

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210045Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABELS 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: May 24, 2018
Requesting Office or Division: Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number: NDA 210045
Product Name and Strength: Consensi (Amlodipine Besylate/Celecoxib) Tablets,
2.5 mg/200 mg, 5 mg/200 mg, 10 mg/200 mg
Applicant/Sponsor Name: Kitov Pharmaceuticals Ltd. (Kitov)
FDA Received Date: May 23, 2018
OSE RCM #: 2017-1605-1
DMEPA Safety Evaluator: Sarah Thomas, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised Consensi container labels, as well as the proposed Medication Guide (MG) and Prescribing Information (PI) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review.^a

2 CONCLUSION

The revised Medication Guide (MG) and Prescribing Information (PI) are acceptable from a medication error perspective.

While Kitov implemented all of our previous recommendations for the container labels, our review of the newly added NDC numbers and newly relocated net quantity statement on the revised container labels noted the labels may be further improved to promote safe use.

^a Thomas S. Labels and Labeling Review for Consensi (NDA 210045). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 29. RCM No.: 2017-1605.

3 RECOMMENDATIONS FOR KITOV PHARMACEUTICALS LTD. (KITOV)

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

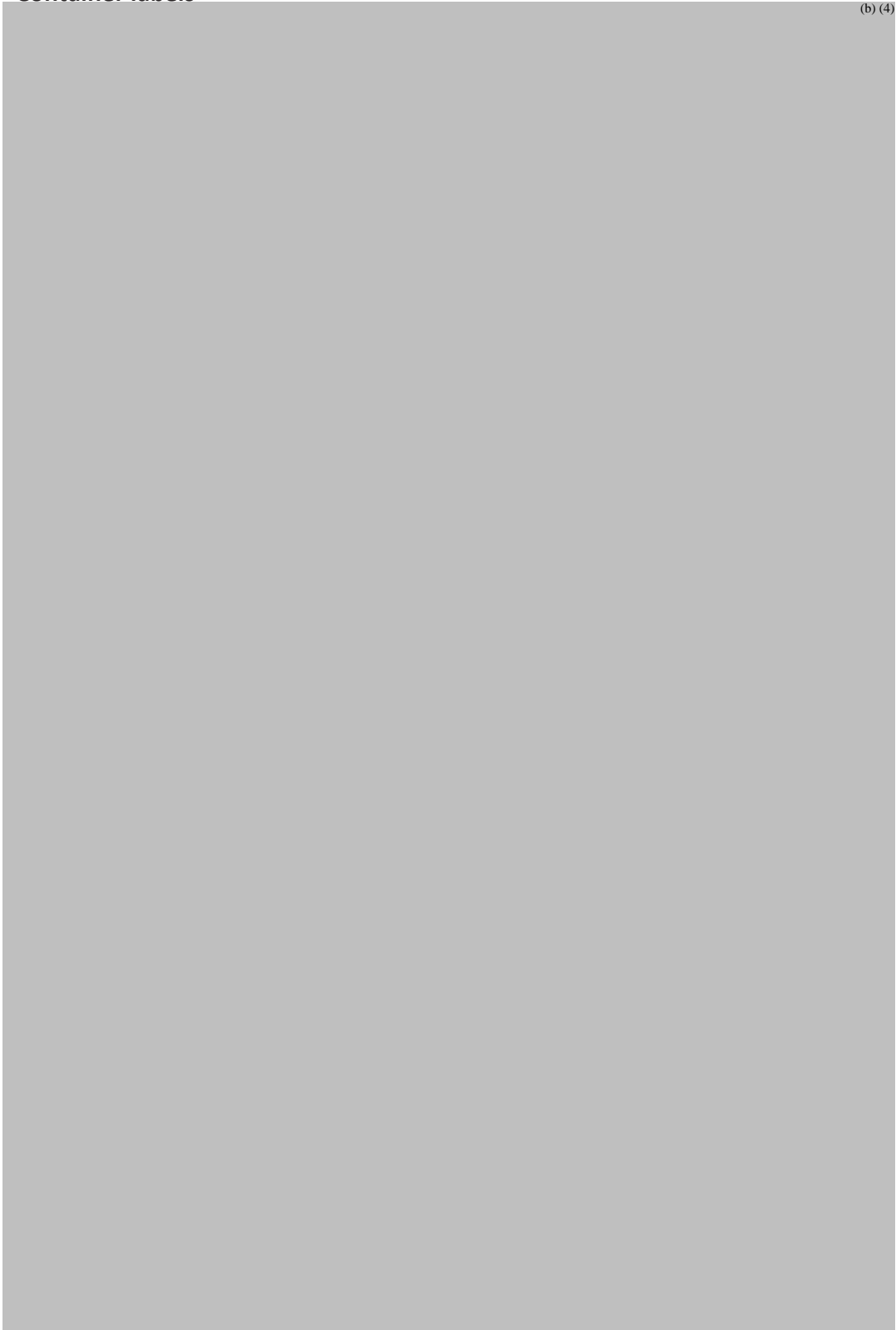
A. Container Labels

1. Revise the middle digits of the NDC numbers for the three strengths on the container labels, or alternatively, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type.^b Ensure revisions to NDC numbers are carried over to Section 16 of the Full PI as well. The use of sequential numbers for the product code (middle digits) of the NDC numbers for the 2.5 mg/200 mg, 5 mg/200 mg, and 10 mg/200 mg strengths is not an effective differentiating feature. The middle digits are traditionally used by healthcare providers to check the correct product and strength, and so similarity of product code numbers has led to selection and dispensing errors of the wrong strength.
2. Relocate the net quantity statement away from the product strength on the container labels, such as towards the bottom of the principal display panel below the “Dispense the enclosed Medication Guide to each patient.” phrase and before the “Kitov” logo.^b From post-marketing experience, presenting the strength and the net quantity statements in close proximity increases the risk of numerical confusion between the strength and net quantity.

