phase*

Subjects who completed Study 203 could enter a double blind extension period. All subjects in the double blind extension period continued allopurinol at the same dose level as during the core study (200 to 600 mg OD) and received the same study medication (lesinurad or placebo) as in the core study. All subjects began treatment with lesinurad at 200 mg OD or matching placebo. Subjects then had the dose of lesinurad or matching placebo adjusted to 400 mg OD and to 600 mg OD based on sUA levels. Colchicine prophylaxis was used up to week 20. The extension study continued for up to 44 weeks.

A total of 126 subjects entered the extension phase and received treatment: 78 in the lesinurad group and 48 in the placebo group.

Reductions in sUA concentrations achieved with lesinurad were greater than those achieved with placebo, and were maintained over the period of the study. Differences between treatments were not subjected to statistical testing.

#### *Open label extension phase*

Subjects who completed the double blind extension phase could enter an open label extension phase. Subjects previously treated with placebo (that is, allopurinol alone) were commenced on lesinurad 200 mg if the sUA was > 6.0 mg/dL at any time. Treatment could continue indefinitely. All subjects continued to receive allopurinol.

A total of 87 subjects entered the study. A total of 54 subjects continued with lesinurad, 25 subjects commenced lesinurad after previously receiving allopurinol alone and 8 subjects remained on allopurinol alone.

sUA concentrations were lower in subjects receiving lesinurad than those receiving allopurinol alone. Mean reductions in sUA concentrations were maintained over the duration of the study (up to 30 months).

### **Evaluator's conclusions on efficacy**

The three pivotal studies were well designed and executed. They have demonstrated that, when used in combination with a XO inhibitor (allopurinol or febuxostat), lesinurad is significantly better than placebo in lowering sUA concentrations to target levels of < 5 mg/dL (300 µmol/L) or < 6 mg/dL (360 µmol/L). These findings were supported by a phase 2 study (study 203).

The magnitude of the demonstrated efficacy benefit is considered to be clinically significant as control of hyperuricaemia is achieved in an additional 25-30% of subjects with the proposed 200 mg dose used in combination with allopurinol. When used in combination with febuxostat the figure was approximately 20%.

In Study 304, there was some evidence that lesinurad may result in a significant reduction in the total surface area of gouty tophi. However none of the studies demonstrated an

advantage in terms of complete resolution of individual tophi. There were also no benefits demonstrated in terms of reduction in the occurrence of gout flares and no meaningful benefits were demonstrated for lesinurad on a variety of patient reported outcomes.

Evidence for the efficacy of lesinurad is therefore largely based on reductions in sUA concentrations. This is a surrogate endpoint for efficacy. There do not appear to be any current EMA or FDA guidance documents relating to appropriate endpoints for gout/hyperuricaemia clinical trials. However, it is noted that the TGA approval for febuxostat appears to have been based on reductions in sUA concentrations.<sup>32</sup>

The effect on sUA concentrations was sustained over the 12 month period studied in the pivotal studies, and the open label extension of Study 203 suggested that efficacy is sustained for even longer periods. Long term efficacy has therefore been satisfactorily demonstrated.

In Studies 301 and 302, efficacy was demonstrated in most subgroups examined, including subjects with mild to moderate renal impairment. Although there was a trend towards reduced efficacy in females in these studies, there was a trend towards *increased* efficacy in females in Study 304. These inconsistent findings are probably due to the small numbers of females enrolled in all the pivotal studies.

The only comparator used in the efficacy studies was placebo. There are no efficacy (or PD) data to establish that lesinurad has an efficacy advantage over probenecid.

Overall, the evidence to support the efficacy of lesinurad for the proposed indication is considered adequate.

## Safety

### Studies providing safety data

The following studies provided evaluable safety data:

#### *Pivotal efficacy studies*

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed at each study visit. Severity of AEs was graded using Rheumatology Common Toxicity Criteria (RCTC), Version 2.0. Serious AEs (SAEs) were defined. All AEs were classified as not related, unlikely to be related or possibly related to study medication. AEs were reported using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.
- AEs of particular interest were renal AEs and cardiovascular AEs.
- Laboratory tests were generally performed at monthly intervals. Tests performed included the following:
  - Haematology: Haematocrit (Hct), haemoglobin (Hgb), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC) count, and white blood cell (WBC) count with differential.
  - Biochemistry: Albumin, alkaline phosphatase, ALT, AST, amylase, urea, calcium, carbon dioxide, chloride, creatinine, CK, C-reactive protein (CRP), GGT, glucose, lactate dehydrogenase (LDH), phosphate, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol, total protein and triglycerides.

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<sup>32</sup> Febuxostat AusPAR, 2015.

- Urinalysis: Appearance, bilirubin, colour, glucose, ketones, microscopic examination of sediment, nitrite, occult blood, pH, protein, specific gravity, and urobilinogen.
- 12 lead ECGs were collected at baseline, Month 6 and Month 12.
- Vital signs (temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate) were measured at each study visit.
- Physical examination was performed at baseline and at Month 12.

***Pivotal studies that assessed safety as a primary outcome***

There were no pivotal studies that assessed safety as a primary outcome.

***Dose response and non-pivotal efficacy studies***

The dose response and non-pivotal efficacy studies provided safety data. In general, safety monitoring was similar to that undertaken in the pivotal studies.

**Patient exposure**

A total of 2,586 unique individuals were exposed to lesinurad in the submitted studies.

A total of 1,799 unique gout subjects were exposed to lesinurad in the phase 2 and phase 3 studies. Of these, total of 1,224 subjects were exposed for approximately 6 months (at least 24 weeks), and 919 were exposed for approximately 1 year (at least 48 weeks).

Exposure to lesinurad and placebo is summarised in Table 8 below.

**Table 8. Exposure to lesinurad and placebo in clinical studies.**

Study type/ Indication	Controlled studies		Uncontrolled studies	Total Lesinurad
	Lesinurad	Placebo	Lesinurad	
<b>Clinical pharmacology</b>				
• Phase I studies	-	-	-	687
• Special populations	-	-	-	100
<b>Gout</b>				
<i>Combination with XO inhibitor</i>				
• Studies 301, 302, 304	1021	516	-	1021
• Study 306	-	-	715 <sup>(1)</sup>	715 <sup>(1)</sup>
• Study 307	-	-	196 <sup>(1)</sup>	196 <sup>(1)</sup>
• Study 203 (core period)	136	72	-	136
• Study 203 (DB extension)	78	48	-	78 <sup>(1)</sup>
• Study 203 (open extension)	-	-	79	79 <sup>(1)</sup>
<i>Monotherapy</i>				
• Study 303	107	107	-	107
• Study 305	-	-	143 <sup>(1)</sup>	143 <sup>(1)</sup>
• Study 202 (core period)	96	27	-	96
• Study 202 (open extension)	-	-	50 <sup>(1)</sup>	50 <sup>(1)</sup>
Total gout subjects				1799 <sup>(2)</sup>
<b>TOTAL</b>	<b>1438</b>	<b>770</b>	<b>1183</b>	<b>2586<sup>(2)</sup></b>

<sup>(1)</sup> A proportion of these subjects had also received lesinurad in the preceding controlled study.

<sup>(2)</sup> Unique subjects

## Safety issues with the potential for major regulatory impact

### *Liver toxicity*

Laboratory testing of liver function did not provide any evidence of hepatotoxicity due to lesinurad. In particular, there were no cases that met Hy's law criteria.

### *Haematological toxicity*

Laboratory monitoring of haematology parameters did not suggest that lesinurad is associated with haematological toxicity. There were no reports of pancytopenia or aplastic anaemia.

**Serious skin reactions**

There were no serious skin reactions observed with lesinurad.

**Unwanted immunological events**

There were no serious hypersensitivity reactions reported with lesinurad.

**Post marketing data**

There were no post marketing safety data included in the submission.

**Evaluator's conclusions on safety**

The safety data clearly indicate that lesinurad treatment is associated with renal toxicity, with the most common manifestation being an elevation in serum creatinine. Renal toxicity was more common with the 400 mg dose than the 200 mg dose, and was more common with lesinurad monotherapy than with use of the drug in combination with a XO inhibitor. In most subjects the toxicity was reversible. At the 200 mg dose lesinurad was not associated with an increased incidence of urolithiasis.

Cardiovascular safety was a safety issue of special interest. In the Phase III, placebo controlled studies there were no increases in the incidence of overall cardiac or vascular AEs (apart from hypertension) among subjects treated with lesinurad. There was also no increase in the incidence of *adjudicated* cardiovascular events. However, there were small increases in the incidence of *serious* cardiac AEs and cardiovascular deaths. Furthermore, the 400 mg dose was associated with an increase in the incidence of major adverse cardiovascular events (MACE), most notably non-fatal myocardial infarction.

However, on balance it is considered that the available data do not establish that lesinurad treatment will be associated with an increased risk of cardiovascular toxicity. The observed differences between the placebo and lesinurad groups were small and may have been a chance finding. Although the incidence of serious cardiac AEs was increased in the pivotal studies (301, 302 and 304) the Phase III monotherapy study (303), which used a 400 mg dose, did not suggest an increased risk. The proposed 200 mg dose was also not associated with an increased incidence of MACE events. It is recommended that the issue of cardiovascular toxicity should be the subject of ongoing pharmacovigilance in the post-market setting.

The pivotal Phase III studies suggest that lesinurad may also be associated with a small increased incidence of the following AEs compared to placebo:

- Hypertension;
- Headache and dizziness;
- Fatigue.

The subgroup analyses indicated that use of NSAIDs for flare prophylaxis was not associated with any increase in lesinurad renal toxicity, compared to use of colchicine. Colchicine is not considered to be nephrotoxic, and concomitant use of NSAIDs and lesinurad should therefore be safe. However, an interaction study demonstrated increase systemic exposure to indomethacin with lesinurad treatment. This interaction should be described in the PI, as both indomethacin and lesinurad are potentially nephrotoxic, and in some subjects it may be prudent to use an alternative NSAID (for example, naproxen).

