CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217927Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: October 4, 2023

To: Elizabeth Kilgore, Clinical Reviewer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Jane Mun, Regulatory Project Manager, DAAP

Lisa Basham, Associate Director for Labeling, DAAP

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for COXANTO (oxaprozin) capsules, for oral use

NDA: NDA 217927

In response to DAAP's consult request dated January 25, 2023. OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for COXANTO (oxaprozin) capsules, for oral use.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 20, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on September 29, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on June 30, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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

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LATOYA S TOOMBS
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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:	September 29, 2023
To:	Jane Mun, PharmD Regulatory Project Manager **Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** L. Sheneé Toombs, PharmD, CPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	COXANTO (oxaprozin)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 217927
Applicant:	Solubiomix, LLC

1 INTRODUCTION

On December 22, 2022, Solubiomix, LLC submitted for the Agency's review an original 505(b)(2) New Drug Application (NDA) 217927 for COXANTO (oxaprozin) capsules. The reference listed drug (RLD) for this application is DAYPRO (oxaprozin) caplets, NDA 018841. The proposed indications for COXANTO (oxaprozin) capsules are:

- For relief of signs and symptoms of osteoarthritis
- For relief of signs and symptoms of rheumatoid arthritis
- For relief of signs and symptoms of juvenile rheumatoid arthritis.

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 Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on January 25, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for COXANTO (oxaprozin) capsules.

2 MATERIAL REVIEWED

- Draft COXANTO (oxaprozin) capsules MG received on December 22, 2022, and received by DMPP and OPDP on September 20, 2023.
- Draft COXANTO (oxaprozin) capsules Prescribing Information (PI) received on December 22, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 20, 2023.
- Approved DAYPRO (oxaprozin) caplets, NDA 018841 comparator labeling dated November 9, 2022.

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 reformatted the MG document using the font size 10.

In our collaborative review of the MG we:

- 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)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

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/

JESSICA M CHUNG
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09/29/2023 03:39:35 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics 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 Pediatrics and Maternal Health Memorandum

Date: August 24, 2023 **Date consulted:** February 8, 2023

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

Through: Tamara Johnson, M.D., MS, Team Leader, Maternal Health, DPMH

To: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Drug: Oxaprozin Capsules

Drug Class: NSAID

NDA: 217927

Applicant: Solubiomix, LLC.

Subject: Labeling review as per Pregnancy and Lactation Labeling Rule (PLLR).

Indication: Indicated for

- Relief of signs and symptoms of Osteoarthritis (OA)
  - Relief of signs and symptoms of Rheumatoid Arthritis (RA)
  - Relief of signs and symptoms of Juvenile Rheumatoid Arthritis (JRA)

Materials Reviewed:

- DPMH consult request dated February 8, 2023, in DARRTS Reference ID: 5123187
- Applicant's submission for NDA 217927, a 505(b)(2) application, dated December 22, 2022
- Feldene labeling review by Christos Mastroyannis, MD, in DARRTS and

dated July 10, 2017, Reference ID: 4121882[1]

- Safety Labeling Change Notification for NSAIDs by LCDR Mark A. Liberatore, PharmD, RAC, Deputy Director for Safety, DAAP,

Consult Question:
DAAP requests DPMH assistance with reviewing the applicant's Pregnancy and Lactation labeling subsections as per Pregnancy and Lactation Labeling Rule (PLLR).

[1] DPMH did not rely on data in the Feldene NDA or the agency's finding of safety and effectiveness for Feldene to support labeling sections of this oxaprozin capsules NDA. Rather, the cross-reference to the Feldene consult is included to avoid duplicating background information relevant to this class of products. DPMH's recommendations for the oxaprozin labeling discussed below are based solely on information from literature that is not specific to a particular NDAID product, and which was independently located and considered for the oxaprozin application.

INTRODUCTION

This is an original 505(b)(2) new application for Oxaprozin Capsules, submitted on December 22, 2022, and indicated for:

- Relief of signs and symptoms of Osteoarthritis (OA)
- Relief of signs and symptoms of Rheumatoid Arthritis (RA)
- Relief of signs and symptoms of Juvenile Rheumatoid Arthritis (JRA).

This 505(b)(2) application relies on FDA's previous finding of safety and effectiveness of the listed drug (LD) Daypro (oxaprozin), NDA 018841 by Pfizer. The proposed drug product is a change in dosage form from Daypro's 600 mg immediate-release caplet, while the proposed dosage form is a 300 mg capsule. No change in indications is sought by this application; the 505(b)(2) application aligns with the LD's indications. The applicant has provided labeling in PLLR format which depends on the labeling of Daypro. The applicant has not performed any studies except for the Oxaprozin Capsules (300 mg) bioequivalence trials. The applicant states:

The current labeling for Daypro includes language on risks of fetal toxicity. Because Oxaprozin Capsules (300 mg) are bioequivalent to Daypro in all clinically relevant measurements, the same considerations will apply to Oxaprozin Capsules (300 mg)
and are included in our proposed labeling.

