CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209203Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 209203	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Duzallo Established/Proper Name: lesinurad/allopurinol Dosage Form: FDA tablets Strengths: 200mg/300mg and 200mg/200mg		
Applicant: Ardea Bioscience		
Date of Receipt: October 20, 2016		
PDUFA Goal Date: August 20, 2017	Action Goal Date (if different): August 18, 2017	
RPM: Susan Rhee		
Proposed Indication(s): treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with allopurinol alone.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Zyloprim (allopurinol)	safety and efficacy, nonclinical and labeling
NDA 20298 Aloprim	safety and efficacy, nonclinical and labeling

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

A bioavailability/bioequivalence study (study RDEA594-501) was performed comparing the two co-administered single agents to Duzallo to support the bridge from the lesinurad NDA (207988) to the lesinurad/allopurinol FDC NDA (209203).

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Aloprim	20298	Yes
Zyloprim (allopurinol)	016084	Yes

Application referred to the listed products and NDA #'s in an attachment to Form 356h dated October 20, 2016.

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides two approved products, Zurampic (lesinurad) and Zyloprim (allopurinol) in a fixed-dose combination tablet formulation.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): Zurampic (lesinurad)/ 8003681, 8084483, 8283369, 8357713, 8546436, 8546437, 9216179. All patents are held by Ardea Biosciences, the applicant for this NDA.

No patents listed ☒ (for allopurinol) *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the

application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☒ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

SUSAN RHEE
08/22/2017

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
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Division of Pediatric and Maternal Health Memorandum

Date: August 17, 2017 **Date Consulted:** December 9, 2016

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

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

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

To: Division of Pulmonary, Allergy and Rheumatology Products

Drug: Duzallo (Lesinurad/allopurinol FDC (Fixed Dose Combination))

Class: Uric acid transporter 1 (URAT1) inhibitor (lesinurad), and xanthine oxidase inhibitor (XOI) (allopurinol)

NDA: 209203

Applicant: Ardea Biosciences/AstraZeneca PLC.

Subject: Labeling review of an initial NDA application to be compliant with PLLR

Indication: For the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with allopurinol alone

Materials Reviewed:

- DPMH consult request dated December 9, 2016, DARRTS Reference ID 4025575
- Mastroyannis, Christos M.D., Zurampic (lesinurad) review in DARRTS, August 25, 2015, Reference ID: 3807433
- Applicant's original submission, October 20, 2016
- Applicant's Labeling submission, October 20, 2016
- Annual report/safety information for Zurampic, February 17, 2017
- Whittaker, Matthew Ph.D., Non-clinical review in DARRTS, July 5, 2017 Reference ID: 4120450

Consult Question:

The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) is seeking recommendations on Pregnancy and Lactation labeling as per PLLR. The current USPI for allopurinol is not in PLLR format.

INTRODUCTION

On October 20, 2016 the applicant (Ardea Biosciences) submitted this Duzallo (lesinurad/allopurinol FDC (Fixed Dose Combination)) 505(b)(2) application. The applicant is seeking approval of two lesinurad/ allopurinol fixed dosage combinations, 200/300 mg and 200/200 mg. Zurampic is the RLD for lesinurad and Zyloprim the RLD for allopurinol. Duzallo is recommended only for the patient's convenience (take one pill instead of two) and to mitigate the renal safety risk of misuse of lesinurad monotherapy. A Right of Reference to the lesinurad NDA 207988 has been provided.

The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) consulted the Division of Pediatric and Maternal Health (DPMH) on December 9, 2016, to provide input for appropriate labeling of the pregnancy and lactation subsections of the Duzallo (lesinurad/ allopurinol FDC (Fixed Dose Combination)) labeling and to ensure compliance with the Pregnancy and Lactation Labeling Rule formatting requirements.

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

REGULATORY HISTORY

The applicant relies on the FDA's findings of safety and effectiveness for the approved Zurampic (lesinurad) NDA 207988, and the Agency's findings of safety and effectiveness and published literature on allopurinol.

Zurampic (lesinurad), NDA 207988 (Ironwood Pharmaceuticals, Inc.) was approved on December 22, 2015, and its current labeling is in PLLR format. The recommended dose is 200mg orally, once daily. Zurampic is indicated in combination with a xanthine oxidase

inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone

Zyloprim (allopurinol), NDA 016084 (Prometheus Laboratories) was approved on August 19, 1966. The current labeling was approved on July 17, 2002 and is not in PLLR format. The average recommended dose is 200 to 300 mg/day orally for patients with mild gout and 400 to 600 mg/day for those with moderately severe tophaceous gout

Zyloprim is indicated for:

1. the management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy).
2. the management of patients with leukemia, lymphoma and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels. Treatment with Zyloprim should be discontinued when the potential for overproduction of uric acid is no longer present.
3. the management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients. Therapy in such patients should be carefully assessed initially and reassessed periodically to determine in each case that treatment is beneficial and that the benefits outweigh the risks.

BACKGROUND

Drug Characteristics

Lesinurad/allopurinol FDC tablet is comprised of two currently approved oral products at doses that are within the recommended dosing limits for both products.