The subgroup analyses also suggested that the safety of lesinurad is acceptable in subjects with pre-existing mild or moderate renal impairment. However, subjects with severe renal impairment were excluded from the pivotal studies.

## **First round benefit-risk assessment**

### **First round assessment of benefits**

The benefits of lesinurad in the proposed usage are:

- Clinically significant reductions in serum urate concentrations;
- There was also some evidence that lesinurad is effective in reducing the size of gouty tophi, with prolonged treatment.

### **First round assessment of risks**

The risks of lesinurad in the proposed usage are:

- Renal toxicity, most commonly presenting as an increase in serum creatinine concentrations.
- A possible small increase in the incidence of some other AEs (for example, hypertension, headache, fatigue).

There were some inconsistent signals of a small increased risk of cardiovascular toxicity.

Use of a 400 mg dose of lesinurad was associated with a greater risk of renal toxicity than the proposed 200 mg dose.

### **First round assessment of benefit-risk balance**

The efficacy benefits produced by lesinurad are clinically significant with an additional 20-30% of subjects being able to reach recommended serum urate target levels, when the drug is added to a XO inhibitor. These benefits are sustained with long term treatment.

Renal toxicity is the major risk associated with the drug. In most subjects renal toxicity was reversible. At the proposed 200 mg dose, in combination with a XO inhibitor, the incidence of reports of 'renal failure' or 'renal impairment' was not increased compared to placebo.

Overall, the benefit-risk balance of lesinurad, given the proposed usage, is considered favourable.

### **First round recommendation regarding authorisation**

It is recommended that the application be approved. The indication proposed by the sponsor is considered acceptable.

### **Clinical questions**

None

### **Second round evaluation**

The benefit risk assessment is unchanged from that from the first round. The recommendation regarding authorisation is also unchanged.



## V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted a Risk Management Plan (EU RMP) version 1 (dated 9 December 2014, DLP 20 September 2014) with an Australian Specific Annex (ASA) version 1 (dated February 2015), which was reviewed by the RMP evaluator.

### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 9.

**Table 9: Ongoing safety concerns.**

Important identified risks	Renal related events Gout flares
Important potential risks	Nil
Missing information	Use in children Use in pregnant or lactating women Use in pre-existing hepatic impairment Use in pre-existing severe renal impairment or end-stage renal disease (ESRD) Off label use

### *RMP reviewer comment*

Given lesinurad's mechanism of action the sponsor should provide a justification as to why nephrolithiasis (kidney stones) is not considered a separate important risk.

The draft PI currently contains advice that female patients should practice additional methods of contraception and not rely on hormonal contraception alone when taking lesinurad due to a possible drug-drug interaction. It is noted however that this has not been specifically studied. The sponsor should justify not including "interaction with hormonal contraception" as missing information even though gout is uncommon in that demographic (females of childbearing age).

The acceptability of the summary of safety concerns remains subject to assessment by the clinical and non-clinical evaluators.

In addition, advice will be sought from the Advisory Committee on the Safety of Medicines (ACSOM) regarding the completeness of the summary of safety concerns.

### Pharmacovigilance plan

Routine pharmacovigilance is proposed for all safety concerns.

Routine pharmacovigilance includes the use of a targeted questionnaire for the important identified risk 'renal related events'.

No additional pharmacovigilance activities are proposed in the EU RMP and ASA.

***RMP reviewer comment***

The sponsor should confirm that the targeted questionnaire attached to the EU RMP is the same targeted questionnaire that will be employed in Australia for the important identified risk 'renal related events'.

Lesinurad is not yet approved elsewhere. It is unusual for a new chemical entity that no additional pharmacovigilance activities are proposed to further characterise the safety profile in the post marketing period.

Advice will be sought from the ACSOM regarding the sufficiency of the pharmacovigilance plan to monitor risks associated with lesinurad.

**Risk minimisation activities**

Routine risk minimisation only is proposed to mitigate the risks associated with lesinurad.

***RMP reviewer comment***

Advice will be sought from the ACSOM regarding the adequacy of routine risk minimisation to satisfactorily mitigate the risks associated with lesinurad.

**Reconciliation of issues outlined in the RMP report**

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

***Recommendation #1 in RMP evaluation report***

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

***Sponsor response***

No specific response provided.

***Evaluator's comment***

N/A

***Recommendation #2 in RMP evaluation report***

Given lesinurad's mechanism of action the sponsor should provide a justification as to why nephrolithiasis (kidney stones) is not considered a separate important risk.

***Sponsor response***

No specific response provided. The sponsor has provided the requested justification (see Section 31 response).

***Evaluator's comment***

The justification provided is acceptable at this time from an RMP perspective.

**Summary of recommendations**

It is considered that the sponsor's response to the TGA Section 31 Request has not adequately addressed all of the issues identified in the RMP evaluation report.

There are outstanding issues.

There are additional recommendations.

### ***Outstanding issues***

*Issues in relation to the RMP*

#### **Safety specification**

Based on the sponsor's response and consideration of the ACSOM advice, clinical and nonclinical evaluation reports, it is recommended to the Delegate that:

- 'Use of lesinurad as monotherapy' should be included as an important potential risk (new recommendation based on advice from the ACSOM)
- 'Use in elderly patients > 75 years' should be included as missing information (new recommendation based on advice from the ACSOM)
- 'Cardiovascular events' should be included as an important potential risk (new recommendation based on advice from the ACSOM and the clinical evaluation report)
- 'Drug-drug interactions' should be considered for inclusion as a safety concern
- The sponsor has agreed to add 'interaction with hormonal contraception' as an item of missing information in the ASA.

#### **Pharmacovigilance plan**

The post authorisation safety study (PASS) alluded to in the Section 31 response to the clinical evaluation report is considered to be an additional pharmacovigilance activity and should be detailed as such in the RMP documentation and assigned to the relevant safety concerns, including the recommended additional important potential risk 'cardiovascular events'.

#### **Risk minimisation plan**

It is considered that routine risk minimisation is not acceptable from an RMP perspective. It is recommended to the Delegate that the sponsor be required to develop and implement an educational program as additional risk minimisation for healthcare professionals and patients. The education should include, but not be limited to:

- Approved indications
- Contraindications
- Dosage information including:
  - the need to take lesinurad with a XO inhibitor
  - the need for gout flare prophylaxis
  - the need to take lesinurad in the morning with food and water and at the same time as the morning dose of the XO inhibitor
  - the need to interrupt treatment with lesinurad if XO inhibitor therapy is interrupted
  - the need to stay well hydrated
- The recommendation for evaluation of renal function prior to initiation and periodically thereafter
- Information on important adverse events
- Information on important drug-drug interactions
- Healthcare professional educational materials

- Patient-specific educational materials

The need for an educational strategy is supported by the ACSOM. The ASA should be revised to include relevant details of the educational program including any educational materials, the distribution strategy and proposed measures of effectiveness.

#### *Advice from ACSOM*

The evaluator sought advice from the ACSOM which has been considered in the reconciliation of outstanding of RMP issues.

The full advice is below.

#### **Advice**

The committee advised that the currently proposed indication, 'the treatment of hyperuricaemia associated with gout **in combination with** a XO inhibitor' [emphasis added], does not adequately convey that it is essential that lesinurad is co-administered with a XO inhibitor and that non adherence (that is, taking lesinurad without the XO inhibitor) may increase the risk of renal events.

1. *Can the committee comment on the completeness of the summary of safety concerns presented in the RMP? If considered incomplete, can the committee suggest additional risks which should be added to the summary of safety concerns?*

The committee advised that monotherapy with lesinurad is a particular risk that should be categorised as an important potential risk and be treated separately to the missing information of off label use. Monotherapy with lesinurad in clinical trials was associated with serum creatinine elevation, compared to dual therapy with a XO inhibitor. In a 6 month placebo controlled monotherapy study of lesinurad, renal related adverse reactions and serious renal related adverse reactions (including transient acute renal failure) were reported in 17.8% and 4.7% of patients receiving lesinurad 400 mg alone and in no patients receiving placebo.

Patient exposure in clinical studies (total of 2586 patients with a mean age of 52 years) has included a minority of older patients (237 patients aged over 65 years of age; 36 patients aged over 75 years of age; nil patients over 85 years of age). In routine use, patients will likely be older than those in the clinical studies. Use in patients aged over 75 years of age should be considered as missing information.

The high rate (78%) of subjects in the clinical studies with at least one cardiovascular comorbidity or cardiovascular disease history at baseline; shows the high background risk of cardiovascular diseases in patients with gout. There were a higher number of non-fatal myocardial infarctions with 400 mg lesinurad in clinical trials, compared to the recommended dose of 200 mg or placebo. The committee also noted that lesinurad is a first-in-class, new chemical entity and has not yet been approved by other regulators. Taking these points into consideration, the committee advised that cardiovascular events should be added to the summary of safety concerns as important potential risks.

The committee advised that the important identified risk of renal related events should explicitly mention nephrolithiasis (renal calculi). For patients on lesinurad excreting a higher load of uric acid, there is potential for urine uric acid concentrations to exceed the uric acid solubility limits and result in acute uric acid nephropathy, including kidney stones.

DDIs should be included as both important identified and potential risks in the summary of safety concerns, as only some interactions have been explored.

The committee noted the lack of information on when lesinurad therapy can be stopped; for example, whether the medicine could/should be ceased when the target serum urate level has been achieved and maintained for a certain period of time. Such de-prescribing

information can be regarded as missing information for the purposes of the summary of safety concerns.

2. *Given this medicine is not yet approved elsewhere, can the committee comment upon the sufficiency of routine pharmacovigilance activities to monitor risks associated with lesinurad?*

The committee noted that routine pharmacovigilance is proposed for all safety concerns, with a targeted questionnaire for the important identified risk of renal-related events.

