CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207988Orig1s000

<u>OTHER REVIEW(S)</u>

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA# 207988
Product Name: Lesinurad

PMR/PMC Description: A randomized, controlled, clinical trial to evaluate the safety of lesinurad 200mg on a background of concomitant xanthine oxidase inhibitor, with respect to renal function and renal adverse events in gout patients who have not achieved target serum uric acid with a xanthine oxidase inhibitor alone. Enrollment should be enriched with subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/min). The minimum treatment duration should be 2 years. The trial must also include an assessment of cardiovascular (CV) safety based on an independent adjudication of prospectively defined and collected CV events.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	10/31/2016
	Trial Completion:	6/30/2025
	Final Report Submission:	12/31/2025
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☒ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   The clinical program for lesinurad included 1 year efficacy and safety data. While the clinical program established the efficacy and safety of the product, renal toxicity was identified as a safety signal. No serious renal adverse events were seen in the clinical program, but long term data is needed to understand the renal toxicity in patients with renal impairment. A small imbalance in non-fatal MI was also noted in the clinical program and long term data is needed to further investigate whether there is a cardiovascular safety signal.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Renal toxicity was identified as a safety signal in the lesinurad clinical program. Renal toxicity included elevations in serum creatinine, but no serious renal adverse events were seen in the clinical program (e.g. ESRD). Long term data is needed to understand the renal toxicity in patients with renal impairment. A small imbalance in non-fatal MI was also noted in the clinical program and long term data is needed to further investigate whether there is a cardiovascular safety signal.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**
     - ☐ Accelerated Approval (subpart H/E)
     - ☐ Animal Efficacy Rule
     - ☐ Pediatric Research Equity Act
     - ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - ☒ Assess a known serious risk related to the use of the drug?
     - ☐ Assess signals of serious risk related to the use of the drug?
     - ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - ☐ Analysis of spontaneous postmarketing adverse events?
       Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
     - ☐ Analysis using pharmacovigilance system?
       Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
     - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
     - ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, controlled, clinical trial to evaluate the safety of lesinurad 200mg on a background of concomitant xanthine oxidase inhibitor, with respect to renal function and renal adverse events in gout patients who have not achieved target serum uric acid with a xanthine oxidase inhibitor alone. Enrollment should be enriched with subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/min). The minimum treatment duration should be 2 years. The trial must also include an assessment of cardiovascular (CV) safety based on an independent adjudication of prospectively defined and collected CV events.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☒ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☒ There is a significant question about the public health risks of an approved drug
☒ There is not enough existing information to assess these risks
☒ Information cannot be gained through a different kind of investigation
☒ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☒ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

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/s/

SALLY M SEYMOUR
12/21/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 10, 2015
To:	Badrul Chowdhury, MD, PhD Director **Division of Pulmonary, Allergy and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Roberta Szydlo, RPh, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ZURAMPIC (lesinurad)
Dosage Form and Route:	Tablets for oral use
Application Type/Number:	NDA 207988
Applicant:	Ardea Biosciences

1 INTRODUCTION

On December 29, 2014, Ardea Biosciences submitted for the Agency's review an original New Drug Application (NDA) for ZURAMPIC (lesinurad). ZURAMPIC (lesinurad) tablets, for oral use, is proposed to treat hyperuricemia associated with gout in combination with xanthine oxidase inhibitor.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) on March 3, 2015, and February 26, 2015, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ZURAMPIC (lesinurad) tablets.

2 MATERIAL REVIEWED

- Draft ZURAMPIC (lesinurad) MG received on December 29, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on November 23, 2015.
- Draft ZURAMPIC (lesinurad) MG received on December 29, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on November 30, 2015.
- Draft ZURAMPIC (lesinurad) Prescribing Information (PI) received on December 29, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on November 23, 2015.
- Draft ZURAMPIC (lesinurad) Prescribing Information (PI) received on December 29, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on November 30, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
12/10/2015

ROBERTA T SZYDLO
12/10/2015

SHAWNA L HUTCHINS
12/10/2015

LASHAWN M GRIFFITHS
12/10/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 7, 2015

To: Jessica Lee, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Roberta Szydlo, Senior Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Twyla Thompson, Deputy Division Director, OPDP

Subject: NDA 207988
OPDP labeling comments for ZURAMPIC® (lesinurad) tablets, for oral use (Zurampic)

In response to DPARP's consult request dated February 26, 2015, OPDP has reviewed the draft labeling (Package Insert [PI], and Carton/Container Labeling) for Zurampic and offers the following comments. We note that the February 26, 2015, consult request form requested review of the PI only. However, per email clarification from DPARP (Jessica Lee) dated December 1, 2015, OPDP comments are requested on the draft PI, carton/container labeling, and Medication Guide.