Lesinurad decreases reabsorption of uric acid from the renal proximal tubule by inhibiting the function of carrier proteins that transport uric acid (e.g. URAT1) (i.e. increases uric acid excretion). Lesinurad is highly protein-bound (> 98%). Allopurinol is an inhibitor of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid (i.e. inhibits uric acid production). Therefore, the combination of lesinurad and an XO inhibitor (allopurinol) provides a dual mechanism approach for the treatment of gout that may more effectively lower serum uric acid levels.

It is not known if either drug crosses the placenta barrier.

Disease Background

Gout and Treatment Options

Gout is the most common form of inflammatory arthritis.[1] It affects more than 8 million people in the United States, approximately 9 million people in Europe, and more than 3 million in Japan.[2,3] 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

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[1] Doghramji PP, Wortmann RL. Hyperuricemia and gout: new concepts in diagnosis and management. *Postgrad Med*. 2012;124(6):98–109.

[2] de Oliveira EP, Burini RC. High plasma uric acid concentration: causes and consequences. *Diabetol Metab Syndr*. 2012;4:12.

[3] 5Kuo 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.

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.

STATUS OF THE CURRENT LESINURAD AND ALLOPURINOL LABELINGS

The current labeling for Zurampic (lesinurad) states:

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available human data on use of ZURAMPIC in pregnant women to inform a drug-associated risk. No teratogenicity or effects on fetal development were 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. [*see Data*]
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 and did not affect fetal development or survival 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 and did not affect fetal development 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 postnatal 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). In rats, plasma and milk concentrations of lesinurad were approximately equal.

8.2 Lactation
Risk Summary There is no information regarding the presence of

ZURAMPIC in human milk, the effects on the breastfed infant, or the effects on milk production. Lesinurad is present in the milk of rats [*see Use in Specific Populations (8.1)*]. The developmental 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.

The current labeling for Zyloprim (allopurinol) states[4]:

Pregnancy

Teratogenic Effects: Pregnancy Category C.

(b) (4)

Reproductive studies have been performed in rats and rabbits at doses up to twenty times the usual human dose (5 mg/kg per day), and it was concluded that there was no impaired fertility or harm to the fetus due to allopurinol. (b) (4) there is a published report in pregnant mice (b) (4) It (b) (4) whether these (b) (4) represented a fetal effect or an effect secondary to maternal toxicity. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if (b) (4)

Experience with allopurinol during human pregnancy has been limited partly because women of reproductive age rarely require treatment with allopurinol. Two unpublished reports and one published paper (b) (4) women giving birth to normal offspring after receiving (b) (4) allopurinol during pregnancy. (b) (4)

Nursing Mothers

Allopurinol and oxypurinol have been found in the milk of a mother who was receiving allopurinol. Since the effect of allopurinol on the nursing infant is unknown, caution should be exercised when allopurinol is administered to a nursing woman.

REVIEW OF PREGNANCY DATA

Nonclinical experience

Lesinurad

The nonclinical development programs for each component of the FDC have been reviewed

[4] Zyloprim USPI, Prometheus Laboratories, Inc., November 30, 2009.

previously. (See NDA nonclinical reviews for NDA 207988 [lesinurad] and NDA 20298 [allopurinol]). Also, Zyloprim (oral allopurinol) and Aloprim (IV allopurinol), have been reviewed [see nonclinical review for Aloprim (NDA 20298, dated 1/4/96)].

The applicant has also conducted a 13-week lesinurad/allopurinol combination toxicology study in rats in support of the proposed FDC. No additive toxicity was observed in this study. No additional nonclinical studies were conducted (or required) to support approval.

Reviewer's comment
From the animal data during the drug development process of Zurampic, as per P/T reviewer, lesinurad was not teratogenic during the embryo-fetal development studies in rats and rabbits. The reader is referred to the Nonclinical Review by Whittaker, Matthew Ph.D.[5], Non-clinical review in DARRTS., July 5, 2017 (Reference ID: 4120450) for further details.

Allopurinol
As per the USPI and the nonclinical reviewer, allopurinol produced facial clefts and minor skeletal defects in mice but was not teratogenic at high dose levels in rats, rabbits or piglets. Reproductive studies have been performed in rats and rabbits at doses up to twenty times the usual human dose (5 mg/kg per day), and it was concluded that there was no harm to the fetus due to allopurinol. A study in pregnant mice, at allopurinol doses of 50 or 100 mg/kg, given intraperitoneally on gestation day 10 or 13 demonstrated increased numbers of fetal mortality, external and skeletal malformations. The clinical significance of these findings is unknown.

Human Experience
Lesinurad and allopurinol have been used separately for the same indication as Duzallo. No studies have been performed on Duzallo (the fixed dose combination). The applicant combined lesinurad and allopurinol in one pill.

Lesinurad
During the clinical development of the drug, no pregnancies occurred in any of the studies. The applicant has conducted no studies of lesinurad in pregnant women. In the annual reports that have been submitted up to now, no pregnancies have been reported.