Regulatory History

The listed drug relied upon, Daypro, was approved on October 29, 1992.

State of Existing Labeling for Daypro of November 9, 2022[2]

The labeling is in Physician Labeling Rule (PLR) and PLLR format. Pregnancy letter category has been removed.

HIGHLIGHTS OF PRESCRIBING INFORMATION

---------WARNINGS AND PRECAUTIONS---------

- Fetal Toxicity: Limit use of NSAIDs, including DAYPRO, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal

---------USE IN SPECIFIC POPULATIONS---------

- Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of DAYPRO in women who have difficulties conceiving

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.11 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including DAYPRO, in pregnant women at about 30 weeks gestation and later. NSAIDs, including DAYPRO, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

[2] Existing Daypro labeling, approved November 9, 2022.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including DAYPRO, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit DAYPRO use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid, if DAYPRO treatment extends beyond 48 hours. Discontinue DAYPRO, if oligohydramnios occurs and follow up according to clinical practice *[see Use in Specific Populations*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including DAYPRO, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

Because of these risks, limit dose and duration of DAYPRO use between about 20 and 30 weeks of gestation, and avoid DAYPRO use at about 30 weeks of gestation and later in pregnancy (*see Clinical Considerations, Data*).

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including DAYPRO, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies, oral administration of oxaprozin to pregnant rabbits at doses 0.1-times the maximum daily human dose (based on body surface area) resulted in evidence of teratogenicity; however, oral administration of oxaprozin to pregnant mice and rats during organogenesis at doses equivalent to the maximum recommended human dose revealed no evidence of teratogenicity or embryotoxicity. In rat reproduction studies in which oxaprozin was administered through late gestation failure to deliver and a reduction in live birth index was observed at doses equivalent to the maximum recommended human dose. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as oxaprozin, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus:
Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including DAYPRO, can cause premature closure of the fetal ductus arteriosus (*see Data*).

Oligohydramnios/Neonatal Renal Impairment:
If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If DAYPRO treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue DAYPRO and follow up according to clinical practice (*see Data*).

Labor or Delivery

There are no studies on the effects of DAYPRO during labor or delivery. In animal studies, NSAIDS, including oxaprozin, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data

Premature Closure of Fetal Ductus Arteriosus: Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment: Published studies and post marketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these post marketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal data
Teratology studies with oxaprozin were performed in mice, rats, and rabbits in pregnant animals administered oral doses up to 200 mg/kg/day, 200 mg/kg/day, and 30 mg/kg/day, respectively, during the period of organogenesis. In rabbits, malformations were observed at doses greater than or equal to 7.5 mg/kg/day of oxaprozin (0.1 times the maximum recommended human daily dose [MRHD] of 1800 mg based on body surface area). However, in mice and rats, no drug-related developmental abnormalities or embryo-fetal toxicity were observed at doses up to 50 and 200 mg/kg/day of oxaprozin, respectively (0.1 times and 1.1 times the maximum recommended human daily dose of 1800 mg based on a body surface area comparison, respectively).
In fertility/reproductive studies in rats, 200mg/kg/day oxaprozin was orally administered to female rats for 14days prior to mating through lactation day (LD) 2, or from gestation day (GD) 15 through LD 2 and the females were mated with males treated with 200mg/kg/day oxaprozin for 60days prior to mating. Oxaprozin administration resulted in failure to deliver and a reduction in live birth index at 200 mg/kg/day (1.1-times the maximum recommended human daily dose of 1800 mg based on a body surface area comparison).

8.2 Lactation

Risk Summary

Lactation studies have not been conducted with DAYPRO. It is not known whether DAYPRO is excreted in human milk. DAYPRO should be administered to lactating women only if clearly indicated. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DAYPRO and any potential adverse effects on the breastfed infant from the DAYPRO or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility
Females
Based on the mechanism of action, the use of prostaglandin mediated NSAIDs, including DAYPRO, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including DAYPRO, in women who have difficulties conceiving or who are undergoing investigation of infertility.