OPDP's comments regarding the proposed Medication Guide will be incorporated into a collaborative review by the Division of Medical Policy Programs (DMPP) and OPDP and will be provided under separate cover.

PI:

OPDP's comments on the PI are provided directly below and are based on the draft labeling titled "NDA 207988_Ardea Clean_PI_11.23.15.docx" (attached) that was obtained from DPARP's SharePoint site on December 1, 2015.

Carton/Container Labeling:

OPDP has reviewed the proposed carton and container labeling submitted by the applicant on November 19, 2015, (eCTD sequence # 0030) and attached below.

We have no comments at this time on the proposed carton and container labeling.

Thank you for your consult. If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
12/07/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	Nov 4, 2015
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 207988
Product Name and Strength:	Zurampic (lesinurad) Tablets, 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Ardea Biosciences, Inc. (a member of the AstraZeneca Group)
Submission Date:	December 29, 2015 and May 21, 2015
OSE RCM #:	2015-51
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Team Leader:	Kendra Worthy, PharmD

1 REASON FOR REVIEW

This review evaluates the Prescribing Information (PI)) and container labels for Zurampic (lesinurad) for areas of vulnerability that could lead to medication errors. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested this review as part of their evaluation of NDA 207988 for Zurampic.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the Prescribing Information (PI) and container labels identified the following areas that could be improved from a medication error perspective:

- The NDC numbers in Section 16 (Titled 'How Supplied/Storage and Handling') of the PI and the NDC numbers on the container labels are denoted by placeholders.
- The Professional Sample-Not For Sale statement is not displayed on the principal display panel of the container label.
- There is a designated placeholder on the container labels that is in close proximity to the lot and expiration number.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Prescribing Information (PI) and container labels can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

The NDC numbers in Section 16 (Titled 'How Supplied/Storage and Handling') of the PI are denoted by placeholders. Request that the applicant replace all placeholders with the actual NDC numbers.

4.2 RECOMMENDATIONS FOR ARDEA BIOSCIENCES

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels (All)

1. Replace the NDC number placeholders with the actual NDC numbers.
2. Revise the Usual Adult Dosage statement to the following:
   "See full prescribing information"
3. You have designated a placeholder (XXXX-XX) that is in close proximity to the lot and expiration number and may be mistaken as the lot and/or expiration number. Ensure that this placeholder (XXXX-XX) is clearly differentiated, distinguishable, and in reasonable proximity away from the lot and expiration numbers to avoid misinterpretation.

B. Professional Sample Container Label

1. Relocate the "PROFESSIONAL SAMPLE-NOT FOR SALE" statement to the principal display panel under the "Rx only" statement. Relocate the AstraZeneca name and logo to the side panel to ensure there is adequate space on the principal display panel for more important information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zurampic that Ardea Biosciences submitted on December 29, 2014.

Table 2. Relevant Product Information for Zurampic	
Initial Approval Date	N/A
Active Ingredient	lesinurad
Indication	Indicated in combination with a xanthine oxidase inhibitor for the (b) (4) treatment of hyperuricemia associated with gout in patients who have achieved target serum uric acid levels with a xanthine oxidase inhibitor alone.
Route of Administration	Oral
Dosage Form	Tablets
Strength	200 mg
Dose and Frequency	200 mg once daily in combination with a xanthine oxidase inhibitor, including allopurinol or febuxostat
How Supplied	5, 30, 90 count bottles
Storage	20°C to 25°C (68° to 77°F); excursions permitted 15 – 30°C (59°F – 86°F)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Zurampic labels and labeling submitted by Ardea Biosciences, Inc. on December 29, 2015 and May 21, 2015.

- Container label
- Prescribing Information-No image

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

G.2 Label and Labeling Images

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TERESA S MCMILLAN
11/04/2015

KENDRA C WORTHY
11/04/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: August 4, 2015

From: Christos Mastroyannis, M.D.
Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S.
Acting Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, MD
Division Director,
Division of Pediatric and Maternal Health

To: The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Drug: Zurampic (lesinurad)

NDA: 207988

Subject: Maternal Health Labeling Recommendations

Applicant Ardea Biosciences

Materials Reviewed:

December 29, 2014; NDA– Original NDA submission from Ardea Biosciences
April 9, 2015; Draft Labeling Text (tracked Changes) to comply with PLLR requirements by Ardea Biosciences
April 30, 2015; 4-Month Safety Update Report
July 15, 2015; Proposed edits to Ardea's draft pregnancy labeling for lesinurad by Matthew Whittaker, PT reviewer.
Literature review.

Consult Question: "To comply with the Pregnancy and Lactation Labeling Rule, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) would like to request that the Maternal Health Team review Section 8.1 of the label. DPARP will provide revised labeling for the Animal Data component."