The committee advised that, upon completion, the ongoing studies cited in the EU-RMP being conducted as part of the routine pharmacovigilance should be provided to the TGA. Use in the elderly and use in patients with cardiovascular comorbidities should be given particular attention in these studies. If trends emerge in these populations, the sufficiency of routine pharmacovigilance should be reviewed.

The potential for off label use (for example, secondary hyperuricaemia, for which no studies have been conducted; monotherapy and dosage above 200 mg/day) is unclear and such use should be monitored.

The committee noted that gout flares will be expected in any drug therapy that lowers serum urate and this event does not require additional monitoring.

The absence of information of use of lesinurad in children and pregnant or lactating women was not a concern, as the medicine is unlikely to be used in these populations.

3. *Can the committee comment on the adequacy of the routine risk minimisation activities to mitigate the risks associated with lesinurad?*

The committee noted that advice to the patient includes: "lesinurad must be taken at the same time as the morning dose of the XO inhibitor; if treatment with the XO inhibitor is interrupted, lesinurad therapy must also be interrupted" and "that failure to follow the instructions may increase the risk of renal events". The committee also noted that patients are required to stay well hydrated (for example, 2 L of liquid per day). The committee advised that all health practitioners need to emphasise these points to the patients, as there is a high risk for medication error due to non-adherence with these instructions.

The committee advised that health practitioner education will be important as a risk minimisation activity given that co-prescribing of lesinurad and a XO inhibitor is essential, the target population has numerous comorbidities, and the potential for drug interactions with lesinurad.

Lesinurad is an inhibitor of two transporter proteins in the kidney, creating the potential for various drug interactions. Given the patient population is very likely to have multiple comorbidities and drug therapies, the discussion in the PI on drug interactions is very modest. Additional information should be provided in the PI on DDIs, including management strategies. In particular, while acknowledging that gout is uncommon in females of childbearing age, the statement in the PI that oral hormonal contraceptives 'may not be reliable' is vague and additional information should be provided.

The PI recommends gout flare prophylaxis (colchicine or a NSAID) for at least five months when starting therapy with lesinurad. Medicines expected to be co-administered with lesinurad should be discussed under their own subheadings in the "Interactions with other medicines" section of the proposed PI.

The committee advised that it would be useful for the PI to include a tabulation of the serum creatinine elevations that occur when lesinurad is used as monotherapy. This would illustrate the significance of co-administration of a XO inhibitor to minimise renal effects.

The PI should use the units of measurement for serum urate that are commonly used in Australia, that is, mmol/L.

The PI (“Adverse reactions by system organ class and frequency”) should include specific information on the extent of ‘blood creatinine increase’.

The Consumer Medicine Information (CMI) states that the medicine should not be taken by persons with tumour lysis syndrome. Use of this technical terminology is not appropriate in a CMI.

### ***Comments on the safety specification of the RMP***

#### *Clinical evaluation report*

The sponsor states that a post market prospective observational cohort study is now planned to compare the risk of cardiovascular events (MACE plus hospitalisations for unstable angina) between gout patients who are new users of lesinurad in combination with a XO inhibitor and those who are continuing users of an XO inhibitor (as monotherapy). The study will also compare the rates of hospitalisation for acute kidney injury.

It is not clear whether the RMP has been amended to include cardiovascular toxicity as a potential risk of lesinurad.

#### **RMP evaluator comment**

Details of the proposed PASS are not included in the EU RMP, the ASA, or the RMP evaluation Section 31 response. This is unacceptable. Details of this activity should be appropriately included in the RMP documentation (see outstanding RMP issues above).

#### *Nonclinical evaluation report*

Results and conclusions drawn from the nonclinical program for lesinurad detailed in the sponsor’s draft RMP are in general concordance with those of the nonclinical evaluator. The RMP cites slightly different relative exposures associated with toxicological effects in the nonclinical species. This is mainly due to the use of different time points for plasma exposure data (that is, use of average exposure throughout the repeat dose studies versus exposure data from the last sampling point). In all cases the animal toxicities were seen at adequate multiples of human exposure, and so these discrepancies are not of clinical significance.

The mechanism for drug interactions only considers the potential effect of lesinurad on other co-administered drugs. Based on the nonclinical data, the pharmacokinetics of lesinurad may potentially be affected by inhibitors or inducers of CYP2C9, mitochondrial epoxide hydrolase, and inhibitors of organic anion transport.

### ***Suggested wording for conditions of registration***

#### *RMP*

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

Given the outstanding issues, the Australian RMP documentation requires revision and therefore no RMP condition of registration can be proposed.

## **VI. Overall conclusion and risk/benefit assessment**

The submission was summarised in the following Delegate’s overview and recommendations:

## Quality

There are no chemistry issues that would preclude approval. The manufacturing and quality control of the drug substance (including the drug substance specification) is acceptable.

Lesinurad is a white crystalline non-hygroscopic powder. The drug substance exists as a racemic mixture (50:50) of two atropisomers (that is, atropisomer 1 and atropisomer 2). Studies to date suggest that the atropisomers do not readily interconvert, even under extreme conditions.

The proposed drug product is a blue, oval, film coated tablet containing 200 mg of the active pharmaceutical ingredient as the free acid, and the conventional excipients hypromellose, microcrystalline cellulose, lactose, crospovidone and magnesium stearate. The tablets measure 5.7 x 12.9 mm and are debossed with "LES200" on one side and are blank on the other. The drug product is intended for oral administration.

The product is to be supplied in PVC/PCTFE-Al blisters and in cartons of 10 tablets (starter pack) and 30 tablets (commercial pack). The manufacturing and quality control of the finished product is acceptable. However, the GMP Clearance for the proposed finished product manufacturer will expire prior to the decision date and a renewed clearance has not been issued. This matter remains outstanding, but is expected to be resolved in due course.

The chemistry evaluation of the food effect study has concluded that lesinurad should be taken with food.

## Nonclinical

There were no nonclinical objections to registration of lesinurad. The nonclinical evaluator has noted that while the nonclinical data provide information on the likely mechanism of action of lesinurad as a uricosuric agent in humans, there are no supporting animal data in vivo owing to the lack of a suitable animal model to investigate lesinurad as a potential treatment of hyperuricaemia in gout.

Lesinurad's uricosuric effects in humans are likely to be mediated by inhibition of apical uric acid reabsorption through an effect on the human URAT1 transporter, with a possible additional effect mediated through inhibition of the organic anion transporter OAT4. Lesinurad's major metabolites and the disproportionate human metabolite M4 are unlikely to contribute to its pharmacodynamic activity. No clinically relevant secondary pharmacodynamic activity was identified in an extensive screen of receptors, ion channels and transporters, which was supported by functional assays as required.

Safety pharmacology studies examining the CNS, cardiovascular, respiratory, renal and gastrointestinal systems did not reveal any safety issues of clinical relevance. The target organs for lesinurad mediated toxicity were the kidney, gastrointestinal tract, liver, bile duct and thyroid. These effects were not anticipated clinically based on relative exposure levels at the NOEL being adequate multiples of human exposure at the MRHD.

Lesinurad is not considered to pose a genotoxic or carcinogenic hazard.

## Clinical

### Pharmacology

Absolute bioavailability of lesinurad is estimated to be 100%, absorption is therefore complete. Typical T<sub>max</sub> values after a single dose were 1.0-2.0 h suggesting rapid

absorption. Co-administration of the Phase III, 400 mg formulation (FN22) with a high fat, high calorie meal resulted in an approximate 18% reduction in C<sub>max</sub> with no significant effect on AUC. T<sub>max</sub> was delayed by 0.5 h. C<sub>max</sub> and AUC increased in an approximately dose proportional manner over the 5-200 mg dose range in the fasted state. However, increases in AUC appeared to be greater than dose proportional over the 100-600 mg dose range in the fed state. There was no evidence of accumulation with repeated once daily dosing. The estimated volume of distribution of steady state was 20.3 L.

Estimated total clearance was 5.98 L/h. Following oral administration, ~30% of the dose was recovered unchanged in the urine. Estimates of renal clearance of lesinurad were generally 30-40 mL/min and active secretion occurs. Eight metabolites were identified in humans with 4 of these (M2, M3, M4 and M6) inactive. The major metabolite excreted in urine and faeces was M4 which accounted for ~21% of the administered dose followed by M3 with ~12%. Two subjects in the PK studies were CYP2C9 poor metabolisers and these individuals had increases in lesinurad plasma AUC (111% and 79% respectively) and an increased amount of lesinurad excreted unchanged in the urine (271% and 124% increases respectively), suggesting CYP2C9 is the primary metabolising hepatic enzyme in humans. In the population PK (popPK) analysis, the co-efficient of variation for clearance was 63% indicating moderate variability. A separate review of the popPK suggested its results were not.

Mild hepatic impairment (Child-Pugh A) increased the mean AUC of lesinurad by ~7% and the C<sub>max</sub> by ~11%. Moderate hepatic impairment increased the mean AUC by ~33% and the C<sub>max</sub> by ~8%. The effect of severe hepatic impairment was not assessed. In single dose studies the mean AUC of lesinurad in subjects with mild (CrCl ≤ 75 mL/min)/moderate (CrCl ≤ 45 mL/min)/severe renal impairment (CrCl ≤ 22 mL/min) increased by 33%/ 41% and 123% respectively.

Comprehensive interactions studies were performed and are summarised in the clinical evaluation report. The strong CYP2C9 inhibitor, fluconazole increased mean AUC by 56%. The CYP2C9 inhibitor, rifampicin decreased mean AUC by 38%. Ranitidine and antacids had no significant effect on the PK of lesinurad, however and when taken fasted antacids may reduce systemic exposure. Co-administration with allopurinol, naproxen, indomethacin and febuxostat did not affect the AUC of lesinurad. Lesinurad has no significant effect on tolbutamide metabolism (CYP 2C9 substrate).