Allopurinol
The applicant conducted a search in PubMed, Embase and Insight Meme from January 1966 to June 2016 about allopurinol in pregnancy.
Terms used include:
Allopurinol AND childbirth OR pregnan*: disorder OR pregnancy outcome, prenatal development OR prenatal disorder OR prenatal drug exposure puerperium OR teratogenesis OR spontaneous abortion OR miscarriage OR congenital disorde* OR congenital abnormalities OR congenital defect OR congenital malformation OR birth defect OR congenital anomaly.
No adequate and well-controlled studies of allopurinol use during pregnancy and lactation in humans were identified. In total, 8 publications were identified as relevant to an assessment of risks for allopurinol.[6] Six of the 8 publications describe

[5] Whittaker, Matthew Ph.D., Non-clinical review in DARRTS., July 5, 2017 Reference ID: 4120450
[6] Applicant's submission, , 5.3.5.4 Allopurinol pregnancy review, October 20, 2016

favorable pregnancy outcomes[7] [8] [9] [10] [11] [12], while the two with unfavorable pregnancy outcomes are further described below. [13,14]

Kozenko and colleagues (2011) reported on a single case of multiple congenital anomalies in a newborn infant whose mother was on allopurinol treatment throughout the pregnancy. The anomalies included diaphragmatic hernia, unilateral microtia and absence of external auditory canal, micrognathia, microphthalmia, optic nerve hypoplasia, hypoplasia of the corpus callosum, unilateral renal agenesis, pulmonary agenesis, and cleft lip and palate. Another child with similar malformations was identified by Hoeltzenbein and colleagues (2013). The authors described a case series of 31 prospectively followed pregnancies with 27 newborn infants exposed to allopurinol at least during the first trimester. Congenital abnormalities were reported in 6 infants exposed to allopurinol. Table 1 below refers to congenital anomalies found in the literature.

[7] Awidi AS, Tarawneh MS, Shubair KS, Issa AA, Dajani YF. Acute leukemia in pregnancy: report of five cases treated with a combination which included a low dose of adriamycin. Eur J Cancer Clin Oncol. 1983;19(7):881-884.
[8] Belli S, Mazzola S, Luongo R, et al. Genetic counseling for teratogenic risk due to exposure to medications: 89 pregnancies conceived during oral contraceptive use. American journal of medical genetics Part A. 2009;149A(7):1555-1557.
[9] Bull C, Sheikh M, Nelson-Piercy C, et al. Successful Pregnancies With Thiopurine-Allopurinol Co-Therapy for Inflammatory Bowel Disease. 2016:1.
[10] Fazal MW, Doogue MP, Leong RW, Bampton PA, Andrews JM. Allopurinol use in pregnancy in three women with inflammatory bowel disease: safety and outcomes: a case series. BMC gastroenterology. 2013;13:172.
[11] Seinen ML, de Boer NK, van Hoorn ME, van Bodegraven AA, Bouma G. Safe use of allopurinol and low-dose mercaptopurine therapy during pregnancy in an ulcerative colitis patient. Inflamm Bowel Dis. 2013;19(3):E37.
[12] Sheikh M, Nelson-Piercy C, Duley J, Florin T, Ansari A. Successful Pregnancies with Thiopurine-Allopurinol Co-Therapy for Inflammatory Bowel Disease. J Crohns Colitis. 2015;9(8):680-684.
[13] Hoeltzenbein M, Stieler K, Panse M, Wacker E, Schaefer C. Allopurinol use during pregnancy: outcome of 31 prospectively ascertained cases and a phenotype possibly indicative for teratogenicity. PloS one. 2013;8(6):e66637.
[14] Kozenko M, Grynspan D, Oluyomi-Obi T, Sitar D, Elliott AM, Chodirker BN. Potential teratogenic effects of allopurinol: a case report. American journal of medical genetics Part A. 2011;155A(9):2247-2252.

Table 1: Summary of Literature Findings in Newborn Infants Exposed to Allopurinol in Utero

Number of infants with Anomalies	**Awidia**	**Bellib**	**Bullc**	**Fazald**	**Seinene**	**Sheikhf**	**Hoeltzenbeing**	**Kozenkoh**	**Total**
None	2	1	8	3	1	14	21	0	50
Minor	0	0	0	0	0	0	5i	0	5i
Major	0	0	0	0	0	0	1	1	2
Total exposed to allopurinol	2	1	8	3	1	14	27	1	57

a. Patients with acute leukemia on allopurinol and Adriamycin combination therapy.
b. Patient being counseled for genetic risk after 2 weeks of allopurinol treatment.
c. Patients on allopurinol and thiopurine combination therapy; 8 live births, 3 ongoing pregnancies.
d. Patients with irritable bowel syndrome on allopurinol and thiopurine combination therapy.
e. Patient with ulcerative colitis on allopurinol and thiopurine combination therapy.
f. Patients with irritable bowel syndrome on allopurinol and thiopurine combination therapy; 13 pregnancies, 14 newborn infants.
g. Included 31 prospectively ascertained pregnancies with allopurinol exposure at least during first trimester. Pregnancy outcomes were 2 spontaneous abortions, 2 elective terminations of pregnancy, and 27 live born infants.
h. Patient on allopurinol throughout pregnancy.
i. Minor contains case of autosomal dominant congenital hypoparathyroidism.

A review of published literature in PubMed and MicroMedex was conducted by DPMH to evaluate the use of lesinurad and allopurinol in pregnant women. No further information was identified.