INTRODUCTION

On December 29, 2014, Ardea Biosciences submitted NDA 207988 for Zurampic (lesinurad) tablets for oral use to be used for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor (XOI). NDA 207988 is an original 505(b)(1) New Molecular Entity (NME) NDA.

DPARP consulted the Division of Pediatric and Maternal Health (DPMH) to review the proposed Pregnancy (8.1), Lactation (8.2), and Females and Males of Reproductive Potential (8.3) sections in the Zurampic product labeling.

On December 4, 2014, the Food and Drug Administration (FDA) published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling", also known as the Pregnancy and Lactation Labeling Rule (PLLR)[1]. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential (if applicable). Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological products labeling and a new format is required for all drug products that are subject to the 2006 Physician Labeling Rule (PLR)[2], to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR took effect on June 30, 2015. This pending new drug application was submitted to the FDA prior to June 30, 2015, and the applicant has chosen to comply voluntarily with the PLLR conversion of the lesinurad labeling with the approval of this NDA.

This review provides recommended revisions and structuring of information related to the Pregnancy (8.1), Lactation (8.2), and Females and Males of Reproductive Potential (8.3) subsections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with PLLR regulatory requirements.

BACKGROUND

Gout and Treatment Options

Gout is the most common form of inflammatory arthritis.[3] It affects more than 8 million people in the United States, approximately 9 million people in Europe, and more than 3

[1] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).
[2] Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).
[3] Doghramji PP, Wortmann RL. Hyperuricemia and gout: new concepts in diagnosis and management. *Postgrad Med*. 2012;124(6):98–109.

million in Japan.[4,5] Gout occurs more often in men, primarily because women tend to have lower uric acid levels. After menopause, however, women's uric acid levels approach those of men. Men also are more likely to develop gout earlier, usually between the ages of 30 and 50, whereas women generally develop signs and symptoms of gout after menopause.

Gout results from a metabolic disorder, hyperuricemia, where excessive concentrations of uric acid in the blood lead to deposition of monosodium urate crystals in and around the joints and other connective tissues.[6] Hyperuricemia results from either the overproduction of uric acid (10%) or under-excretion of the urate (90%). Treatment of hyperuricemia relies on two major modalities of therapy: non-pharmacological and pharmacological. Clinical studies revealed that lifestyle modification alone reduces serum uric acid levels by ~ 10-18%.[7]
Pharmacological management involves:
i) decreasing the *in vivo* production of uric acid, with use of xanthine oxidoreductase inhibitors (XOI) such as allopurinol
ii) promoting increased excretion of uric acid in the urine by using uricosuric agents
iii) metabolizing uric acid to allantoin using pegloticase, a PEGylated uricase, allowing more efficient removal through urinary excretion.[8]

Conceptually, an additive serum uric acid (SUA) lowering effect will occur with the combination of two different modes of action, i.e., a production inhibitor (XOI) plus a uricosuric, such as blocker of urate transporter 1(URAT1), organic anion transporters (OAT1, OAT3 or OAT4) and/or glucose transporter 9.[9,10] Uricosuric agents inhibit the uric acid reabsorption thus decreasing the SUA levels. Drugs that target uric acid transporters are emerging as potential new therapies.

Lesinurad is a selective uric acid reabsorption inhibitor, which acts on both URAT1 and OAT4, located in the proximal tubule of the kidney, and thus promoting the excretion of uric acid. URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. By inhibiting URAT1 and OAT4, lesinurad acts as an uricuretic agent, promoting uricuresis and thereby lowering SUA.

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[4] de Oliveira EP, Burini RC. High plasma uric acid concentration: causes and consequences. *Diabetol Metab Syndr*. 2012;4:12.
[5] Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis*. 2015;74(4):661–667.
[6] Bieber JD, Terkeltaub RA. Gout: on the brink of novel therapeutic options for an ancient disease. *Arthritis Rheum*. 2004;50(8):2400–2414.
[7] Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. Curr Opin Rheumatol. 2010 Mar;22(2):165-72.
[8] Crittenden DB, Pillinger MH. New therapies for gout. Annu Rev Med. 2013;64:325-37.
[9] Caulfield MJ[1], Munroe PB, O'Neill D, Witkowska K, Charchar FJ, Doblado M, Evans S, et al. SLC2A9 is a high-capacity urate transporter in humans. PLoS Med. 2008;5(10).
[10] Shahid A, Singh JA. Investigational drugs for hyperuricemia. Expert Opin Investig Drugs. 2015;24(8):1013-1030.

Regulatory History

- On September 30, 2009, Investigational New Drug application (IND) 102,128 was submitted to the FDA for lesinurad for the treatment of gout.
- On July 15, 2011, Ardea was granted an End of Phase 2 (EOP2) meeting by Division of Pulmonary, Allergy, and Rheumatology Products (DPARP).
- On September 26, 2014, the pre-NDA meeting took place.
- On December 29, 2014, NDA 207988 for Zurampic was submitted to the FDA.