Lesinurad did not affect the PK of tolbutamide, a single dose of S-warfarin (CYP 2C9 substrate), or multiple doses of repaglinide (CYP 2C8 substrate). Lesinuride was an inducer of CYP3A4 and reduced systemic exposure to sildenafil by up to 72% and reductions in the AUC for colchicine (up to 35%), R-warfarin (~20%), atorvastatin (~27%), and amlodipine (~40%).

As noted by the evaluator, probenecid, another uricosuric agent, inhibits renal organic anion transporters OAT1/3, with resulting drug interactions. Lesinurad did not affect clearance of frusemide, a substrate for OAT1/3. Lesinurad did not affect the AUC of probenecid but did lead to a 25-35% reduction in the AUC of its active metabolite, oxypurinol. Lesinurad 400 mg daily increased the AUC of febuxostat by up to 31% but the proposed 200 mg dose had no significant effect on the PK of febuxostat. Lesinurad increased the AUC of indomethacin by ~30% and had no significant effect on the PK of naproxen.

Lesinurad treatment was not associated with significant QT prolongation or other ECG effects.

A separate expert review of the popPK analysis is included in papers to be provided to the committee. The reviewer of the popPK analysis stated that the sponsor concluded that a weak relationship may exist between serum creatinine concentrations and lesinurad



exposure, that this is more obvious in a monotherapy trial (RDEA594-303), but that the current analysis cannot prove cause and effect.

### **Efficacy**

Doses of 200, 400 and 600 mg were studied in patients with gout in Phase I and II studies. Doses of 600 mg were only marginally more effective than 400 mg. Therefore doses of 200 mg and 400 mg were chosen for the pivotal studies. Three pivotal studies were performed, two with lesinurad as adjunctive to allopurinol and one as adjunctive to febuxostat.

The CLEAR studies, 301 and 302 had the same design and were evaluated together. These studies were randomised, double blind, and placebo controlled with three parallel groups. Subjects were randomised to receive lesinurad (200 or 400 mg) or placebo once daily for 12 months in combination with allopurinol. The primary objective was to determine the efficacy of lesinurad by Month 6 when used in combination with allopurinol compared to allopurinol monotherapy. Efficacy at Month 12 was a secondary objective.

Subjects included in these studies had to meet the American Rheumatism Association (ARA) criteria for the diagnosis of gout and have a serum uric acid level of  $\geq 357 \mu\text{mol/L}$  (6.0 mg/dL) at the Day -7 Visit, despite a stable dose of allopurinol of at least 300 mg per day for at least 8 weeks. Subjects with severe renal impairment (creatinine clearance  $< 30 \text{ mL/min}$ ) were excluded, as were those with a recent history of cardiovascular disease.

All subjects were to continue allopurinol at their previous dose. The dose was not altered during the course of the study unless safety issues arose. All subjects also received prophylaxis for gout flares with colchicine, starting on day -14. The dose was either 0.5 or 0.6 mg OD, depending on available tablet sizes. NSAIDs could be prescribed in those subjects intolerant to colchicine. Prophylaxis was continued until the end of Month 5.

The main efficacy variables were: sUA concentrations; acute gout flares; change in size of gouty tophi; and patient reported outcomes to assess extent of disability and quality of life. The primary efficacy outcome was the proportion of subjects with a sUA level  $< 6.0 \text{ mg/dL}$  ( $< 360 \mu\text{mol/L}$ ) by Month 6. Key secondary efficacy outcomes were: mean rate of gout flares requiring treatment for the 6 month period from the end of Month 6 to the end of Month 12; and the proportion of subjects with  $\geq 1$  target tophus at baseline who experienced complete resolution of at least 1 target tophus by Month 12. After commencing blinded treatment subjects were reviewed in the clinic at week 2 and then every month. sUA concentrations were assessed at monthly intervals by a central laboratory. Gout flares were recorded in a patient diary.

Randomisation was stratified by renal function at Day -7 (eCrCl  $\geq 60 \text{ mL/min}$  vs.  $< 60 \text{ mL/min}$ ) and presence or absence of at least 1 tophus. The difference in sUA response rates between placebo and each lesinurad group was tested using the Cochran-Mantel Haenszel (CMH) test statistic, stratifying by Day -7 renal function and tophus status during screening. To account for multiple comparisons, each of the 2 treatment comparisons with placebo were tested at the  $\alpha = 0.025$  level. If both doses were shown to be significantly superior to placebo, the key secondary outcomes were to be tested in hierarchical order at an alpha level of 0.05.

The intention-to-treat (ITT) population for both studies comprised 1213 patients. Median duration of gout was  $\sim 10$  years in both studies with 9% of patients in Study 301 and 15.9% in Study 302 having at least one tophus. Median sUA was  $\sim 410 \mu\text{mol/L}$ . Most subjects were receiving 300 mg per day of allopurinol and were prescribed colchicine as flare prophylaxis.

Of particular note around 25% of subjects taking lesinurad in the combined studies were taking acetyl salicylic acid. The protocol for these studies was amended to allow for alkalinisation of urine in subjects with 3 episodes of elevated serum creatinine  $\geq 2 \times$  their

baseline value or if the subject developed a kidney stone. Additionally, if a subject experienced a serum creatinine value above  $\geq 3$  x their Baseline, randomised study medication was temporarily stopped.

Statistically significant superiority of both the 200 mg and 400 mg doses of lesinurad compared to placebo was demonstrated in both studies. In Study 301, target sUA levels were reached by 27.9%/ 54.2% / and 59.2% of patients given placebo, 200 mg and 400 mg lesinurad respectively ( $p < 0.0001$  for both doses). In Study 302, target sUA levels were reached by 23.3%, 55.4%, and 66.5% of patients given placebo, 200 mg and 400 mg lesinurad respectively ( $p < 0.0001$  for both doses).

Subgroup analyses by age, weight, sex, ethnicity, weight, degree of renal impairment (within mild or moderate impairment), use of aspirin or thiazides and presence of tophi of the combined study population show consistency of efficacy across these subgroups. Only 4.9% (59) of the combined ITT study population were women.

For the secondary endpoints of rate of gout flares and resolution of at least 1 target tophus there were no clinically or statistically significant differences favouring lesinurad.

Absolute reductions in mean sUA were generally around 1.3-2.0 mg/dL for the lesinurad groups, with greater reductions in the 400 mg group. Percentage reductions were approximately 15-20% with lesinurad. Reductions were achieved by Month 1 and sustained over the 12 months of randomised treatment. There was minimal change in sUA concentrations with placebo treatment.

Study 304 (CRYSTAL) was a randomised, double blind, placebo controlled trial with three parallel groups. Subjects were randomised to receive lesinurad (200 or 400 mg) or placebo once daily for 12 months in combination with febuxostat 80 mg daily. The primary objective was to determine the efficacy of lesinurad by Month 6 when used in combination with febuxostat compared to febuxostat monotherapy. The efficacy variables were the same as in Studies 301 and 302, that is, sUA concentrations, acute gout flares, change in gouty tophi and report-reported outcomes concerning disability and quality of life.

The primary efficacy outcome was the proportion of subjects with a sUA level  $< 5.0$  mg/dL ( $< 300$   $\mu\text{mol/L}$ ) by Month 6. Key secondary efficacy outcomes were: proportion of subjects who experience complete resolution of at least 1 target tophus by Month 12; proportion of subjects with a complete or partial resolution of at least one target tophus by Month 12; and proportion of subjects with an improvement from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) of at least 0.25 at Month 12.

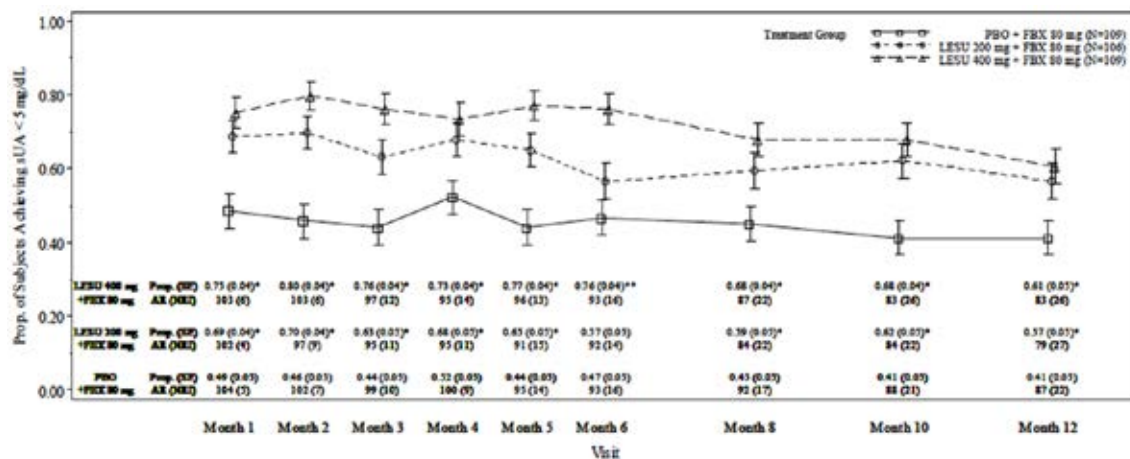
Randomisation was stratified by renal function ( $\text{eCrCl} \geq 60$  mL/min versus  $< 60$  mL/min) and sUA at Day -7 of study ( $\text{sUA} \geq 6.0$  versus  $< 6.0$  mg/dL). The differences in sUA response rates between the placebo and each lesinurad treatment group were tested using the CMH test statistic, stratifying by Day -7 renal function and Day -7 sUA status. To account for multiple comparisons, each of the 2 treatment comparisons with placebo were tested at the  $\alpha = 0.025$  level.

A total of 324 subjects were randomised. Mean sUA at screening for the whole population was 8.71 mg/dL. At baseline, after 21 days of febuxostat, this had fallen to 5.27 mg/dL. Mean time since diagnosis of gout was 14.7 years. These subjects had more gouty tophi at baseline compared with subjects in Studies 301 and 302 with only 1 subject not having a tophus at baseline. 55.9% of study subjects had 1 target tophi at baseline with remaining subjects having 2 or more target tophi. 67 (20.7%) had  $\text{eCrCl} < 60$  mL/min at Day -7. Most patients were not taking urate lowering therapy prior to study entry with 92 (28.4%) taking allopurinol and 12 (3.7%) febuxostat.