Males
Testicular degeneration was observed in beagle dogs treated with 37.5 mg/kg/day (0.7-times the maximum recommended human daily dose based on body surface area) of oxaprozin for 42 days or 6 months [*see Nonclinical Toxicology (13.1)*]

13 NONCLINICAL TOXICOLOGY

Mutagenesis

Oxaprozin was not genotoxic in the Ames test, forward mutation in yeast and Chinese hamster ovary (CHO) cells, DNA repair testing in CHO cells, micronucleus testing in mouse bone marrow, chromosomal aberration testing in human lymphocytes, or cell transformation testing in mouse fibroblast.

Impairment of Fertility
Oxaprozin administration was not associated with impairment of fertility in male and female rats at oral doses up to 200 mg/kg/day (1.1-times the maximum recommended human daily dose [MRHD] of 1800 mg based on a body surface area comparison). However, testicular degeneration was observed in beagle dogs treated with 37.5 mg/kg/day (0.7-times the MRHD based on body surface area) of oxaprozin for 42 days or 6 months, a finding not confirmed in other species. The clinical relevance of this finding is not known.

17 PATIENT COUNSELLING INFORMATION

Female Fertility
Advise females of reproductive potential who desire pregnancy that NSAIDs, including DAYPRO, may be associated with a reversible delay in ovulation [*see Use in Specific Populations (8.3)*].

Fetal Toxicity
Inform pregnant women to avoid use of DAYPRO and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with DAYPRO is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours [*see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)*].

Drug Characteristics[1]
The recommended doses are:
For OA, the dosage is 1200 mg (four 300 mg capsules) given orally once a day
For RA, the dosage is 1200 mg (four 300 mg capsules) given orally once a day
For JRA, in patients 6 to 16 years of age, the recommended dosage given orally once per day should be based on body weight of the patient as given in Table 1:

Table 1. Recommended Daily Dose of OXAPROZIN CAPSULES by Body Weight in Pediatric Patients for JRA

Body Weight Range (kg)	Dose (mg)
22–31	600
32–54	900
≥55	1200

Table 2. Oxaprozin drug characteristics

Half Life	41.4-54.9 Hours For unbound drug it is 2.33-3.03 Hours
Molecular Weight	293 Da
Protein bound	99%
Oral Bioavailability	95%
Administration	Oral Capsules
Treatment duration	The lowest effective dosage for the shortest duration consistent with individual patient treatment goals
Mechanism of action	It involves inhibition of cyclooxygenase (COX-1 and COX-2). Oxaprozin is a potent inhibitor of prostaglandin synthesis in vitro. Oxaprozin concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because oxaprozin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

NSAIDs and Adverse Events During Pregnancy

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a drug class that groups together drugs that provide analgesic (pain-control) and antipyretic (fever-reducing) effects, and in higher doses, anti-inflammatory effects.

Vane[3] in 1971 proposed that the action mechanism of NSAIDs was through the inhibition of prostaglandins (PG) synthesis. The key enzyme in the prostaglandin synthesis is prostaglandin endoperoxide synthetase (PGHS) or cyclooxygenase (COX). There are two major isoforms of COX, coded by two distinct genes, and referred to as COX-1 and COX-2.

NSAID-mediated prostaglandin inhibition can cause severe adverse effects (AEs) in the fetus, especially when given in late pregnancy (more than 30 weeks). These AEs include prenatal closure of the ductus arteriosus and acute renal failure resulting in oligohydramnios. Oligohydramnios is most of the times reversible within 6 days from the day the drug is discontinued. The sensitivity for such AEs increases with advancing pregnancy.

The most serious cases of oligohydramnios were documented after week 30 of gestation, but such AEs (oligohydramnios) are rare before week 28. However, Hickok *et. al.* published a case of oligohydramnios after seven days treatment with indomethacin at week 21[4] and Schernec *et. al.* reported pathological findings of oligohydramnios that were detected at gestational weeks 22 and 23 after long-term diclofenac exposure of at least 150 mg per day.[5]

[3] Vane, J.R. Inhibition of prostaglandin synthesis as a mechanism of action for the aspirin-like drugs. Nature, 1971, 231, 232-235

[4] Hickok DE, Hollenbach KA, Reilley SF, Nyberg DA, The association between decreased amniotic fluid volume and treatment with nonsteroidal anti-inflammatory agents for preterm labor, Am. J. Obstet. Gynecol. 160(1989) 1525–1530.