Reviewer's comment

There is no data to draw any safety conclusions about the effects of lesinurad during pregnancy. The limited data for allopurinol also did not provide any new safety concerns.

Summary

The available data from limited published literature failed to demonstrate an association of adverse developmental outcomes and lesinurad and allopurinol use.

REVIEW OF LACTATION DATA

Nonclinical experience

Lesinurad

Lesinurad is present in the milk of rats (as per nonclinical reviewer, plasma and milk concentrations of lesinurad were approximately equal).

Human experience

No information was available about Zurampic. The applicant identified 4 publications on lactation and breastfeeding that mention allopurinol.

- Kamilli I, Gresser U (1993).[15]
- Kamilli I, *et.al (*1991)[16]
- Manakova E, et. al. (2008)[17]
- Needs CJ, Brooks PM. (1985)[18]

Allopurinol is present in breast milk.

Manakova and colleagues analyzed 58 consultation cases of exposure to any drug during lactation from the Czech Teratology Information Service. The authors did not discuss or identify any cases of allopurinol exposure during lactation. They did, however, mention that allopurinol is not recommended during breastfeeding. Needs and colleagues provide a guide to the prescription of medication for rheumatic disease in lactating women. These authors hypothesized that infants of lactating women would most likely be exposed to modest amounts of allopurinol and its metabolite, alloxanthine, because alloxanthine has been demonstrated to have prolonged clearance

[15] Kamilli I, Gresser U. Allopurinol and oxypurinol in human breast milk. Clin Investig. 1993;71(2):161-164

[16] Kamilli I, Gresser U, Schaefer C, Zollner N. Allopurinol in breast milk. Adv Exp Med Biol. 1991;309A:143-145.

[17] Manakova E, Hubickova-Heringova L, Novakova L. Drugs during lactation accenting boron exposure. Neuro endocrinology letters. 2008;29(5):631-634.

[18] Needs CJ, Brooks PM. Antirheumatic medication during lactation. Br J Rheumatol. 1985;24(3):291-297.

from the body.

DPMH conducted a search of Medications and Mother's Milk[19], the Drugs and Lactation Database (LactMed)[20], Micromedex[21], and of published literature in PubMed using the search terms "lesinurad and lactation", "Zurampic and lactation" "lesinurad and breastfeeding", Zurampic and breast feeding", "allopurinol and lactation", "allopurinol and breastfeeding". No additional reports of clinical lactation studies or case reports of Zurampic or allopurinol use in lactating women were found in the databases or in published literature.

Allopurinol and its major metabolite oxypurinol have been detected in human milk in small amounts. Data on this drug were only collected from one lactating mother who was ingesting 300 mg/day allopurinol orally for 4 weeks. The 2- and 4-hour milk/plasma ratios for allopurinol were 0.9mg/L and 1.4mg/L. The corresponding values for oxypurinol were 3.9 and 2.4. No side effects were seen in the exposed infant.[22] The authors calculated that the exclusively breastfed infant would receive between 0.14 and 0.2 mg/kg of allopurinol and between 7.2 to 8 mg/kg of oxypurinol daily. The 5-week-old infant whose mother had been taking allopurinol 300 mg daily for 4 weeks had a plasma level of allopurinol that was undetectable (<0.5 mg/L) and of oxypurinol that was 6.6 mg/L 2 hours after nursing and 4 hours after the mother's dose of allopurinol. This plasma level was 33 to 48% of the measured maternal plasma oxypurinol levels. Therefore, if allopurinol is required by the mother, a risk/benefit analysis should be considered before continuing with breastfeeding.[27,23]

A national survey of gastroenterologists in Australia identified 21 infants who were breastfed by mothers taking a combination of allopurinol and a thiopurine (e.g. azathioprine, mercaptopurine) to treat inflammatory bowel disease. All mothers had taken the combination during pregnancy also. Two postpartum infant deaths occurred, both at 3 months of age. One was a twin (premature birth-related) and the other from SIDS. The authors did not believe the deaths were medication related.[28] No information has been found on effects on lactation and breastfeeding."

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[19] Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing
[20] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. 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 information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[21] Truven Health Analytics information, http://www.micromedexsolutions.com/.
[22] Kamilli I, Gresser U: Allopurinol and oxypurinol in human breast milk. Clin Investig 71: 161-4, 1993
[23] Walter-Sack I, de Vries JX, Ernst B et al. Uric acid lowering effect of oxipurinol sodium in hyperuricemic patients - therapeutic equivalence to allopurinol. J Rheumatol. 1996;23:498-501.

Reviewer's comment

This reviewer concludes that there are no clearly identified risks of allopurinol or lesinurad exposure through breast milk, and therefore, breastfeeding should not be discouraged. The clinical importance of oxypurinol presence in the infant's circulation is not known. This reviewer recommends that the following statement be incorporated into labeling, "the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Duzallo and any potential adverse effects on the breastfed infant from Duzallo or from the underlying maternal condition".

It is not known whether Lesinurad 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. .