HUMAN REPRODUCTION AND PREGNANCY DATA

Discussion: Review of Data

A search of published literature was performed and no information was found reporting the use of Zurampic in pregnant women.

The applicant has conducted no studies of lesinurad in pregnant women. In addition, no studies have been conducted to determine whether lesinurad is present in breast milk or to assess the effects of lesinurad in breast-fed infants.

Lesinurad was studied mostly in males (92-100%), and of white race (83-100%). The age ranged from 21 to 75 years, with means among the treatment groups from 48 to 60 years. In the current submission, there were no pregnancies during the treatment period. There have been no reports of use of lesinurad during lactation in the clinical program. In the submitted 120 days safety report by the applicant, no reports of use of lesinurad during pregnancy or lactation exist. As this is the first marketing application for lesinurad, there is no postmarketing data at this time.

Reviewer's comment

There is no data to draw any safety conclusions about the effects of Zurampic (lesinurad) during pregnancy and lactation.

A. Zurampic and Pregnancy

Animal Data

As per Pharmacology –Toxicology reviewer, Matthew Whittaker, PhD, during the mid-cycle review meeting, there were no nonclinical issues that would affect the approvability of Zurampic. In his review of the labeling, he states that in pregnant rats dosed during the period of organogenesis (from gestation days 6-17), lesinurad was not teratogenic at dose exposures up to approximately 45 times the MRHD (on an AUC basis at maternal oral doses up to 300 mg/kg/day). He also states that when pregnant rabbits were dosed during the period of organogenesis (from gestation days 7-20), lesinurad was not teratogenic at dose exposures up to approximately 10 times the MRHD (on an AUC basis at maternal oral doses up to 75 mg/kg/day). In reference to mutagenesis, lesinurad was negative in the *in vitro* Ames assay and chromosomal aberration test in Chinese hamster ovary (CHO) cells, and *in vivo* micronucleus assay in rat bone marrow.

In a pre- and post-natal development study in pregnant female rats dosed from gestation day 7 through lactation day 20, lesinurad had no effects on delivery or growth and development of offspring at a dose approximately 5 times the MRHD (on a mg/m^2 basis at a maternal oral

dose of 100 mg/kg/day). No effects on fertility endpoints were observed. "However, offspring survival was reduced and surviving offspring had decreased mean body weights at birth and during lactation along with delayed sexual maturation (females only) at exposures ≥10 times the MRHD (on a mg/m^2 basis at maternal oral doses of 200 mg/kg/day and higher). These findings occurred in the presence of severe maternal toxicity, including mortality".

Reviewer's comment
From the animal data during the drug development process as per P/T reviewer, lesinurad was not teratogenic during the embryo-fetal development studies in rats and rabbits. In the pre- and post-natal development study in pregnant female rats dosed from gestation day 7 through lactation day 20, lesinurad had no effects on delivery or growth and development of offsprings. DPMH does not recommend studying the drug during pregnancy formally as a post-marketing requirement because animal reproductive studies failed to identify a drug associated risk and the use of the drug in females of reproductive potential is relatively low. As stated above, gout does not affect younger individuals during their reproductive years, and women tend to develop gout after menopause.

B. Zurampic and Lactation

The Drugs and Lactation Database (LactMed)[11] was searched for available lactation data on with the use of Zurampic. No entries were found. There is no information regarding the presence of lesinurad in human milk, the effects on the breastfed infant, or the effects on milk production. Lesinurad is present in the milk of rats (as per P/T reviewer, plasma and milk concentrations of lesinurad were approximately equal).

The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Reviewer's Comment:
It is not known whether Zurampic is present in human milk. DPMH does not recommend studying the drug during lactation formally as a post-marketing requirement because use of the drug in lactating women is predicted to be relatively low (see reviewer comment above). However, DPMH acknowledges that there are no data available on levels of this drug in breast milk, and any data regarding the presence of the drug in breast milk would be informative. Further studies may provide a better understanding of use of Zurampic during lactation.

C. **Zurampic and Females and Males of Reproductive Potential**

Infertility
There are no human data available regarding the effects of Zurampic on fertility. No fertility or early embryonic development studies were conducted in humans. Therefore, the Infertility ~~subheading is omitted from su~~bsection 8.3 of the labeling.

[11] United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed*). http://toxnet nlm.nih.gov/cgi-bin/sis/htmlgen?LACT

Lesinurad's effects on fertility were assessed in animals. Fertility and reproductive performance were unaffected in male or female rats who received oral doses up to 300 mg/kg/day (approximately 15 times the MRHD on an mg/m^2 basis).

Contraception
There are no recommendations for contraception use with Zurampic in labeling because no drug-associated risks to the pregnant women or the fetus have been demonstrated.