[5] Scherneck S, Schöpa FL, Entezami M, Kayser A, Weber-Schoendorfer C, Schaefer C. Reversible oligohydramnios in the second trimester of pregnancy in two patients with long-term diclofenac exposure. Reproductive Toxicology, 58,61-64;2015

Reviewer Comment
Based on the literature reviewed, use of NSAIDs starting at 20 weeks (second trimester) may cause oligohydramnios. L*anguage regarding this potential risk has been included in NSAIDs labelings in the past.*

REVIEW
PREGNANCY
Animal Data
As per Daypro labeling of November 9, 2022, in animal reproduction studies, oral administration of oxaprozin to pregnant rabbits at doses 0.1-times the maximum daily human dose resulted in evidence of teratogenicity; however, oral administration of oxaprozin to pregnant mice and rats during organogenesis at doses equivalent to the maximum recommended human dose revealed no evidence of teratogenicity or embryotoxicity. In rat reproduction studies in which oxaprozin was administered through late gestation, failure to deliver and a reduction in live birth index was observed at doses equivalent to the maximum recommended human dose. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as oxaprozin, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

Review of Literature
Applicant's Review
The applicant states that recent literature on oxaprozin, and post-marketing experience with oxaprozin provided no new information on use in pregnancy and lactation. No further information is provided to document this statement.

DPMH Review
DPMH also conducted a literature search in PubMed, Embase, and the TERIS and ReproTox databases for oxaprozin use in pregnancy. No publications were identified on human data other than those already mentioned in the existing Daypro labeling.

GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk states:

> Reproductive studies in mice and rats at about 0.2 times the maximum recommended human dose based on BSA revealed no teratogenic or embryotoxic effects. In rabbits, maternally toxic doses were embryotoxic but not teratogenic. In four animal studies that used mice, rats, rabbits, and monkeys no adverse fetal effects or congenital malformations were detected.
>
> It is not known if oxaprozin crosses the human placenta. The molecular weight (about 293 Da) is low enough that passage to the fetus should be expected.

Summary
There are no new safety data apart from what is currently reported in labeling for Daypro. Review of the literature by the applicant and DPMH has failed to produce any new safety signals on oxaprozin use in pregnancy. No additional associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes has been identified.

LACTATION

Applicant's Review

The applicant states that no lactation studies have been conducted with Oxaprozin Capsules. It is not known whether oxaprozin is present in human milk.

DPMH Review

DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for oxaprozin and use in lactation. No publications were identified on human data. There are no new risks identified in addition to the ones mentioned in the existing Daypro labeling.

GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk state:

> No publications on oxaprozin use during human lactation have been located. The molecular weight (about 293 Da) is low enough that excretion into breast milk should be expected. Several NSAIDs (diclofenac, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, ketorolac, and tolmetin) are considered safe alternatives to other agents (oxaprozin not mentioned) if a NSAID is required while nursing. Because of the long terminal elimination half-life (approximately 42 hours or longer) in adults and the unknown amount of oxaprozin that is excreted into milk, any of these choices is probably preferable.

LactMed database states:

> Because there is no published experience with oxaprozin during breastfeeding, other agents may be preferred, especially while nursing a newborn or preterm infant.
> No information on maternal or infant levels have been found. Also, no information on the effects in breastfed infants or on lactation exists.

Thomas Hale in halesmeds.com/monographs does not provide any additional information.

Summary

There are no new potential safety concerns about oxaprozin use during lactation.
The following risk/benefit statement will be placed in section 8.2, Lactation: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Oxaprozin and any potential adverse effects on the breast fed infant from Oxaprozin or from the underlying maternal condition".

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

No additional information has been identified by the applicant or DPMH related to oxaprozin and its effects on fertility
Based on its mechanism of action, prostaglandin inhibition appears to increase the incidence of luteinized unruptured follicle syndrome, a condition in which normal ovarian follicular development is followed by an elevation of serum progesterone compatible with ovulation, but the cycle remains anovulatory because the follicular wall remains unruptured.[6] In women, ultrasound scans of follicular development showed a fivefold increase in the incidence of this syndrome in the presence of some

[6] Armstrong DT, Grinwich DL: Blockade of spontaneous and LH-induced ovulation in rats by indomethacin, an inhibitor of prostaglandin synthesis. Prostaglandins 1972:1:21.

NSAIDS.[7,8] The prolonged use of NSAIDs is most likely to be associated with this antifertility effect. Similar findings have been reported for both COX-1 and COX-2 NSAIDs.

DPMH reviewed the NSAIDs data and literature in prior reviews that are available in DARRTS. Additionally, DPMH provided review and content for the Drug Safety Communication on *the Possible Risks of Pain Medicine Use During Pregnancy* issued January 9, 2015 and for Safety Labeling Change Notification for NSAIDs, 2020.

Summary
Oxaprozin is not mutagenic, genotoxic or clastogenic. Therefore, there is no need for pregnancy testing or contraception during treatment with oxaprozin.