Summary

Allopurinol is present in the breastmilk. It is not known whether Lesinurad is present in human milk. Because only limited lactation information exists, the following statement should be included in the risk summary of the labeling: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Duzallo (Lesinurad/allopurinol FDC and any potential adverse effects on the breastfed child from Duzallo (Lesinurad/allopurinol FDC or from the underlying maternal condition."

REVIEW OF FEMALES AND MALES OF REPRODUCTIVE POTENTIAL DATA

Nonclinical experience

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).[24]

Dosages in rats and rabbits up to 20 times the usual human dosage of allopurinol have not revealed evidence of impaired fertility.[12]

Clinical experience

Infertility

There are no human data available regarding the effects of Zurampic on fertility. No

[24] Mastroyannis, Christos M.D., Zurampic (lesinurad) review in DARRTS, August 25, 2015, Reference ID: 3807433

fertility studies were conducted in humans. Neither did the applicant nor this reviewer identify any published literature on allopurinol and its effects on females and males of reproductive potential.

Contraception/Birth Control

There are no recommendations for contraception or birth control use with Zurampic in labeling because no drug associated risks to the pregnant women or the fetus have been demonstrated.[33]

Summary

Because of no human data available on the effect of Zurampic and allopurinol on fertility and no evidence from animal data to inform a potential clinical risk, as well as no drug associated risks to the pregnant women or the fetus to recommend contraception use, Section 8.3, Females and Males of Reproductive Potential, will not be included in the labeling.

CONCLUSIONS

DPMH attended labeling meetings with DPARP during May 15, May 22, June 13 and June 29, 2017.

The Pregnancy and Lactation, sections of lesinurad/allopurinol labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of lesinurad/allopurinol labeling was formatted in the PLLR format to include: "Risk Summary", and "Data" sections.
- **Lactation, Section 8.2**
  - The "Lactation" section of lesinurad/allopurinol labeling was formatted in the PLLR format to include the "Risk Summary" section.
- **Females and Males of Reproductive Potential, Section 8.3**
  - Females and Males of Reproductive Potential, Section 8.3 is omitted because there is nothing to be reported.
- **Patient Counseling Information, Section 17**
  - The "Patient Counseling Information" section of labeling does not include any pregnancy or lactation recommendation.

DPMH LABELING RECOMMENDATIONS

DPMH Proposed Lesinurad/Allopurinol Pregnancy Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on use of TRADENAME or lesinurad in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Limited published data on allopurinol use in pregnant women do not demonstrate a clear pattern or increase in frequency of adverse developmental outcomes. 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), revealed no evidence of harm to the developing fetus. 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.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. 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

Lesinurad

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-17, lesinurad was not teratogenic and did not affect fetal development or survival 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 and did not affect fetal development 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). In rats, plasma and milk concentrations of lesinurad were approximately equal.

Allopurinol

(b) (4)

The clinical significance of these findings is unknown.

8.2 Lactation

Risk Summary

There is no information regarding the presence of TRADENAME or lesinurad in human milk, the effects on the breastfed infant, or the effects on milk production. Lesinurad was present in the milk of rats [see *Use in Specific Populations (8.1)*]. Based on information from a single case report, allopurinol and its active metabolite, oxypurinol, were detected in the milk of a mother at five weeks postpartum at an estimated relative infant dose of 0.14 and 0.2 mg/kg of allopurinol and between 7.2 to 8 mg/kg of oxypurinol daily. There was no report of effects of allopurinol on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

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/s/

CHRISTOS MASTROYANNIS
08/18/2017

TAMARA N JOHNSON
08/18/2017

LYNNE P YAO
08/18/2017

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:	August 1, 2017
To:	Badrul Chowdhury, M.D., 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)** Sharon W. Williams, MSN, BSN, RN Acting Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kyle Snyder, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TRADENAME (lesinurad and allopurinol)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 209203
Applicant:	Ardea Biosciences, Inc.

1 INTRODUCTION

On October 20, 2016, Ardea Biosciences, Inc. submitted for the Agency's review an original New Drug Application (NDA) for TRADENAME (lesinurad and allopurinol) tablets, for oral use. TRADENAME (lesinurad and allopurinol) tablets, for oral use is a combination of lesinurad (a URAT1 inhibitor) and allopurinol (a xanthine oxidase inhibitor), indicated for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with (b) (4) daily doses of allopurinol alone.

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 November 14, 2016, and November 16, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME (lesinurad and allopurinol) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft TRADENAME (lesinurad and allopurinol) tablets, for oral use MG received on October 20, 2016 and received by DMPP and OPDP on July 18, 2017.
- Draft TRADENAME (lesinurad and allopurinol) tablets, for oral use Prescribing Information (PI) received on October 20, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 18, 2017.
- Approved ZURAMPIC (lesinurad) tablets, for oral use comparator labeling dated December 12, 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.

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
08/01/2017

KYLE SNYDER
08/01/2017

SHARON W WILLIAMS
08/01/2017

LASHAWN M GRIFFITHS
08/01/2017

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

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

Memorandum

Date: July 26, 2017

To: Susan Rhee, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Kyle Snyder, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 209203
OPDP comments on draft PI, MG, and carton/container labels for Duzallo™ (lesinurad and allopurinol) tablets, for oral use

---

Reference is made to DPARP's consult request dated November 16, 2016, requesting review of the proposed Package Insert (PI), Medication Guide (MG), and carton/container labels for Duzallo™ (lesinurad and allopurinol) tablets, for oral use.