For the ITT population, 51 (46.8%) subjects given adjunctive placebo, 60 (56.5%) given adjunctive lesinurad 200 mg daily and 83 (76.1%) given adjunctive lesinurad 400 mg daily achieved a sUA of  $< 5$  mg/dL (300  $\mu\text{mol/L}$ ) at Month 6. The difference between lesinurad

and placebo was statistically significant for the 400 mg dose ( $p < 0.0001$ ), but not for the 200 mg dose ( $p = 0.1298$ ). For the primary efficacy outcome the per protocol (PP) analysis also showed statistically significant superiority for the lesinurad 400 mg dose but not the proposed 200 mg dose. The proportion of subjects with sUA  $< 5.0$  mg/dL over time is illustrated in Figure 4. Of particular interest, Month 6 was the only time point at which efficacy of the 200 mg dose was not significantly greater than that of placebo.

**Figure 4. Study 304 – Proportion of subjects with sUA  $< 5.0$  mg/dL at each study visit.**



Abbreviations: AR, at risk; ITT, Intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; Prop, proportion; SE, standard error; sUA, serum urate.

\* Indicates  $p < 0.05$ .

\*\* Indicates statistical significance of treatment group vs. placebo at the 0.025 level 2-sided using Cochran-Mantel Haenszel test stratified by Day-7 renal function and Day-7 sUA status (randomized values) after adjustment for multiple comparisons (primary endpoint).

Note: Months 7, 9, and 11 data are excluded because the timing of the last protocol amendment (Protocol Amendment 5), which added sUA assessments at these timepoints, resulted in minimal data collection at these timepoints for NRI analysis.

Complete or partial resolution of at least 1 target tophus by Month 12 was achieved by 50.5% in the placebo group, 56.6% in the 200 mg group and 58.7% in the 400 mg group. Differences between lesinurad and placebo were not statistically significant. No benefit from lesinurad was seen in patient reported disability by Month 12 using the HAQ-DI.

Study 303 was a 6 month study of monotherapy lesinurad 400 mg daily compared with placebo in subjects intolerant to or with a contraindication for either allopurinol or febuxostat with sUA at screening of  $\geq 6.5$  mg/dL demonstrated superior reduction in sUA levels to  $< 6.0$  mg/dL at Month 6 for lesinurad. Study 306 was an extension study for subjects previously enrolled in studies 301 or 302. Study 307 was an extension study for those subjects who had completed study 304. Subjects who had received lesinurad 200 mg or 400 mg in the pivotal studies were maintained on the same dose. Subjects who had received placebo in the pivotal studies were randomised (1:1) to receive either lesinurad 200 mg or lesinurad 400 mg. These extension studies were ongoing at the time of submission and no efficacy data were presented.

A pooled analysis of efficacy results for the two CLEAR studies was performed which included an examination of efficacy of various subgroups. These included subjects taking concomitant low dose aspirin ( $< 325$  mg daily) and concomitant thiazine diuretics. Lesinurad as add-on therapy to allopurinol was statistically superior to placebo in reducing sUA to target levels for both these patient sub-groups.

## Safety

A total of 2,586 unique individuals were exposed to lesinurad in the submitted studies with 1,799 subjects with gout exposed to lesinurad in the Phase II and III studies. Of these 1,224 subjects were exposed for  $\sim 6$  months and 919 for  $\sim 1$  year. This degree of exposure is consistent with the requirements of the TGA adopted guideline on the clinical investigation of medicinal products for long term use.

Of most concern is the effect of lesinurad, a uricosuric agent on renal function, particularly since hyperuricaemia/ gout can also cause impairment of renal function. In the pivotal studies creatinine increases were reported more frequently as AEs (6.1% with lesinurad versus 2.3% with placebo).

The incidence was dose-related (4.3% at 200 mg versus 7.8% at 400 mg). Blood urea increases were also more commonly reported with lesinurad (1.4% versus 0.6%). In Study 303 in which lesinurad was given as monotherapy there were 3 AE reports of renal impairment/failure in subjects given lesinurad cf. nil for placebo. There were also 9 (8.4%) reports of blood creatinine increased in subjects given lesinurad compared with nil given placebo.

The sponsor analysed the incidence of “renal-related AEs” using a list of MedDRA preferred terms suggestive of a decline in renal function. There was an increased incidence of such events in the 400 mg dose group compared to placebo (11.8% versus 4.5%). The incidence in the 200 mg dose group was slightly increased compared to placebo (5.7% versus 4.5%), due to an increased incidence of serum creatinine and blood urea elevations. Reports of ‘renal failure’ or ‘renal impairment’ were not increased in the 200 mg dose arm compared to placebo. There was no notable difference in incidence between the allopurinol studies (301 and 302) and the febuxostat study (304).

In the long-term extension studies (306 and 307) there was no evidence of an increasing incidence of renal related AEs with increasing duration of lesinurad treatment.

The incidence of renal calculi was not notably increased in subjects given lesinurad in the pivotal studies or in the extensions of these studies. While there was a higher incidence in the 200 mg versus 400 mg dose group in the pivotal studies this was based on small numbers and there were 1.7% of subjects given placebo with nephrolithiasis, compared with 0.6% given lesinurad 200 mg and 2.5% given lesinurad 400 mg.

There were a total of 13 deaths in the lesinurad clinical development program. All were considered by the sponsor to be not related or unlikely to be related to study medication. There was an excess of deaths in the lesinurad treatment groups with 10 of the deaths occurring in subjects given lesinurad and 3 in subjects given placebo. The majority of deaths were due to cardiovascular events. During the four randomised placebo controlled Phase III trials, there were a total of six deaths (1 in Study 301; 2 in Study 302; 2 in Study 304; and 1 in Study 303). Another death occurred in the placebo controlled double blind extension phase of Study 203. All these deaths occurred in the lesinurad arms of the studies. There were no deaths during placebo treatment. If deaths were unrelated to study treatment 4 deaths would have been anticipated in the placebo arms if deaths were unrelated to treatment. This raises concern that lesinurad may be responsible for the imbalance.

### **Risk management plan**

The RMP evaluator considers the Australian RMP documentation requires revision and has not recommended conditions of registration pertaining to the RMP at this time.

The advice of ACSOM was requested and is included as an attachment to the RMP report which will be provided to the committee. The ACSOM provided the following advice regarding the proposed indication for lesinurad:

*... the currently proposed indication, ‘the treatment of hyperuricaemia associated with gout in combination with a XO inhibitor’, does not adequately convey that it is essential that lesinurad is co-administered with a XO inhibitor and that non-adherence (i.e. taking lesinurad without the XO inhibitor) may increase the risk of renal events.*

The RMP evaluator recommended additions to the safety specifications:

- 'Use of lesinurad as monotherapy' should be included as an important potential risk
- 'Use in elderly patients > 75 years' should be included as missing information
- 'Cardiovascular events' should be included as an important potential risk
- 'Drug-drug interactions' should be considered for inclusion as a safety concern

The RMP evaluator noted that a post market prospective observational cohort study is now planned to compare the risk of cardiovascular events (MACE plus hospitalisations for unstable angina) between gout patients who are new users of lesinurad in combination with a XO inhibitor and those who are continuing users of an XO inhibitor (as monotherapy). The study will also compare the rates of hospitalisation for acute kidney injury. However details of that study have not been provided to the TGA.

## **Risk-benefit analysis**

### **Delegate's considerations**

Lesinurad has both hepatic metabolism and active renal secretion, giving an opportunity for drug interactions from multiple causes. In the studies presented interactions have not been demonstrated to cause large shifts in the PK of either lesinurad or the interacting medicine. Of interest is the potential for lesinurad to reduce the efficacy of probenecid by reducing the AUC of its active metabolite. For medicines with a narrow therapeutic window the effects of lesinurad may require dose adjustment of the co-administered medicine. There is no opportunity for dose adjustment for lesinurad. The effects of mild to moderate hepatic and renal impairment do not suggest that this medicine should not be taken by these individuals as changes in the AUC of lesinurad in individuals with these conditions are relatively small.

Dose selection was appropriate and the minimal dose for sustained effect on serum urate was selected. Three pivotal studies were performed, 2 assessed efficacy and safety of lesinurad in combination with allopurinol and one with febuxostat. The relative efficacy of adjunctive lesinurad has not been compared with adjunctive probenecid.

Lesinurad has been proposed to be used only as adjunctive treatment in combination with a XO inhibitor. Combination oral urate lowering therapy with a XO inhibitor agent and a uricosuric agent is appropriate when the serum urate target has not been met by appropriate dosing of a XO inhibitor. Achievement of target sUA levels is important to reduce the long-term disabilities caused by gouty arthropathy, nephrolithiasis and chronic urate nephropathy that are associated with hyperuracaemia.

In the pivotal studies the choice of sUA < 6.0 mg/dL (<360 µmol/L) at 6 months as the primary endpoint was made after consultation with the FDA and EMA. This target is also consistent with current EU and US clinical practice guidelines for the management of gout. The Australian Therapeutic Guidelines recommends therapy should aim to bring the plasma urate concentration down to 0.3 mmol/L (300 µmol/L) or below. This lower target was a pivotal efficacy measure in the monotherapy study.

Although Study 304 failed to demonstrate a statistically significant difference from placebo for the proposed 200 mg daily dose of lesinurad, and therefore failed to meet its primary endpoint for the 200 mg dose, given the Month 6 was the only timepoint assessed in the study when the 200 mg dose was not superior to placebo for this efficacy measure, it is reasonable to conclude that the 200 mg dose is more effective than placebo in reducing sUA levels to a target of <5.0 mg/dL when used in combination with febuxostat.