Due to the potential effects on female fertility based on oxaprozin inhibition of prostaglandin, DPMH proposes to align the language for 8.3 Females and Males of Reproductive Potential, Infertility, Females, with the LD labeling:

> Based on the mechanism of action, the use of prostaglandin mediated NSAIDs, including oxaprozin may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including oxaprozin in women who have difficulties conceiving or who are undergoing investigation of infertility.

CONCLUSIONS
There are no new safety data apart from what is currently reported in labeling for Daypro in reference to pregnancy and lactation.
Based on its mechanism of action, prostaglandin inhibition appears to increase the incidence of luteinized unruptured follicle syndrome. The prolonged use of NSAIDs is most likely to be associated with this antifertility effect.
A PMR for a milk only lactation study will be appropriate to be issued because there is no information about oxaprozin presence in human milk, the effects on the breastfed infant, or the effect on milk production.

[7] Marik J, Hulka J: Luteinized unruptured follicle syndrome: a subtle cause of infertility. Fertil Steril 1978; 29:270.
[8] Killick S, Elstein M: Pharmacological production of luteinized unruptured follicles by prostaglandin synthetase inhibitors. Fertil Steril 1987;47:773-7.

LABELING RECOMMENDATIONS

Oxaprozin Capsules product labeling has been edited to comply with the PLLR. DPMH revised subsections 8.1, 8.2, and 8.3 and section 17 of labeling for compliance with the PLLR and DSC and its associated safety labeling change. The proposed labeling has strikethrough changes to highlight differences from the current DAYPRO approved labeling. DPMH refers to the final NDA action for final labeling.

DPMH has the following recommendations for the Oxaprozin Capsules labeling.

(b) (4)

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

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/s/

CHRISTOS MASTROYANNIS
08/24/2023 02:18:19 PM

TAMARA N JOHNSON
08/28/2023 10:45:38 AM

LYNNE P YAO
09/11/2023 03:25:41 PM

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: August 31, 2023

TO: Rigoberto A Roca, M.D.
Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Office of Neuroscience (ON)
Office of New Drugs (OND)

Partha Roy, Ph.D.
Director
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

FROM: Yi-Ying Chen, MS.
Chemist
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Division Director
DNDSI, OSIS

SUBJECT: Remote regulatory assessment (RRA) of (b) (4) (b) (4)

1. RRA Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment (RRA) of the analytical portion of Studies SBX-P0-750 (NDA 217927, Oxprozine) (b) (4) (b) (4) conducted at (b) (4).

I did not observe any objectionable conditions during the RRA. Therefore, I conclude that data from the audited studies are reliable.

2. Reviewed Studies

Study SBX-P0-750 (NDA 217927)

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[1] One set of tools for oversight of regulated products used during the pandemic has been remote regulatory assessments (RRAs). The term "RRA" describes a category of activities for which FDA may use different terminologies, but all are considered to be types of RRAs, including "remote interactive evaluations."

"An Open-Label, Randomized, Balanced, Two-Treatment, Two-Period, Two-Sequence, Crossover, Single Oral Dose Comparative Bioavailability Study of Oxaprozin 300 mg Capsules and Daypro®(Oxaprozin) 600 mg Caplets Following a 600 mg Dose in Healthy Adult Subjects Under Fasting Conditions"

Sample Analysis Period: 4/18/2022 – 4/27/2022

(b) (4)

Analytical firm: (b) (4)

3. Scope of RRA

OSIS scientist Yi-Ying Chen, MS, reviewed the analytical portion of the above studies conducted at (b) (4) (b) (4) from (b) (4)

The firm was previously inspected by OSIS from (b) (4) – (b) (4). At the conclusion of the inspection, no Form FDA 483 was issued, and the final classification was No Action Indicated (NAI).

The current RRA included reviewing the relevant records of method validation, study sample analysis, standard operating procedures (SOPs), sample receipt/storage, facility of bioanalytical operations, calibration and maintenance records, audit trails of instruments used in the reviewed studies, and interviews with the firm's management and staff.

4. RRA Observations

At the conclusion of the RRA, I did not observe any objectionable conditions. No items were discussed with firm's management during the RRA close-out meeting.