OPDP has reviewed the proposed draft PI entitled "SCPI label NDA 209203 les+allo.doc" that was received via email from Susan Rhee on July 18, 2017. OPDP's comments on the proposed PI are provided directly on the attached copy of the labeling (see below).

OPDP has reviewed the proposed carton/container labels in the document entitled "NDA209203-Draft-Container-Labeling.pdf" received via email from Susan Rhee on July 24, 2017. We have no comments on these labels at this time.

Please note that comments on the proposed MG will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions or concerns, please contact Kyle Snyder at 240-402-8792 or kyle.snyder@fda.hhs.gov.

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/s/

KYLE SNYDER
07/26/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	July 19, 2017
Requesting Office or Division:	Division of Pulmonary, Allergy and Rheumatology (DPARP)
Application Type and Number:	NDA 209203
Product Name and Strength:	Duzallo (lesinurad and allopurinol) tablets, 200 mg/200 mg and 200 mg/300 mg
Submission Date:	July 10, 2017
Applicant/Sponsor Name:	Ardea Biosciences, Inc.
OSE RCM #:	2016-2496-1
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 PURPOSE OF MEMO

This memo reviews the revised container labels (Appendix A) submitted by the Applicant in response to our review, OSE RCM #: 2016-2496[a]. Sponsor has accepted all of our recommendations for the container labels and we have no additional comments at this time.

2 CONCLUSION

DMEPA concludes that the container labels are acceptable from a medication error perspective and we have no additional comments at this time.

[a] Abraham.S. Label and Labeling Review for Duzallo (NDA 209203). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 06 16. 32 p. OSE RCM No.:2016-2496

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/s/

SHERLY ABRAHAM
07/19/2017

SARAH K VEE
07/19/2017

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:	June 16, 2017
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 209203
Product Name and Strength:	Duzallo (lesinurad and allopurinol) tablets, 200 mg/200 mg and 200 mg/300 mg
Product Type:	Multi-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Ardea Biosciences, Inc.
Submission Dates:	October 20, 2016 March 9, 2017
OSE RCM #:	2016-2496
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader (Acting):	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that DMEPA review the proposed Prescribing Information (PI) and container labels for areas of vulnerability that may lead to medication errors.

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
Human Factors Study	C– N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
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

Ardea Biosciences, Inc submitted a 505(b)(2) NDA 209203 on October 20, 2016 for Duzallo. Duzallo is a fixed-dose combination (FDC) tablet of lesinurad and allopurinol in 200 mg/200 mg and 200 mg/300 mg. The reference listed drugs are Zurampic (NDA 207988; lesinurad tablets) approved on December 22, 2015, by Ironwood Pharmaceuticals and Zyloprim (NDA 16084; allopurinol tablets) approved on August 19, 1966 by Sebela Ireland Ltd.

DMEPA evaluated the proposed PI and container label to determine whether there are any vulnerabilities that may lead to medication errors. We identified areas in the Prescribing Information that can be improved such as deleting the symbol “oz” and only using metric measurements to prevent medication errors. DMEPA also identified areas in the container labels that can be improved to increase the readability and the clarity of information to promote the safe use of the product. We provide letter-ready recommendation for the Division in Section 4.1 and for the Applicant in Section 4.2.

4 CONCLUSION

DMEPA concludes that the proposed prescribing information and container labels can be improved to increase the clarity of information to promote the safe use of the product. Please see recommendations to the Division in Section 4.1 and for the Applicant in Section 4.2 below:

4.1 Comment to the Division

A. Full Prescribing Information-Section 2.1 Recommended Dosing

1. Consider using only metric measurements to prevent medication errors in the sentence: TRADENAME should be taken once daily by mouth, in the morning with food and water. Patients should be instructed to stay well hydrated (e.g., 2 liters (b) (4) of liquid per day).

4.2 Comments to the Applicant

A. Container label (30 count and 90 count)

1. Move the manufacturer information to the side panel or reduce the size as it competes with the proprietary name for prominence and takes readers' attention away from important information such as proprietary and proper names and strength.

2. Ensure the lot number and expiration date is printed on the container labels.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Duzallo submitted by Ardea Biosciences Inc. on October 20, 2016.

Table 1. Relevant Product Information for Duzallo	
Product	Duzallo
Initial Approval Date	N/A
Active Ingredient	lesinurad and allopurinol
Indication	Treatment of hyperuricemia associated with gout when treatment (b) (4)
Route of Administration	oral
Dosage Form:	tablet
Strength:	200 mg/200 mg; 200 mg/300 mg
Dose and Frequency	Recommended starting dose is the 200 mg /300 mg strength once daily in the morning. The recommended dose for the patients with moderate renal impairment (creatinine clearance [CrCL] of 30-59 mL/min) is lesinurad/allopurinol FDC 200 mg/ 200 mg.
How Supplied:	5-count, 30-count, and 90-count bottles
Storage:	Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
Container and closure system	(b) (4) caps (b) (4).