CONCLUSION/RECOMMENDATIONS

1. DPMH does not recommend studying the drug during pregnancy formally as a post-marketing requirement because animal reproductive studies failed to identify a drug-associated risk and the use of the drug in females of reproductive potential is relatively low.
2. The Pregnancy (8.1) and Lactation (8.2) subsections of labeling were structured to be consistent with the PLLR. The Females and Males of Reproductive Potential (8.3) subsection is omitted because there are no recommendations on contraception or fertility.
3. Edits to the labeling are provided below.
4. DPMH refers to the NDA action for final labeling.

DPMH has the following recommendations for Zurampic labeling:

FULL PRESCRIBING INFORMATION: CONTENTS

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no available data on use of Zurampic in pregnant women to inform a drug-associated risk. No teratogenicity was observed in embryo-fetal development studies with oral administration of lesinurad to pregnant rats and rabbits during organogenesis at doses that produced maternal exposures up to approximately 45 and 10 times, respectively, the exposure at the maximum recommended human dose (MRHD). No adverse developmental effects were observed in a pre- and postnatal development study with administration of lesinurad to pregnant rats from organogenesis through lactation at a dose approximately 5 times the MRHD.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-17, lesinurad was not teratogenic at exposures up to approximately 45 times the MRHD (on an AUC basis at maternal oral doses up to 300 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 7-20, lesinurad was not teratogenic at exposures up to approximately 10 times the MRHD (on an AUC basis at maternal oral doses up to 75 mg/kg/day). Severe maternal toxicity, including mortality, was observed in rats and rabbits at exposures equal to or greater than

approximately 45 and 4 times the MRHD (on an AUC basis at maternal oral doses of 300 mg/kg/day in rats and 25 mg/kg/day and higher in rabbits) respectively.

In a pre- and post-natal development study in pregnant female rats dosed from gestation day 7 through lactation day 20, lesinurad had no effects on delivery or growth and development of offspring at a dose approximately 5 times the MRHD (on a mg/m^2 basis at a maternal dose oral dose of 100 mg/kg/day). (b) (4) In rats, plasma and milk concentrations of lesinurad were approximately equal.

8.2 Lactation

Risk Summary

There is no information regarding the presence of lesinurad in human milk, the effects on the breast-fed infant, or the effects on milk production. Lesinurad is present in the milk of rats *[see Use in Specific Populations (8.1)]*. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Zurampic and any potential adverse effects on the breastfed infant from Zurampic or from the underlying maternal condition.

(b) (4)

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/s/

TAMARA N JOHNSON
08/17/2015

LYNNE P YAO
08/25/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 20, 2015

TO: Michelle Jordan Garner, M.S., OTR/L, Regulatory Project Manager
Rosemarie Neuner, M.D., M.P.H., Medical Officer
Sarah O. Yim, M.D., Associate Director & Supervisory Medical Officer
Division of Pulmonary and Allergy Drug Products (DPARP)

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Susan D. Thompson, M.D., Team Leader for:
Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207988

APPLICANT: Ardea Biosciences, Inc.

DRUG: lesinurad

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review

INDICATIONS: Treatment of patients with gout

CONSULTATION REQUEST DATE (signed):	May 19, 2015
INSPECTION SUMMARY GOAL DATE (original):	August 31, 2015
DIVISION ACTION GOAL DATE	December 21, 2015
PDUFA DATE:	December 29, 2015

I. BACKGROUND:
Allopurinol and febuxostat are oral xanthine oxidase inhibitor agents that block urate production and are considered to be first line drug therapies for gout. The sponsor claims that allopurinol fails to achieve sufficient serum uric acid concentrations below 6 mg/dL in a high proportion of subjects. While febuxostat can lower serum uric acid levels, flare reduction and tophus reduction as clinical study endpoints have not been achieved. Febuxostat is a part of an unapproved drug regimen for subjects with inadequate response, intolerance, or contraindication to allopurinol.

Pegloticase, a recombinant porcine uricase which degrades uric acid, is available for the treatment of refractory gout, but administered intravenously. Probenecid, benzbromarone, and lesinurad may increase uric acid excretion through inhibition of uric acid transporter 1 (URAT1). The sponsor proposes use of lesinurad as a combination treatment agent to either allopurinol or febuxostat in patients with gout.

Two clinical trials were submitted in support of the applicant's NDA. For this NME NDA under the PDUFA V program review, CDER DPARP requested two clinical sites in Study 301 and a single clinical site in Study 302 for inspection. The sites enrolled large numbers of patients. Sites also showed a significant responder rate variability that may have an impact on treatment efficacy in the review division's analysis.