Draft: YC 8/22/2023
Edit: GB 08/23/2023; CB 08/23/2023

ECMS:
https://ecmsweb.fda.gov/webtop/drl/objectId/0b0026f88390280b

cc:
OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza/Pham
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/Chen
OTS/OSIS/DGDSI/Cho/Benson/Skelly/Au/Ou

OSIS File #: BE (b) (4) (NDA 217927), (b) (4)

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/s/

YIYING E CHEN
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GOPA BISWAS
08/31/2023 12:40:15 PM

CHARLES R BONAPACE
08/31/2023 01:00:48 PM

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: August 31, 2023

TO: Rigoberto A Roca, MD
Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Office of Neuroscience (ON)
Office of New Drugs (OND)

FROM: Hasan A. Irier, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly A. Benson, Ph.D.
Deputy Director
DGDSI
OSIS

SUBJECT: Review of Clinical Inspection of Altasciences, Mount-Royal, Quebec, Canada.

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of Study SBX-P0-750 (NDA 217927) conducted at Altasciences, Mount-Royal, Quebec, Canada. This study was conducted under IND 145336.

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. The ORA investigator discussed two items regarding the use of two stand-by subjects to replace the original randomized subjects and the use of an unspecified "SN" abbreviation; it is not clear if this is identifying subject number or screening number. Based on the inspection findings, I conclude that there are no identified concerns for Altasciences regarding reliability of the data and human subject protection for inspected study SBX-P0-750.

2. Inspected Study

NDA 217927

Study Number: Study SBX-P0-750
Study Title: "An Open-Label, Randomized, Balanced, Two-Treatment, Two-Period, Two-Sequence, Crossover, Single Oral Dose Comparative Bioavailability Study of Oxaprozin 300 mg Capsules and Daypro® (Oxaprozin) 600 mg Caplets Following a 600 mg Dose in Health Adult Subjects Under Fasting Conditions"
Dates of study conduct: 02/14/2022 – 05/11/2022
Clinical Investigator: Eric Sicard, M.D.

3. Inspectional Findings

Altasciences, Mount-Royal, Quebec, Canada

ORA investigator Yuanyuan Li inspected Altasciences Company Inc., 1200 Beaumont Ave, Mount-Royal, Quebec, H3P 3PI, Canada from June 12-16, 2023.

3.1 Previous Inspections

The previous BA/BE inspection of Altasciences Company Inc. was conducted on 6/25-28/2019 and was classified NAI. No FDA-483 was issued. The following discrepancies were discussed verbally at the conclusion of the previous inspection:

1) Dating for Period 2 of Subject (b) (6) was incorrect for values at pre-dose, 2 hour and 4.5 hours and were recorded with Period 1 dates in the submitted database. The 1-hour timepoint had the correct date and all values were listed correctly under Period 2.

2) A Subject was to be evaluated before departing but was not. This was recorded by the firm as an SOP deviation however per the protocol should have been listed as a protocol deviation.

3.2 Current Inspection

The current inspection included auditing the following items:

-Case report forms (CRFs)
-Informed consent process
-Protocol deviations
-Institutional review board approvals
-Test article accountability and storage
-Randomization
-Dosing records

-Monitoring records
-Adverse event reporting
-Site staff training logs

3.3 Inspection finding(s)

At the conclusion of the inspection, ORA investigator Yuanyuan Li did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. However, there were two inspection findings related to (a) the use of two stand-by subjects as replacement of two already randomized subjects due to these two original subjects not meeting acceptance criteria before first dosing took place, and (b) the use of unspecified "SN" abbreviation, when providing on-study meal records for subjects who participated and completed the study. This abbreviation was intended to stand for subject number but without the abbreviation being defined, it was not clear and could possibly have stood for screening number.

3.4. Discussion Items

Discussion Item 1: The site removed two subjects (Screening Numbers (b) (6) from participating in the study prior to the application of the first dose of the investigational products, because they failed to meet acceptance criteria ((b) (6) was screened positive for cocaine, and (b) (6) was screened positive in pregnancy test during re-check upon check-in). These two jects had alr y been randomized into the study as Subject (b) (6) and Subject (b) (6) respectively. The site then proceeded to replace these two subjects with two stand-by subjects identified as (b) (6) (48y, female, white) and (b) (6) (40y, male, white) and assigned them the same randomizations numbers (b) (6) (used initially for (b) (6)) and (b) (6) (used initially for (b) (6)).