Evidence of resultant reduction in arthropathy and renal impairment, which are long term effects of hyperuracemia were not well demonstrated in the clinical trials however the association between sUA lowering to the thresholds in the pivotal trials and long term outcomes is accepted given the current treatment guidelines both in Australia and internationally.

Renal and cardiovascular safety are the primary safety concerns. There appears to be a dose related increase in serum creatinine in subjects taking lesinurad. The higher incidence of renal AE was the reason given by the sponsor for not proceeding with the 400 mg daily dose. The sponsor has contended that increases in serum creatinine are due to increased excretion of uric acid. No reference to support this statement was provided in the module 2.5 clinical overview.

Clinical trials subjects were instructed to take all doses of study medication with food and 1 cup of water, to drink 2 L of liquid a day and to remain well hydrated. Given the association between uricosuric agents and nephrolithiasis these instructions should be emphasised in the PI and CMI. This population is already at increased risk of both renal and cardiovascular adverse events and it appears lesinurad may be associated with a small increase in both types of events, though it is not clear whether the cardiovascular events can be attributed to lesinurad.

Given the renal effects of lesinurad, the already increased risk of renal impairment in patients with poorly controlled hyperuracemia it is reasonable that uricosuric agents be second line agents in the management of hyperuracemia. Monotherapy with lesinurad has not been fully assessed and given the increased risk of renal adverse effects compared with XO inhibitors it should remain as adjunctive treatment to a XO inhibitor.

An association between increased cardiovascular AEs was also seen with febuxostat, a XO inhibitor. Febuxostat is not recommended in patients with ischemic heart disease or congestive heart failure. The same restrictions have been proposed for lesinurad. It is unclear whether further assessment of long term cardiovascular safety should be a condition of registration for lesinurad.

Patients taking probenecid are advised to maintain an alkaline urine. Sufficient sodium bicarbonate (3 g to 7.5 g daily) or potassium citrate (7.5 g daily) is recommended. Uric acid stones develop when the urine saturated with uric acid in the presence of an acid urine pH. No such precaution was taken in the clinical studies and it is not clear whether urinary alkalinisation would be of benefit to patients taking lesinurad.

Salicylic acid and pyrazinamide interactions with probenecid due to competition for active urinary excretion. Salicylic acid is subject to active transport via OAT in the kidney. Lesinurad did not affect the PK of frusemide, an OAT1/3 substrate. In the pooled analysis of the CLEAR studies lesinurad was effective in subjects taking <325 mg aspirin daily as well as in subjects taking thiazide diuretics. Many individuals with hyperuricaemia are likely to be taking low dose salicylic acid prophylaxis due to concomitant cardiovascular disease and/or risk factors so this is an important issue.

## **Proposed action**

### ***Summary of issues***

If lesinurad is taken without a XO inhibitor and/or if the recommended dose is exceeded the incidence of renal adverse effects associated with lesinurad including renal failure and kidney stones is much increased. These effects are most likely due to increased excretion of uric acid.

Lesinurad has not been shown to reduce the number of uric acid tophi over a 12 month period. This was a key secondary endpoint in the clinical trials.

An excess of cardiovascular deaths was seen in the clinical trials. The mechanism of association with lesinurad is not clear. A similar association was seen with the XO inhibitor febuxostat.

### **Request for ACPM advice**

The committee is requested to provide advice on the following specific issues:

- An excess of deaths associated with cardiovascular disease was seen in patients given add-on lesinurad in clinical trials. Similar increases have been seen with the XO inhibitor, febuxostat. The committee is requested to comment on whether it would be appropriate to restrict lesinurad so that it is either contraindicated or not recommended in patients with ischemic heart disease or congestive heart failure.
- There has been no comparative assessment of lesinurad and probenecid, a medication with a similar mechanism of action, long history of use and an established safety profile. Does the committee consider that lesinurad should be restricted to those individuals requiring add-on therapy to a XO inhibitor who are unable to take probenecid?
- Does the committee consider that the indication should state that it is essential that lesinurad is co-administered with a XO inhibitor and that non-adherence (that is, taking lesinurad without the XO inhibitor) may increase the risk of renal events specifically state that monotherapy?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

### ***Pre ACPM preliminary assessment***

The Delegate has no reason to say, at this time, that the application for Zurampic should not be approved for registration subject to negotiation of the PI.

### **Response from sponsor**

AstraZeneca welcomes the opportunity to provide comments on the evaluation of the application proposing to register the new chemical entity Zurampic (lesinurad) and specifically on the issues for which the advice of the ACPM are being sought.

Below is the list of items for which the Delegate has requested advice and AstraZeneca's corresponding responses. Please note that the items that overlap with the summary of issues have been consolidated to reduce redundancy.

### ***Delegate's request for advice***

- *An excess of deaths associated with cardiovascular disease was seen in patients given add-on lesinurad in clinical trials. The mechanism of activity with lesinurad is not clear. Similar increases have been seen with the XO inhibitor, febuxostat. The committee is requested to comment on whether it would be appropriate to restrict lesinurad so that it is either contraindicated or not recommended in patients with ischemic heart disease or congestive heart failure.*

### ***Response***

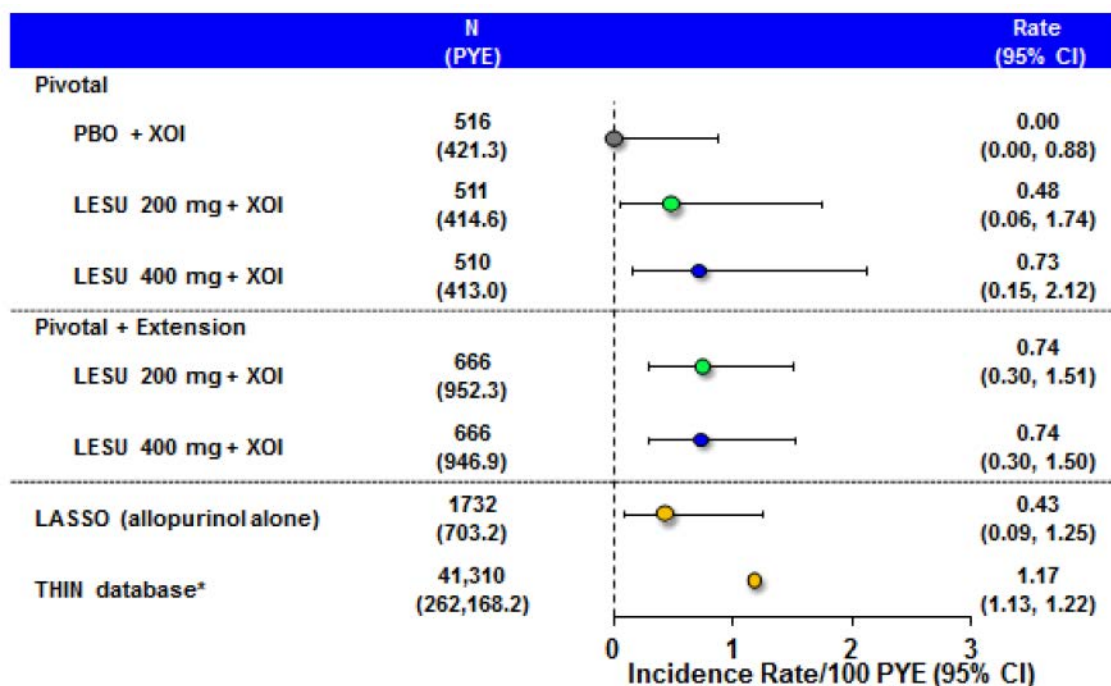
AstraZeneca believes that a restriction on the use of lesinurad in patients with ischemic heart disease or congestive heart failure is not warranted. Lesinurad is a selective inhibitor of reabsorption of uric acid in the kidney. Thus, based on its mechanism of action (MOA), it would not be expected to have adverse cardiovascular (CV) consequences. A review of nonclinical data and data from Phase I and II studies did not identify signals to suggest adverse CV consequences of treatment with lesinurad. In the in vitro and in vivo

CV safety pharmacology studies, lesinurad had no impact on platelet aggregation or other effects suggesting potential adverse CV consequences. In a placebo controlled thorough QT study with positive moxifloxacin control (Study 117), there were no effects on QT interval following lesinurad doses up to 8 times the proposed 200 mg dose and 10 times the exposure observed at 200 mg. There was no effect on heart rate, atrioventricular conduction, or cardiac depolarisation as measured by PR interval and duration of the QRS complex. In addition, there were no clinically relevant morphological changes in electrocardiograms.

In the Phase III randomised controlled clinical studies, the numbers of patients with adjudicated CV deaths (and incidences per 100 patient-years of exposure) were 0 for placebo, 2 (0.5) for lesinurad 200 mg, and 2 (0.5) for lesinurad 400 mg in combination with a XO inhibitor (allopurinol or febuxostat).

As of the most current data cut (2015 interim analyses), the exposure adjusted incidence of overall death for the population of lesinurad treated patients in the pivotal and extension studies was similar to that observed among 1,732 allopurinol treated patients who were followed for 6 months in the LASSO study (also known as ALLO-401), which had similar entry criteria. The exposure adjusted incidence of overall death was also similar to that observed in an analysis of patients with gout in The Health Improvement Network (THIN) database in the United Kingdom, which was performed by an independent epidemiologist (Figure 5). In this latter analysis, 41,310 patients were matched for age, gender, and other key entry criteria that were used in the pivotal Phase III combination therapy studies.