Study 301
Study 301 was a Phase 3 randomized, double-blind, multicenter, placebo-controlled, combination study to evaluate the efficacy and safety of lesinurad and allopurinol compared to allopurinol alone in subjects with gout who have had an inadequate hypouricemic response to standard of care allopurinol. The primary study objective was to determine the efficacy of lesinurad by Month 6 when used in combination with allopurinol compared to allopurinol monotherapy. The primary endpoint was the proportion of subjects with a serum uric acid level that is < 6.0 mg/dL by Month 6.

Study 302
Study 302 was a replicate study similar to Study 301. Study 302 was a Phase 3 randomized, double-blind, multicenter, multi-country, placebo-controlled, combination study comparing the efficacy and safety of lesinurad plus allopurinol to allopurinol plus lesinurad placebo in approximately 600 subjects with gout who have had an inadequate hypouricemic response to standard of care allopurinol. The primary study objective was

to determine the efficacy of lesinurad by Month 6 when used in combination with allopurinol compared to allopurinol monotherapy. The primary endpoint was the proportion of subjects with a serum uric acid level that is < 6.0 mg/dL by Month 6.

II. RESULTS:

Name of CI Location	Study Site/Protocol /Number of Subjects Randomized (n)	Inspection Date	Classification*
Douglas Radman, MD North Chattahoochee Family Physicians, PC 11459 Johns Creek Parkway Suite 250 Johns Creek, GA 30097	Site #05335 Protocol RDEA594-301 Subjects=13	June 9 - 15, 2015	Preliminary: NAI
Waymon Drummond, MD Renaissance Clinical Research and Hypertension Clinic 1151 N. Buckner Boulevard Suite 308 Dallas, TX 75218	Site #05185 Protocol RDEA594-301 Subjects=12	June 1 - 9, 2015	VAI
Alan Miller, MD Alta Pharmaceutical Research Center, Inc. 4553 North Shallowford Road Suite 50B Dunwoody, GA 30338	Site #05394 Protocol RDEA594-302 Subjects=17	June 25- July 15, 2015	Preliminary: VAI
Ardea Biosciences, Inc. 9390 Towne Centre Drive San Diego, CA 92121	SPONSOR	Pending (late September 2015)	Pending

*Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.
OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.
Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATOR

1. **Douglas Radman, M.D., Site #05335**
   Johns Creek, GA

a. What was inspected:

A total of 69 subjects were screened, and 13 subjects were enrolled and randomized. Nine subjects completed the study. An audit of 13 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
The inspection was conducted from June 9 to 15, 2015.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for serum uric acid concentrations were verifiable at the study site for screening and the Day -7 Study Visit before the baseline examination. The serum uric acid concentration was blinded to the site, thus, data could not be verified after the Day -7 Study Visit, including the Month 6 primary efficacy endpoint. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection. In general, this clinical site appeared to be in compliance with Good Clinical Practices.

c. Assessment of data integrity:
The study appears to have been conducted adequately, and the data generated by this site appear acceptable and may be used in support of this specific indication.

2. Waymon Drummond, M.D., Site #05185
Dallas, TX

a. What was inspected:
A total of 21 subjects were screened, and 12 subjects were enrolled and randomized. Nine subjects completed the study. An audit of four screened failure subjects' and seven enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
The inspection was conducted from June 1 to 9, 2015.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for serum uric acid concentration were verifiable at the study site for screening and the Day -7 Study Visit, before the baseline examination. The serum uric acid was blinded to the site, thus, the primary efficacy endpoint (i.e. serum uric acid concentration) could not be verified at the site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection for failure to conduct the clinical investigation according to the investigational plan, failure to obtain proper informed consent, and inadequate drug disposition records. Specifically,

i. Subject 05185-101 was randomized despite an ALT value of 112 U/L, which was greater than the protocol-specified twice the upper limit of normal at any time during the screening period.
ii. Subject 05185-110 was not re-consented on the modified informed consent form document on July 26, 2013. The modified consent document contained updated safety information regarding SAEs of acute kidney failure and kidney stones reported in ongoing gout trials.
iii. The site could not account for 22 kits containing 609 tablets of lesinurad or placebo that were returned by five study subjects (05185-101, 05185-103, 05185-108, 05-185-109, and 05185-110).

OSI Comment:
The items above were considered to be isolated or not clinically significant by DPARP and OSI. Subject 05185-101 was discontinued from the study a few days after randomization. No adverse events were reported for Subject 05185-110.

Dr. Drummond responded to the Form FDA 483 (List of Inspectional Observations) adequately in a letter dated June 18, 2015.

Regarding the drug disposition record issue involving returned unused drug from five study subjects, Dr. Drummond explained that the study drug kits were inadvertently sent to the trash compactor during the unexpected move of the clinical research study site.

c. Assessment of data integrity:
Notwithstanding the above observed violations, data submitted by this clinical site appear acceptable in support of this specific indication.