OSIS Evaluation of the Discussion Item 1: Forty subjects (30 assigned and 10 stand-by) were checked in for the first dose administration of the investigational products (IPs) on (b) (4) (Day-1), according to the subject screening logs, assigned subject identification codes, and ID of the subjects on-site (**Attachment 01**). However, 2 of the 30 assigned subjects (Screening Numbers (b) (6)) were excluded from participating in the study prior to the first dose, because they failed to meet the acceptance criteria during the re-check upon check-in ((b) (6) screened positive for cocaine, and (b) (6) screened positive in a pregnancy test). These two subjects had already been randomized into the study as Subject (b) (6) and Subject (b) (6) respectively. The site then replaced these two subjects with two stand-by (SB) subjects identified as (b) (6) (48

years old, white, female) and (b) (6) (40 years old, white, male) and assigned them the same randomizations numbers of (b) (6) (used initially for subject (b) (6) and (b) (6) (used initially for subject (b) (6)). Note that the replacement subjects ((b) (6) and (b) (6)) were not truly randomized along with the other 28 subjects. Although the inclusion of these stand-by subjects may introduce bias in age and sex of the subjects participated in the study, since the demographic data (i.e., sex and age) of the originally randomized subjects were not collected during investigation, and these originally assigned two subjects were not administered the IPs, therefore, OSIS cannot determine if the replacement will impact the data outcome in PK analysis and BE evaluation. From the OSIS perspective, the inclusion of these two stand-by subjects as replacements may not have impact on the data integrity of Study SBX-P0-750. However, the review division may wish to request further demographic information from the sponsor to evaluate if these substitutions introduced any bias between the treatment arms.

Firm's Response to Discussion Item 1: During the inspection close out, the site acknowledged this discussion item and stated that corrective action will be taken in the future. However, the site did not provide a written response or details if further actions would be needed or taken with respect to this study.

Discussion Item 2: The site used the unspecified "SN" abbreviation in on-study meal records when identifying subjects who participated and completed the study.

OSIS Evaluation of the Discussion Item 2: The site presented an on-study meal intake form (Ref:CLP-3020(T9) (**Attachment 02**) that provides the meal start and end time, and target consumption rates. The study subjects are listed under column "SN", without indicating if SN stands for "Screening Number, Stand-by Number, or Subject number". ORA investigator verified that SN in the form is used to indicate subject number (assigned as part of randomization). The unspecified use of "SN" abbreviation in this form did not result in any issues of subjects missing IP dosing, not receiving their intended meals, or receiving extra meals. Thus, this discussion item has no impact on the data integrity of Study SBX-P0-750 and safety outcome.

Firm's Response: During the inspection close out, the site acknowledged the discussion item and informed the ORA investigator that the site is in the process of implementing an electronic system to replace the paper-based source data collection method then hoping to resolve such reporting issues. The site did not provide a formal written response.

3.4. Specific concerns from OND

OND did not have any specific concerns regarding the clinical or analytical conduct for the Study SBX-P0-750 and requested OSIS to treat the inspection as a surveillance inspection. However, OND did indicate that the sponsor provided data from Study SBX-P0-750 (even though Cmax appears to not fully meet the BE criteria) to demonstrate safety of the test product compared to the reference product.

Attachment(s)
Attachment 1: Assigned Subject List on site for study SBX-P0-750
Attachment 2: On-study Meals Period 1 - 13 pages.pdf

Hasan A. Irier, Ph.D.
Pharmacologist
OTS/OSIS/DGDSI

Draft: HAI 08/08/2023
Edit: MO 08/09/2023; KAB 08/18/2023, 08/28/2023

OSIS file #: 9842
eNSpect # 219911
eNSpect OP ID# 248353

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/s/

HASAN A IRIER
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08/31/2023 10:33:29 AM

KIMBERLY A BENSON
08/31/2023 10:42:26 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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 18, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 217927
Product Name, Dosage Form, and Strength:	Coxanto (oxaprozin) capsule, 300 mg
Applicant/Sponsor Name:	Solubiomix, LLC
TTT ID #:	2023-3208-1
DMEPA 1 Safety Evaluator:	Susan Hakeem, Pharm.D.
DMEPA 1 Team Leader:	Valerie S. Vaughan, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label received on June 30, 2023 for Coxanto. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label for Coxanto (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Hakeem, S. Label and Labeling Review for Coxanto (NDA 217927). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2023 JUN 02. TTT ID No.: 2023-3208.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JUNE 30, 2023

Container labels

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/s/

SUSAN HAKEEM
07/18/2023 12:58:30 PM

VALERIE S VAUGHAN
07/19/2023 01:16:32 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 2, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 217927
Product Name and Strength:	Coxanto (oxaprozin) capsule, 300 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Solubiomix, LLC
FDA Received Date:	December 22, 2022
TTT ID #:	2023-3208
DMEPA 1 Safety Evaluator:	Susan Hakeem, Pharm.D.
DMEPA 1 Team Leader:	Valerie S. Vaughan, Pharm.D.