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, along with postmarket medication error data, we reviewed the following Duzallo labels and labeling submitted by Ardea Biosciences Inc. on October 20, 2016 and March 9, 2017.

- Container labels
- Prescribing information

G.2 Label and Labeling Images

Container labels Professional Sample bottles:

(b) (4)

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/s/

SHERLY ABRAHAM
06/16/2017

SARAH K VEE
06/16/2017

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

DATE: May 3, 2017

TO: Badrul Chowdhury, M.D., Ph.D
Division Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II (ODEII)
Office of New Drugs

FROM: Himanshu Gupta, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of Establishment Inspection Report (EIR) covering NDA 209203 for an analytical inspection conducted at Ardea Biosciences, San Diego, CA

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection at Ardea Biosciences, San Diego, CA from April 3 to April 7, 2017. The inspection included auditing an in vivo study (RDEA594-501) to support NDA 209203.

Based on the inspectional outcomes, this OSIS reviewer recommends accepting the analytical data (lesinurad, allopurinol and oxypurinol) submitted under NDA 209203 for study RDEA594-501 that was conducted at Ardea Biosciences, San Diego, CA for further Agency (FDA) review.

Inspected Study

NDA 209203:	**Lesinurad and allopurinol combination tablet**
Study/Project #:	**RDEA594-501**
Study Title:	A Phase 1, Randomized, Open-Label, Crossover Study to Assess the Relative

Bioavailability of Lesinurad/Allopurinol Fixed Dose Combination Tablets and Coadministered Lesinurad and Allopurinol Tablets and the Effect of Food on the Pharmacokinetics of Lesinurad/Allopurinol Fixed Dose Combination Tablets in Healthy Adult Male Subjects

Sample Analysis dates: November 2015 to July 2016

Note:
Ardea Biosciences (b) (4)

Additional info is provided in **Attachment 1.**

CDER-OSIS reviewer Himanshu Gupta audited the in-vivo study listed above for NDA 209203 at Ardea Biosciences, San Diego, CA. The inspection included the review of records relevant to the audited study, equipment calibration and maintenance, adherence to the SOPs, and sample tracking as well as data verification against source records.

There was no Form FDA 483 issued at the closeout.

Discussion items

The following items were discussed with the firm during the closeout meeting. OSIS received responses to the discussion items from Ardea through email on April 20, 2017 (Attachment 2).

1. The condition of the dry ice or temperature of the samples (e.g. with temperature loggers) was not recorded when the subject samples were received and opened at Ardea. It was recommended to indicate the presence of dry ice in the records or data logger documentation to ensure acceptable sample temperature conditions are met.

   Ardea response:
   The firm stated that the information is provided elsewhere but not in the sample receipt form itself. They will implement it in future studies.

   OSIS Assessment:
   Although the sample temperature or the condition of dry ice in the primary sample receipt forms was not recorded, the total duration of shipment was 18-24 hours. The copy of the box packing slip showed that the samples were shipped in dry ice and the benchtop plasma stability for

all analytes (lesinurad, allopurinol and oxypurinol) validated by the firm covers the 24 hours period, so this issue should not affect the integrity of the shipped samples.

2. Regarding the observed oxypurinol internal standard (IS) variation in calibration standards and QCs, it was mentioned that the IS variation effect was due to DMSO. Further investigation to determine whether the primary contributor to the IS variation effect was DMSO or the presence of oxypurinol would have provided more definitive information on the cause of decreased IS responses with higher oxypurinol concentrations.

Ardea response:
The firm mentioned the presence of DMSO in the calibrators (CC) and quality control (QC) samples as a factor in IS variation, and conducted an investigation to further evaluate its effect on accuracy. The firm also mentioned that an additional factor for this effect can be competitive ionization. However, they claimed that based on the validation data, IS suppression did not impact quantitation.

OSIS Assessment:
The firm conducted an investigation on the effect of DMSO on IS response. The results showed that when compared with baseline (without DMSO), the samples with DMSO present showed lower IS peak areas. Furthermore, a lower DMSO concentration (0.5%) produced a smaller decrease in IS peak area compared to a higher DMSO concentration (5.6%) (**Attachment 3**). However, the decreased IS peak area can be due to oxypurinol concentration as well (lower IS response with increasing oxypurinol concentrations).

During subject sample analysis, the same method (using DMSO in CC and QCs) was used for the sample extraction and analysis of subject plasma samples for both the individual and combination tablet formulations. Therefore, if the accuracy of the method is impacted by the changes in IS response, the same quantification bias would have occurred with both products. Hence, the bioequivalence results will not be affected.

3. Watson LIMS audit trails shows re-importing data from Analyst. However, no documentation was presented that indicates why the data were re-imported once approved by a supervisor in Analyst.

   Ardea response:
   The firm mentioned that they confirmed for each of these occasions that when the data were re-imported into Watson LIMS, there were no changes to the data in the Analyst software and the regression analysis was not performed until after the second import of data from Analyst software.

   OSIS Assessment:
   After supervisory approval, there was an initial importing of data from Analyst to Watson LIMS. For some runs, there was re-importing of data into Watson LIMS from Analyst. The documentation of the reason for re-importing the data into Watson is recommended as a good practice. Based on evaluating the audit trails of the Analyst software and the time gap between the initial importing and re-importing of the data into Watson software, this reviewer concludes that there was no data integrity issue. All events are stored successfully in the audit trail system for both Analyst and Watson.