3. Alan B. Miller, M.D., Site #05394
Dunwoody, GA

a. What was inspected:
A total of 28 subjects were screened, and 17 subjects were enrolled and randomized. Sixteen subjects completed the study. An audit of 9 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
The inspection was conducted from June 25 to July 15, 2015.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for serum uric acid concentration were verifiable at the study site for screening and the Day -7 Study Visit, before the baseline examination. The serum uric acid was blinded to the site, thus, the primary efficacy endpoint (i.e. serum uric acid concentration) could not be verified at the site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection for not conducting the clinical investigation according to the investigational plan. Specifically, Subject 05394-216 experienced an acute gout flare from April 21 to 24, 2013 and was randomized on April 25, 2013, in violation of the exclusion criterion requiring a minimum seven day period of resolution prior to enrollment in the study.

OSI Comment:
The item above was considered an isolated occurrence. Per DPARP, this had no impact on the study's efficacy or safety evaluation. OSI concurred.

c. Assessment of data integrity:
Despite an isolated regulatory deficiency, data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR

4. Ardea Sciencies, Inc.
San Diego, CA

INSPECTION PENDING

OSI Comment:
DPARP selected three clinical sites that participated in clinical studies submitted in support of the applicant's NDA for inspection. Although inspection of the sponsor was not specifically requested by DPARP, OSI requested a sponsor inspection for this NME.

Inspection by the Los Angeles District Office is tentatively scheduled for September 23, 2015. OSI will provide preliminary information regarding the sponsor inspection to DPARP prior to an early October 2015 public Advisory Committee meeting scheduled for this application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two clinical trials submitted in support of the applicant's NDA were audited by FDA. Three domestic clinical study sites (Douglas Radman, MD, Waymon Drummond, MD, and Alan B. Miller, MD) were selected for audit. A sponsor audit is planned and scheduled for September 2015.

The preliminary classification for Dr. Radman is No Action Indicated (NAI). The preliminary classification for Dr. Miller is Voluntary Action Indicated (VAI). The classification for Dr. Drummond is VAI. Although regulatory violations were noted at the Dr. Miller and Dr. Drummond site, they did not have significant impact on assessment of efficacy data or human subject safety. Data as reported by the sponsor for these sites is acceptable for use in support of the requested indication.

Note: *The inspectional observations for Drs. Radman and Miller, are based on preliminary communications with the field investigator. A clinical inspection summary addendum will be generated for the purpose of reporting on inspection of the sponsor and any significant change in conclusions regarding the clinical site inspections of Drs. Radman and Miller, following receipt and review of the Establishment Inspection Report (EIR). The CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.*

{See appended electronic signature page}
Anthony Orencia, M.D.
Medical Officer
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Division of Clinical Compliance Evaluation
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CONCURRENCE:

{See appended electronic signature page}
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/s/

ANTHONY J ORENCIA
08/20/2015

JANICE K POHLMAN
08/20/2015

SUSAN D THOMPSON
08/20/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 207988

Application Type: NME NDA

Name of Drug/Dosage Form: Zurampic (lesinurad) tablets

Applicant: Ardea Biosciences, Inc.

Receipt Date: December 29, 2014

Goal Date: December 29, 2015

1. Regulatory History and Applicant's Main Proposals

Ardea Biosciences submitted a 505(b)(1), NME application, for 200 mg lesinurad tablets, for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase (XO) inhibitor. Ardea has sought and received the following FDA feedback, for the development of lesinurad: PIND (7/21/08); IND safety review (10/31/09); 2 SPAs – rat and mouse carcinogenicity studies (11/20/09 and 3/17/11); 2 EOP2: CMC (7/6/11) DPARP (7/21/11); written feedback:3/30 and 9/12/12, 11/1/13, and 7/1/14; Type C written responses (2/28 and 5/8/14); and a preNDA meeting (9/26/14).

This application includes 3 pivotal studies: RDEA 594-301, 302, and 304, which has evaluated the efficacy and safety of lesinurad 200 mg and 400 mg once daily in combination with an XO inhibitor vs. an XO inhibitor alone; a justification for the proposed once daily dosing of lesinurad; an analysis of the safety in the subset of patients taking more than 300 mg/day of allopurinol (RDEA 594-301/302 studies); and an analysis of the cardiac and renal safety data in all 3 pivotal studies, including adverse events suggestive of volume overload.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by April 17, 2015.The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *HL headings not in 2-column format, and in 14pt font.*

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *Longer than 1/2 page due to large font and lack of 2-column listing of HL headings; no waiver has been requested.*

NO 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment: *There is no horizontal line separating HL from the TOC; or between the TOC and the FPI.*

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *However, formatting is incorrect.*

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

NO 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Need to add year, which if approved will be 2015*

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment: *However, there is an error statement included: "The use of Error! Reference source not found". Needs to be corrected.*

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment: *However, "Patient Counseling Information" needs to be in all CAPS.*

Revision Date in Highlights

NO 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment: *Revision date needs to be included at the end of HL, bolded and right justified "Revised: 12/2015"*

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

NO 25. The TOC should be in a two-column format.