1 REASON FOR REVIEW

As part of the approval process for Coxanto (oxaprozin) capsule, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Coxanto prescribing information (PI) and container labels for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 217927 is a 505(b)(2) NDA and the listed drug product is Daypro, NDA 018841.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

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

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

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI) and container label may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Solubiomix, LLC.

4 RECOMMEDATIONS FOR DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The strength is presented as a large number throughout the PI and appears without commas to improve readability.	Numbers greater than or equal to 1,000 should contain a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000".	We recommend revising the strength statement to include a comma, for example, to read as 1,200 mg instead of 1200 mg. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022).[a]
Highlights of Prescribing Information			
1.	As currently presented, the Dosage and Administration section contains an error-prone symbol (e.g., ≥).	Error prone symbols may lead to misinterpretation and medication error (e.g., mistaken as opposite of intended).	We recommend replacing the symbol with its intended meaning (e.g., greater than or equal to). See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022).[a]
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, Table 1 contains the use of confusing symbols (e.g., ≥).	Error prone symbols may lead to misinterpretation and medication error (e.g., mistaken as opposite of intended).	We recommend replacing the symbols with their intended meanings to prevent misinterpretation and confusion (e.g., greater than or equal to). See *Guidance for Industry: Safety Considerations for Container Labels and Carton*

[a] Guidance for industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). Available at: https://www.fda.gov/media/158522/download.

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			Labeling Design to Minimize Medication Errors (May 2022).[a]
2.	The dosage instructions do not specify if ideal body weight or actual body weight should be used for weight-based dosing.	To ensure that the intended dose is calculated correctly to prevent wrong dose errors.	We recommend specifying whether ideal or actual body weight should be used to calculate the recommended dosage.

5 RECOMMENDATIONS FOR SOLUBIOMIX, LLC

Table 3. Identified Issues and Recommendations for Solubiomix, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s)			
1.	The placement of the graphic at the beginning of the proprietary name competes with the legibility of the proprietary name, which may lead to misinterpretation of the proprietary name as (b) (4).	Placing a logo immediately before, within, or after the proprietary name can lead to misinterpretation because logos may look like an additional letter in the proprietary name or detract from legibility.	Delete, move, and/or decrease the prominence of the graphic at the beginning of the proprietary name.
2.	(b) (4)		

Table 3. Identified Issues and Recommendations for Solubiomix, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The Serial Number is missing within the product identifier.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	We request you add a place holder for the serial number to the container labeling.
4.	(b) (4)		
5.	As currently presented, the format for the expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a

Table 3. Identified Issues and Recommendations for Solubiomix, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. *See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*[b]

[b] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Coxanto that Solubiomix, LLC submitted on December 22, 2022.

Table 4. Relevant Product Information for Coxanto	
Initial Approval Date	N/A
Active Ingredient	Oxaprozin
Indication	A non-steroidal anti-inflammatory drug indicated for: • Relief of signs and symptoms of Osteoarthritis (OA) • Relief of signs and symptoms of Rheumatoid Arthritis (RA) • Relief of signs and symptoms of Juvenile Rheumatoid Arthritis (JRA)
Route of Administration	Oral
Dosage Form	Capsule
Strength	300 mg
Dose and Frequency	• OA: 1200 mg (four 300 mg capsules) given orally once a day • RA: 1200 mg (four 300 mg capsules) given orally once a day • JRA: 600 mg once daily in patients 22-31 kg. 900 mg once daily in patients 32-54 kg. 1200 mg once daily in patients ≥55 kg
How Supplied	COXANTO (oxaprozin) 300 mg capsules are white opaque capsule imprinted “403” on the cap in black ink, supplied as bottle of 60. NDC Number: 69499-403-60.
Storage	Keep bottles tightly closed. Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container with a child-resistant closure. Protect the unit dose from light.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Coxanto labels and labeling submitted by Solubiomix, LLC.

- Container label received on December 22, 2022.
- Prescribing Information and Medication Guide received on December 22, 2022, available from \\CDSESUB1\EVSPROD\nda217927\0002\m1\us\proposed-insert-med-guide-coxanto.pdf

F.2 Label and Labeling Images

Container labels

(b) (4)

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

Summary of Differences Between Proposed and RLD Labeling

1. Replaced Pfizer's distributor information with Solubiomix's distributor inform
2. Change strength to reflect proposed drug product
3. Change NDC to reflect proposed drug product
4. Change package size to reflect proposed packaging configuration
5. Change strength to reflect proposed drug product
6. Replace DAYPRO with (b) (4)

(b) (4)

Carton labeling

N/A

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/s/

SUSAN HAKEEM
06/02/2023 12:00:14 PM

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