**Figure 5. Death Rates Among Patients With Gout (Lesinurad Phase III Combination Therapy Studies, LASSO Study, and THIN Database).**



Abbreviations: CI, confidence interval; LESU, lesinurad; N, number; PBO, placebo; PYE, patient-years of exposure; THIN, The Health Improvement Network; XOI, XO inhibitor (allopurinol/febuxostat). \*Patients in the United Kingdom with gout  $\geq 18$  and  $\leq 85$  years of age, male or female. Matched to lesinurad trial program age and sex distribution. Excluding patients with a malignancy within the past 5 years; patients with a history of angina, myocardial infarction, stroke, deep vein thrombosis, or pulmonary embolism; and patients with anticoagulant use within the past year. Data on file. Note: Lesinurad Pivotal + Extension results based on new analyses including additional data from the ongoing extension studies, Study 306 and Study 307, with data cutoff dates of 15 May 2015 and 12 March 2015, respectively.



Overall, the rate of fatal serious adverse events (SAEs) with lesinurad was low and consistent with this population demographic and the individual patients' medical histories. The small number of CV deaths observed in the pooled analysis of data from the pivotal Phase III combination therapy studies places limitations on assessment of treatment associated differences in risk of CV deaths. However, AstraZeneca proposes to add the following subsection to the "PRECAUTIONS" section of the PI:

***Cardiovascular events***

*In clinical studies, major adverse cardiovascular events (defined as cardiovascular deaths, non-fatal myocardial infarctions, or non-fatal strokes) were observed with Zurampic. A causal relationship with Zurampic has not been established.*

In addition, AstraZeneca proposes to include the following subsection in the "ADVERSE EFFECTS" section of the PI:

***Cardiovascular safety***

*Cardiovascular events and deaths were adjudicated as major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in the Phase 3 randomised controlled studies of Zurampic. In the randomised controlled studies, the numbers of patients with adjudicated MACE events (incidences per 100 patient-years of exposure) were: 3 (0.71) for placebo, 4 (0.96) for lesinurad 200 mg, and 8 (1.94) for lesinurad 400 mg when used in combination with a XO inhibitor.*

While a causal relationship between lesinurad and CV events has not been established due to the low number of CV events, AstraZeneca plans to further evaluate the potential for a CV signal in a robust prospective observational cohort database study (PASS). The study will serve as a signal detection tool to evaluate CV risk, and additionally will further characterise renal safety for lesinurad. AstraZeneca believes this study will allow for a rapid accumulation of valid data and thus can provide timely results to address the question of potential CV risk and better define renal risk. Multiple databases in the US and EU will be utilised to compare new users of lesinurad in combination with an XO inhibitor with users of an XO inhibitor alone. The primary outcome will be major adverse cardiovascular events (MACE) plus hospitalisation for unstable angina (MACE-plus) in order to assess the potential CV risk of lesinurad 200 mg in clinical practice. To further characterise renal safety, hospitalisations for acute kidney injury will be included as a secondary outcome. The patient population will be stratified by baseline CV risk.

***Delegate's request for advice***

- There has been no comparative assessment of lesinurad and probenecid, a medication with a similar mechanism of action, long history of use and an established safety profile. Does the committee consider that lesinurad should be restricted to those individuals requiring add-on therapy to a XO inhibitor who are unable to take probenecid?*

***Response***

Although probenecid and lesinurad have a similar MOA (inhibition of uric acid transporter 1 [URAT1]), AstraZeneca did not conduct a comparative assessment, but believes that lesinurad should not be restricted to those requiring add-on therapy to an XO inhibitor who are unable to take probenecid, as discussed below.

Probenecid is a rarely prescribed uricosuric agent, accounting for only 1.1% of all anti-gout prescriptions in Australia (IMS Health National Sales Audit). This is likely due to the dosing frequency (2 to 4 times a day) and multiple DDIs with medications commonly used in patients with gout (for example, NSAIDs, renin angiotensin aldosterone system inhibitors, loop diuretics, analgesics, and muscle relaxants; sulfonylureas, antibiotics,

antimicrobials, antiretrovirals).<sup>33</sup> Many of the DDIs are related to the inhibition of 2 important renal transporters involved in the disposition of many drugs; that is, OAT1 and OAT3.

The safety profile of probenecid as a ULT in patients with gout in randomised clinical studies is not well understood. A recent Cochrane review identified only 2 randomised controlled studies in gout comparing probenecid monotherapy with another ULT, benzbromarone (benzbromarone is not registered in Australia), with 35 patients in each study receiving probenecid, and one “quasi-randomised” study with 17 patients receiving probenecid monotherapy compared to allopurinol.<sup>34</sup> A review of the literature showed that evaluation of probenecid in combination with an XO inhibitor in patients with gout is limited to 2 small open-label studies with 20 or fewer patients receiving the combination.<sup>35</sup>

Lesinurad was specifically developed as a second line treatment option for patients unable to achieve target serum uric acid with an XO inhibitor alone. Unlike probenecid, lesinurad is a selective uric acid reabsorption inhibitor and does not inhibit the renal transporters OAT1 and OAT3 in humans. Thus, use of lesinurad is not limited by the multiple OAT1 and OAT3 mediated DDIs. Of note, nearly 40% of the patients in the pivotal Phase III lesinurad studies received a concurrent medication that has a known DDI with probenecid.

Moreover, in contrast to probenecid, the safety and efficacy of lesinurad is well characterised with use in approximately 1,800 patients with gout, including more than 1,500 patients treated with lesinurad in combination with an XO inhibitor in Phase III studies. The recommended dose of lesinurad 200 mg in combination with an XO inhibitor has a safety profile comparable to an XO inhibitor alone with the exception of transient and reversible sCr elevations.

It is for these reasons that AstraZeneca believes that lesinurad should not be restricted only to patients who are unable to take probenecid.

#### ***Delegate's request for advice***

- *Does the committee consider that the indication should state that it is essential that lesinurad is co-administered with a XO inhibitor and that non adherence (that is, taking lesinurad without the XO inhibitor and/or if the recommended dose is exceeded) may increase the risk of renal adverse effects (including renal failure and kidney stones)? These effects are most likely due to increased excretion of uric acid.*

#### ***Response***

The importance of co-administration of lesinurad with an XO inhibitor is already emphasised throughout the PI with appropriate language in the INDICATIONS, PRECAUTIONS, ADVERSE EFFECTS, and the DOSAGE AND ADMINISTRATION sections. However, AstraZeneca agrees with the Delegate's request to amend the indication to further clarify that Zurampic must be taken with an XO inhibitor (that is, allopurinol or febuxostat) as follows:

#### ***INDICATIONS***

*Zurampic is indicated for use in combination with a XO inhibitor, allopurinol or febuxostat, in patients with gout who have uncontrolled disease and warrant additional therapy.*

<sup>33</sup> Probenecid 500 mg tablet (Australian package insert) Rev May 2013.

<sup>34</sup> Kydd AS, Seth R, Buchbinder R, Edwards CJ, Bombardier C. Uricosuric medications for chronic gout. The Cochrane database of systematic reviews. 11: CD010457 (2014).

<sup>35</sup> Reinders MK, et al. Biochemical effectiveness of allopurinol and allopurinol-probenecid in previously benzbromarone-treated gout patients. *Clin Rheumatol*. 26: 1459-1465 (2007); Stocker SL, et al. Pharmacokinetic and pharmacodynamic interaction between allopurinol and probenecid in patients with gout. *J Rheumatol*. 38: 904-910 (2011).

AstraZeneca acknowledges that renal events, including transient increases in sCr, renal-related AEs, and kidney stones were observed during treatment with lesinurad. These events were likely related to the MOA of lesinurad and were mitigated by co-administration with an XO inhibitor. Renal events were observed more frequently with lesinurad 400 mg, which is twice the dose proposed for registration. For the recommended dose of 200 mg lesinurad in combination with an XO inhibitor, the incidence of transient and reversible sCr elevations was higher than that for XO inhibitor alone, but the incidences of renal related AEs and kidney stone AEs (5.7% and 0.6%, respectively) were similar to those for XO inhibitor alone (4.5% and 1.7%, respectively). In the pivotal Phase III studies, the incidence of renal related SAEs was low and comparable across treatment groups with no dose ordering. No renal related SAEs were reported in the lesinurad 200 mg in combination with XO inhibitor group.

Use of lesinurad 200 mg as a monotherapy was not evaluated in long-term clinical studies, however, data from a Phase IIb study in 96 patients treated for up to 4 weeks did not reveal an increase in renal related or kidney stone AEs. Three patients experienced sCr elevations of  $\geq 1.5x$  Baseline, all of which resolved on study. Based on these data, the transient intermittent use of lesinurad 200 mg as monotherapy is not anticipated to result in significant renal toxicity. However, monotherapy use is not recommended for lesinurad. Lesinurad should only be used in combination with an XO inhibitor, which is stated throughout the PI. In addition, AstraZeneca has revised the entire "PRECAUTIONS, Renal events" section per the Delegate's comments:

#### **Renal events**

*Zurampic must not be given as monotherapy. A higher incidence of serum creatinine (sCr) elevations and renal-related adverse reactions including serious adverse reactions (e.g. acute renal failure) was observed with Zurampic 400 mg (twice the maximum daily dose) when given alone or in combination with a XO inhibitor, with the highest incidence when Zurampic 400 mg was given as monotherapy. This effect is likely due to the increased amount of uric acid being handled and excreted by the kidney. If while taking Zurampic a patient experiences signs or symptoms suggestive of acute renal failure (reduced urinary output, generally feeling unwell, fatigue, nausea, vomiting, metallic taste, loss of appetite) or nephrolithiasis (flank pain, hematuria), renal function should be assessed.*

*Treatment with Zurampic 200 mg in combination with a XO inhibitor was associated with an increased incidence of transient sCr elevations. There was no association between baseline renal function and the incidence of these sCr elevations. Adverse reactions related to renal function can occur after initiating Zurampic (see ADVERSE EFFECTS).*

*Renal function should be evaluated prior to initiation of Zurampic and periodically thereafter. Interruption of Zurampic should be considered if sCr is elevated to greater than 2 times the pre-treatment value. Interrupt treatment in patients who report symptoms that may indicate acute uric acid nephropathy including flank pain, nausea or vomiting, and measure sCr promptly. Zurampic may be resumed when sCr returns to pre-treatment levels.*

Text has also been added to the "DOSAGE AND ADMINISTRATION" section of the PI regarding the maximum recommended dose of lesinurad as follows:

*The recommended dose of Zurampic is 200 mg once daily in the morning. This is also the maximum daily dose.*

AstraZeneca believes that the proposed language in the PI is sufficient to allow for the safe and appropriate use of Zurampic.