Recommendation

Following review of the inspectional findings, this OSIS reviewer recommends accepting the analytical data (lesinurad, allopurinol and oxypurinol) from study RDEA594-501.

Final Site Classification:

NAI – Ardea Biosciences, San Diego, CA
FEI: 3011545177

cc:
OSIS/Kassim/Choe/Haidar/Nkah/Fenty-Stewart/Kadavil
OSIS/DGDBE/Cho/Choi/Skelly/Au/Gupta
OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OND/ODEII/Chowdhury

Draft: HG 04/23/2017, 4/27/17, 5/1/17
Edit: SA 4/25/17, 4/28/17, 5/1/17, JC 5/1/17, 5/2/17

ECMS:
Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/Ardea Biosciences, San Diego, CA/NDA 209203_Lesinurad Allopurinol FDC

OSI file #: 7347
FACTS: 11710147

Himanshu Gupta, Ph.D.
Division of Generic Drug Bioequivalence Evaluation

Stanley Au, Pharm.D., BCPS
Division of Generic Drug Bioequivalence Evaluation

Seongeun (Julia) Cho, Ph.D.
Division of Generic Drug Bioequivalence Evaluation

Attachments:
Attachment 1– News regarding shutdown of Ardea Biosciences
Attachment 2- Response to discussion items from Ardea
Attachment 3- DMSO investigation report and data

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/s/

HIMANSHU GUPTA
05/03/2017

STANLEY AU
05/03/2017
Acting Team Lead

SEONGEUN CHO
05/03/2017

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

DATE: 2/2/2017

TO: Division of Pulmonary, Allergy and Rheumatology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209203

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	(b) (4)	

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/s/

SHILA S NKAH
02/13/2017

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 # 209203	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) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Duzallo Established/Proper Name: lesinurad/allopurinol Dosage Form: fixed dose combination tablet Strengths: 200mg/200mg and 200mg/300mg		
Applicant: Ardea Biosciences Agent for Applicant (if applicable):		
Date of Application: October 20, 2016 Date of Receipt: October 20, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA Goal Date: August 20, 2017	Action Goal Date (if different): August 18, 2017	
Filing Date: December 19, 2016	Date of Filing Meeting: December 7, 2016	
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 ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with allopurinol alone.		
Type of Original NDA: AND (if applicable)		☐ 505(b)(1) ☒ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 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): IND 102128 and IND 119031	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***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 electronic archive.				
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.***	☒	☐	☐	Standard Review
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 been notified of the submission? **If yes,** date notified:	☐	☐		
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 ID #: PD 3016295

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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	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. Contact the User Fee Staff. If appropriate, send UN letter.	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?	☐	☒		
• 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)].**	☐	☒		
• 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.***	☐	☒		
• 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:	☒	☐		Zurampic (lesinurad) exclusivity – Ironwood has licensed the rights to Ardea. Zyloprim (allopurinol) – no unexpired exclusivity

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
N207988	Zurampic (lesinurad)	NCE	12/22/20

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 orphan or 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)(14)]**? ***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, CDER Purple Book Manager*** ***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:	☒	☐		

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.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."***	☒	☐		

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]***	☒	☐		

[2]

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage 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.***	☐	☒	☐	
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."***	☒	☐	☐	
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***	☐	☐	☒	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labeling ☐ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format?	☐	☐		

http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

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

If no, request applicant to submit SPL before the filing date.				
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
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.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☐ ☐	☒ ☐	☐ ☐	The current USPI for allopurinol is not in PLLR format. DPMH consult requested.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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 PLLR format before the filing date.***	☐	☒	☐	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
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			

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

	☐ 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:***	☒	☐	☐	OSI Consult Request for Biopharmaceutical Inspection
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):**	☐	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐			

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 17, 2016

BACKGROUND: File/Planning Meeting

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Susan Rhee	Y
	CPMS/TL:	Sandy Barnes	Y
Cross-Discipline Team Leader (CDTL)	Nikolay Nikolov		Y
Division Director/Deputy	Badrul A. Chowdhury		Y
Office Director/Deputy			
Clinical	Reviewer:	Rosemarie Neuner	Y
	TL:	Nikolay	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Renu Singh	Y
	TL:	Anshu Marathe	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Greg Levin	Y
	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Matthew Whittaker	Y
	TL:	Tim Robison	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Craig Bertha	Y
	RBPM:	Bamidele (Florence) Asida	N
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:		
• Process	Reviewer:	Chaoying Ma	N
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Taylor Burnett	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Sherly Abraham	N
	TL:	Mishale Mistry	
OSE/DRISK (REMS)	Reviewer:	Michael Sinks	
	TL:	Nichelle Rashid	
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines (OMP/OMPI) Patient Labeling: Nyedra Booker/Marcia Williams (TL)			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o 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., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ 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**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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 determined 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 **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☐ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☐ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☐ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **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?	
• 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: **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **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
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	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.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	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: April 2016

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

/s/

SUSAN RHEE
01/31/2017