Comment: *TOC is only one column format; needs to be changed to a 2-column format*

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

NO 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment: *None of the section headings are bolded, but are all in UPPER CASE.*

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *All subsections need to be indented under heading titles;*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *However there are sections that are N/A and/or have "None" stated. Therefore these sections need to be eliminated from the HL, TOC, and FPI;without re-numbering remaining sections.*

NO 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment: *There is no "*" nor have any sections been omitted.*

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or "[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment: *However, "The use of Error! Reference source not found" is found*

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or ***www.fda.gov/medwatch.***

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

MICHELLE Y JORDAN GARNER
03/12/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 207988 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Animal Rule Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Pediatric
Proprietary Name: Zurampic Established/Proper Name: lesinurad Dosage Form: tablet Strengths: 200 mg		
Applicant: Ardea Biosciences, Inc. Agent for Applicant (if applicable):		
Date of Application: 12/22/14 Date of Receipt: 12/29/14 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 12/29/15	Action Goal Date (if different): 12/21/15	
Filing Date: 2/27/15	Date of Filing Meeting: 2/13/15	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of hyperuricemia associated with gout		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 102128	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☐	☒		Standard review of a 10-month cycle vs. PDUFA V The Program 12-months
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐	X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☒		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	X	
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐	X	
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐	X	
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☒	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☐	☒		Datasets for Study 304 not included

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☐	☒		Submitted 1/14/15

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Applicant requested a full waiver
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Decision to be made 4/12/15
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☒	☐	☐	Consists of plan to develop communication plan and MG
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☒	☐		However, Word version in incorrect format
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	Need to request Word version of MG
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent: pending***	☒	☐	☐	QT-IRT consult; OSI clinical site audit; PMHS

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? **Date(s):** ***DPARP 7/21/11; CMC 7/6/11*** ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***9/26/14*** ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***11/20/09(rat), 3/17/11(mouse)*** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☒	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2/13/15

BACKGROUND:
Ardea Biosciences submitted a 505(b)(1), NME application, for 200 mg lesinurad tablets, for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase (XO) inhibitor.

This application includes 3 pivotal studies: RDEA 594-301, 302, and 304, which has evaluated the efficacy and safety of lesinurad 200 mg and 400 mg once daily in combination with an XO inhibitor vs. an XO inhibitor alone; a justification for the proposed once daily dosing of lesinurad; an analysis of the safety in the subset of patients taking more than 300 mg/day of allopurinol (RDEA 594-301/302 studies); and an analysis of the cardiac and renal safety data in all 3 pivotal studies, including adverse events suggestive of volume overload. This application is an NME, therefore will be reviewed under "The Program" (12-month standard review).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Michelle Jordan Garner	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Sarah Yim		Y
Division Director/Deputy	Badrul Chowdhury/Lydia Gilbert McClain		Y/Y
Office Director/Deputy	Curt Rosebraugh/Mary Parks		N/N
Clinical	Reviewer:	Rosemarie Neuner	Y
	TL:	Sarah Yim	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Jianmeng Chen	Y
	TL:	Ping Ji (for – Satjit Brar)	Y
Biostatistics	Reviewer:	Yu Wang	Y
	TL:	Greg Levin	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Matthew Whittaker	Y
	TL:	Tim Robison	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Art Shaw	Y
	TL:	Craig Bertha	Y
Biopharmaceutics	Reviewer	Fang Wu	N
	TL:	Sandra Suarez	N
Quality Microbiology	Reviewer:	N/A	
	TL:		
CMC Labeling Review	Reviewer:	N/A	
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	None Assigned	
	TL:		
OSE/DRISK (REMS)	Reviewer:	Jasminder Kumar	Y
	TL:	Jamie Wilkins Parker	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Anthony Orencia (OSI)	Y
	TL:	?	N

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers/disciplines	Reviewer:	Peter Starke, ADL	Y
	TL:		
Other attendees	Carol Hill, SRPM Sara Stradley, ADRA (ODE II)		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**: Will determine which sites will need inspection	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed?	☒ YES ☐ NO

If no, explain:	
• Advisory Committee Meeting needed? **Comments**: ***suggested date 9/30/15*** ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: ☐ NO ☒ To be confirmed Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: ***filing review checklist pending***	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☒ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization? **Comments**:	☒ Not Applicable ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: ***CMC filing review checklist pending***	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES ☐ NO ☒ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	None
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: ODE II (DD – Mary Parks)

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): ***6/10/15***

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☐	If priority review:

	• notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

MICHELLE Y JORDAN GARNER
03/12/2015