***Delegate's request for advice***

Lesinurad has not been shown to reduce the number of uric acid tophi over a 12 month period. This was a key secondary endpoint in the clinical trials.

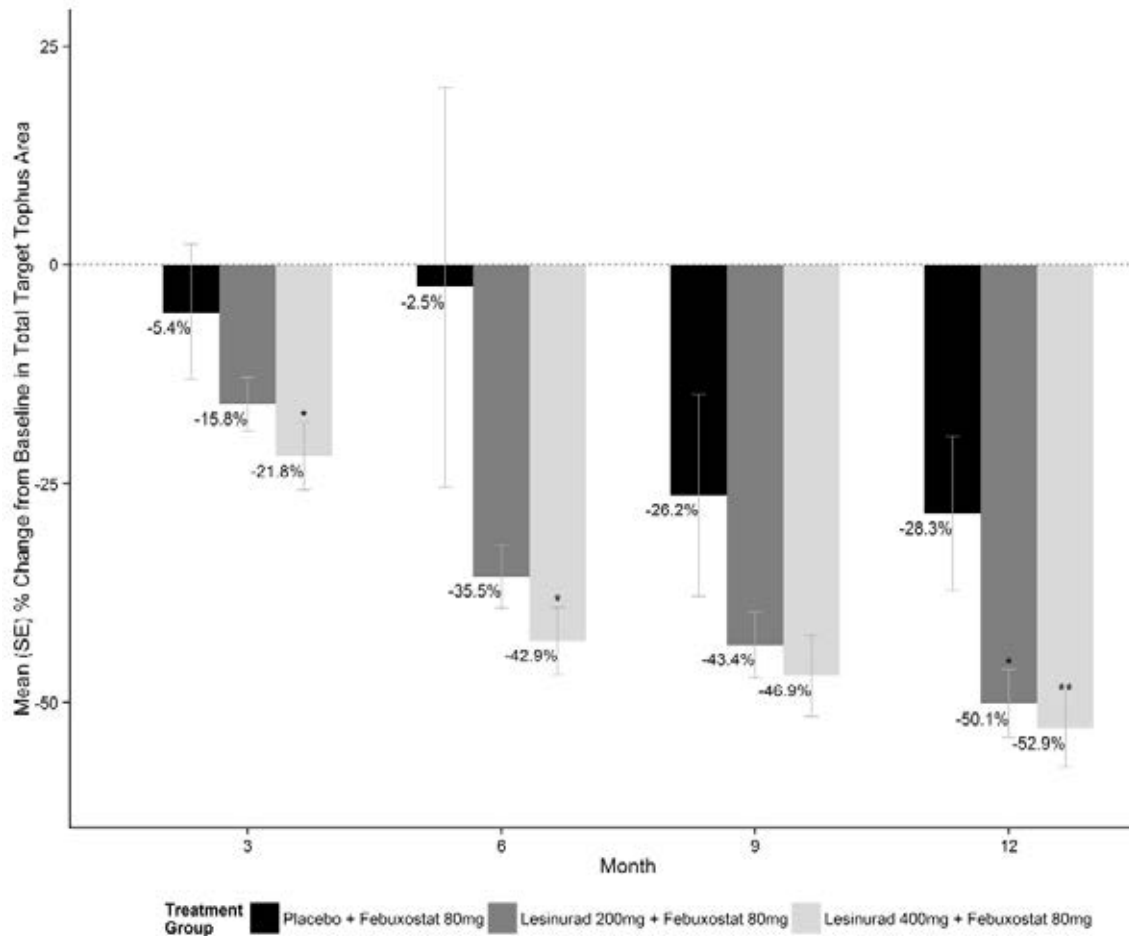
***Response***

AstraZeneca acknowledges that the key secondary endpoints with regard to target tophi resolution were not met. A number of factors limited the ability to observe treatment differences in the pivotal studies, including the small number of patients with tophi in the pivotal allopurinol combination studies and the duration of treatment.

Interpretation of the tophus results for CLEAR1 and CLEAR2 is limited due to the small number of patients with target tophi enrolled in these studies (9% in CLEAR1 and 16% in CLEAR2). CRYSTAL required all patients to have tophaceous gout. Although treatment group differences were not statistically significant, a positive trend favouring lesinurad was noted with more patients in the lesinurad 200 mg and 400 mg in combination with febuxostat groups achieving a complete resolution compared with febuxostat alone: 25.5% and 30.3% versus 21.1%, respectively.

The duration of the lesinurad pivotal studies may not have been sufficient to demonstrate differences between the treatment groups for complete resolution. However, there was evidence of increased tophi reduction in CRYSTAL, as Zurampic 200 mg in combination with febuxostat resulted in a greater mean percent reduction in the sum of areas for all target tophi at Months 3, 6, 9, and 12 (pre-specified secondary endpoint) compared with febuxostat alone, with a p value <0.05 at Month 12 (Figure 6). In addition, data from the long term uncontrolled extension studies of lesinurad in combination with an XOI show that continued treatment and maintenance of target sUA levels over time results in more tophus area reduction as well as more complete resolution of tophi, which AstraZeneca is planning to submit as a post approval variation.

**Figure 6. Per cent change from baseline in sum of the areas for all target tophi by visit in CRYSTAL.**



Abbreviations: ITT, intent-to-treat; LOCF, last observation carried forward; SE, standard error. Figure depicts arithmetic means, statistical significance is based on difference in least square means.

\*p < 0.05 versus placebo + febuxostat 80 mg

\*\* p < 0.01 versus placebo + febuxostat 80 mg

### Advisory committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Zurampic film coated tablets containing 200 mg of lesinurad to have an overall positive benefit-risk profile for the amended indication;

*Zurampic is indicated for use in combination with a xanthine oxidase inhibitor, allopurinol or febuxostat, in patients with gout who have uncontrolled disease and warrant additional therapy.*

In making this recommendation, the ACPM:

- noted efficacy has been demonstrated only as adjunctive therapy with allopurinol or febuxostat
- was of the view that safety appears acceptable with the proposed RMP
- noted possible safety signals identified (cardiovascular and renal); the small numbers of patients exposed and the relatively short duration of treatment reported limit a more detailed assessment of the benefit-risk profile
- noted evidence of resultant reduction in arthropathy and renal impairment, which are long term effects of hyperuraceamia were not well demonstrated in the trials

**Proposed conditions of registration**

The ACPM agreed with the Delegate on the proposed conditions of registration.

**Proposed PI/ CMI amendments**

The ACPM agreed with the delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- the exclusion criteria for renal impairment in the CONTRAINDICATIONS section of the PI and relevant sections of the CMI be set at eGFR > 45 not 30 mL/min
- The terminology used for renal impairment should be Chronic Kidney Disease (CKD 1-6)

**Specific advice**

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. *An excess of deaths associated with cardiovascular disease was seen in patients given add-on lesinurad in clinical trials. Similar increases have been seen with the xanthine oxidase inhibitor, febuxostat. The committee is requested to comment on whether it would be appropriate to restrict lesinurad so that it is either contraindicated or not recommended in patients with ischemic heart disease or congestive heart failure.*

The ACPM noted that patients with recent cardiovascular disease were excluded; however 78% of the trial population had CV co-morbidities but no increased ECG abnormalities with lesinurad including QT prolongation. Nonetheless, of the 13 deaths reported 11 were from cardiovascular adverse events and all were in the lesinurad treatment group. The ACPM was of the view that the PI should clearly indicate the discrepancy in cardiovascular deaths, perhaps under precautions.

2. *There has been no comparative assessment of lesinurad and probenecid, a medication with a similar mechanism of action, long history of use and an established safety profile. Does the committee consider that lesinurad should be restricted to those individuals requiring add-on therapy to a xanthine oxidase inhibitor who are unable to take probenecid?*

The ACPM noted that maximal doses of allopurinol were not used in most patients prior to inclusion and during the trials. The median dose of allopurinol used was 300 mg. There were no comparison studies where allopurinol doses were increased to the maximal  $\geq 600$  mg/day. The ACPM considered it was possible there may have been no significant difference in the primary outcome if this had been the case; however, this was not tested.

Given the considerable experience with allopurinol, the ACPM advised that lesinurad should be considered a second line treatment and its use should be considered only after a maximal dose allopurinol has been adequately trialled.

3. *Does the committee consider that the indication should state that it is essential that lesinurad is co-administered with a xanthine oxidase inhibitor and that non-adherence (i.e. taking lesinurad without the xanthine oxidase inhibitor) may increase the risk of renal events?*

The ACPM advised that the indication should state that it is essential that lesinurad is co-administered with a XO inhibitor. As there appears to be a dose-related increase in serum creatinine in subjects taking lesinurad, the warning with regard to potential renal events is warranted. Given the small patient numbers studied with an eGFR 30 – 45 mL/min and the nephrotoxicity potential, the ACPM recommended CONTRAINDICATION criteria be set at eGFR > 45 not 30 mL/min.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

### **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Zurampic (lesinurad) 200 mg film coated tablet blister pack, indicated for:

*Zurampic is indicated in combination with a xanthine oxidase inhibitor for the treatment of hyperuricaemia associated with gout in patients who have not achieved target serum uric acid levels with an adequate dose of a xanthine oxidase inhibitor alone.*

### **Specific conditions of registration applying to these goods**

- The lesinurad EU-RMP, version 1 (dated 9 December 2004, Data Lock Point 20 September 2014) with an ASA version 1 (dated February 2015) to be revised as agreed with the TGA, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

## **Attachment 1. Product Information**

The PI approved for Zurampic at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

## **Attachment 2. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

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