NDA ######

SAFETY LABELING CHANGE NOTIFICATION

APPLICANT NAME
ADDRESS

Attention: CONTACT NAME
TITLE

Dear CONTACT:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Proprietary Name (ESTABLISHED NAME) DOSAGE FORM.

SAFETY LABELING CHANGE

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety labeling changes based upon new safety information that FDA becomes aware of after approval of the drug or biological product.

FETAL RENAL DYSFUNCTION/ OLIGOHYDRAMNIOS/ NEONATAL RENAL IMPAIRMENT

Since Proprietary Name was approved on DATE, we have become aware of case reports submitted to the FDA's Adverse Event Reporting System and published in the medical literature describing that use of nonsteroidal anti-inflammatory drugs (NSAIDs) at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. We have determined that NSAID products represent a class of products that have the potential for the serious risks of fetal renal dysfunction, oligohydramnios, and neonatal renal impairment. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for NSAID products as shown below. Instructions for each section are indicated in *italics*.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Replace Premature Closure of the Ductus Arteriosus *with the following:*

- Fetal Toxicity: Limit use of NSAIDs, including TRADENAME, 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 renal dysfunction and premature closure of the fetal ductus arteriosus (5.X, 8.1).

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

Delete the bullet, Pregnancy*, under* USE IN SPECIFIC POPULATIONS*.*

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

Change **5.X Premature Closure of the Ductus Arteriosus** *to* **5.X Fetal Toxicity** *and replace existing text with the text shown below.*

5.X Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus:

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

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including TRADENAME, 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 postmarketing

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 TRADENAME use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if TRADENAME treatment extends beyond 48 hours. Discontinue TRADENAME if oligohydramnios occurs and follow up according to clinical practice [*see Use in Specific Populations (8.1)*].

8 USE IN SPECIFIC POPULATIONS

Update the **8.1 Pregnancy** *subsection as shown below.*

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including TRADENAME, 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 TRADENAME use between about 20 and 30 weeks of gestation, and avoid TRADENAME 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 TRADENAME, 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 the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. In animal reproduction studies … ***(Note to Applicant:*** *Existing risk summary statement(s) based on animal data should be included here.)* 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 [active moiety], 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.

Above the subheader titled, **Labor and Delivery***, add the following:*

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 TRADENAME, 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 TRADENAME treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue TRADENAME and follow up according to clinical practice (*see Data*).

Data

Human Data

Note to Applicant*: Insert the following language after any existing information regarding 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 postmarketing 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 postmarketing 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

Note to Applicant: *Include description of animal studies here as appropriate.*

17 PATIENT COUNSELING INFORMATION

Insert new language at the end of the subsection titled, Fetal Toxicity*, and move cross references to the end.*

Fetal Toxicity
Inform pregnant women to avoid use of TRADENAME and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with TRADENAME 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.X) and Use in Specific Populations (8.1)*].

MEDICATION GUIDE

In the section, **Before taking NSAIDS,…***, update the bullet "*are pregnant or plan to become pregnant…*" as shown below. Deletions indicated by strikethrough, additions by underline.*

Before taking NSAIDS, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. ~~Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy.~~ Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after ~~29~~ about 30 weeks of pregnancy.**

DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

Since Proprietary Name was approved on DATE, we have become aware of case reports submitted to the FDA's Adverse Event Reporting System and published in the medical literature describing compelling cases of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) occurring in association with use of nonsteroidal anti-inflammatory drugs (NSAIDs). We have determined that NSAID products represent a class of products that have the potential for the same serious risk of DRESS. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for NSAID products as shown below.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Insert the following immediately after **WARNINGS AND PRECAUTIONS*;*** Serious Skin Reactions*:*

- Drug Rash with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically (5.X).

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

Insert **5.X Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)** *immediately following* **5.X Serious Skin Reactions***.*

5.X Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as TRADENAME. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue TRADENAME and evaluate the patient immediately.

17 PATIENT COUNSELING INFORMATION

*Change the subsection title for Serious Skin Reactions to include DRESS and insert new language as indicated in **bold** and underline. Also update cross references, as appropriate, to reference* **5.X Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)** *and* **5.X Serious Skin Reactions***.*

Serious Skin Reactions**, including DRESS**

Advise patients to stop **taking** TRADENAME immediately if they develop any type of rash **or fever** and to contact their healthcare provider as soon as possible [*see Warnings and Precautions (**5.X,** 5.X)*].

FDA intends to approve a labeling change common to all class members on the same day. In accordance with this policy, we have determined that an extension of the discussion period will be warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for your supplement or rebuttal statement will begin when the submission is received, and will end by April 13, 2021, unless additional discussion extensions are warranted.

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED).

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

We remind you that requirements under section 505(o)(4) also apply to any authorized generic products marketed under this NDA.

If you have any questions, call LCDR Jessica Voqui, PharmD, MS; Safety Regulatory Project Manager, at 301-796-2915.

Sincerely,

{See appended electronic signature page}

LCDR Mark A. Liberatore, PharmD, RAC
Deputy Director for Safety
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research