^b Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON MAY 23, 2018

Container labels



(b) (4)

(b) (4)

Medication Guide and Prescribing Information (Not shown)

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

/s/

SARAH E THOMAS
05/24/2018

CHI-MING TU
05/24/2018



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

Division of Pediatric and Maternal Health Memorandum

Date: May 4, 2018 **Date consulted:** October 25, 2017

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, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Amlodipine Besylate and Celecoxib fixed dose combination tablets, for oral administration

Drug Class: Antihypertensive (calcium channel blocker) and NSAID

NDA: 210045

Applicant: Kitov Pharmaceuticals, Ltd.

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication: For patients who require the use of a calcium channel blocker for the treatment of hypertension, to lower blood pressure and (b) (4) for (b) (4) treatment (b) (4) of osteoarthritis.

Materials Reviewed:

- DPMH consult request dated October 25, 2017, in DARRTS (Reference ID: 4172231)
- Applicant's submission for NDA 210045, a 505(b)(2) application, dated July 31, 2017
- Applicant's response to request for information-Labeling Information Request of September 29, 2017 to provide support for amlodipine besylate and celecoxib combination tablets, for oral administration to comply with the Pregnancy and Lactation Labeling Rule (PLLR, 79 FR 72064) and dated October 20, 2017.
- DPMH review of Norvasc, NDA 19787, in DARRTS by Dr. Miriam Dinatale, Reference ID: 4012763 and dated November 14, 2016

Consult Question:

DCRP requests DPMH assistance with reviewing the applicant's Pregnancy and Lactation labeling subsections to comply with PLLR format.

INTRODUCTION

This is an original 505(b)(2) application for a fixed dose combination product (FDCP), submitted on July 31, 2017, and indicated in patients who require the use of a calcium channel blocker for the treatment of hypertension, to lower blood pressure, and (b)(4) for (b)(4) treatment (b)(4) of osteoarthritis. This 505(b)(2) application relies on FDA's previous finding of safety and effectiveness of the individual reference listed drugs (RLDs): NDA 020998 for Celebrex (celecoxib) capsules held by G.D. Searle, LLC (a subsidiary of Pfizer) and NDA 019787 for Norvasc (amlodipine besylate) tablets) held by Pfizer Inc. The subject of this consult is to review the applicant's Pregnancy and Lactation labeling subsections to comply with the content and format requirements of the Pregnancy and Lactation Labeling Rule (PLLR). The applicant has provided labeling which depends on the labelings of the individual components (Norvasc and Celebrex) and incorporates findings from the applicant's review of the literature.

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

Regulatory History

Both amlodipine besylate and celecoxib are marketed in the United States (US) and worldwide as individual branded and generic prescription drug products (amlodipine besylate was first approved in 1992 and celecoxib was first approved in 1998).

Drug Characteristics¹

The drug product characteristics are similar to the individual components' characteristics. The recommended dose is amlodipine 5 or 10 mg and celecoxib 200 mg.

¹ Fixed dose combination proposed labeling

Amlodipine

- Molecular weight is 567.1 Daltons
- terminal elimination half-life is 30-50 hours
- Absolute bioavailability is 64-90%
- high protein binding (93%)
- not genotoxic or mutagenic

Celecoxib

- Molecular weight is 381.38 Daltons
- mean half-life is 11 hours
- high protein binding (97%)
- It metabolizes to 3 inactive metabolites, an alcohol, the corresponding carboxylic acid and a glucuronide conjugate
- not mutagenic or clastogenic

NSAIDs and Adverse Events During Pregnancy

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

Vane² 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. The mechanism of action of Celebrex is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2).

Celecoxib is a potent inhibitor of prostaglandin synthesis *in vitro*. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Since celecoxib is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.³

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 21⁴ and Scherneck *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

Reviewer Comment

Based on the literature reviewed, use of NSAIDs starting at 20 weeks (second trimester) may cause oligohydramnios. Physicians are already considering the potential risk of

² Vane, J.R. Inhibition of prostaglandin synthesis as a mechanisms of action for the aspirin-like drugs. *Nature*, 1971, 231, 232-235

³ Celebrex approved labeling of May 9, 2016

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

Current RLDs Labelings

The current labelings for Norvasc (amlodipine)⁶ of October 30, 2017 and Celebrex (celecoxib)⁷ of May 9, 2016, are in Physician Labeling Rule (PLR), and in PLLR format. They state:

Norvasc (amlodipine besylate)

FULL PRESCRIBING INFORMATION: CONTENTS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data based on post-marketing reports with NORVASC use in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled hypertension in pregnancy [*see Clinical Considerations*]. In animal reproduction studies, there was no evidence of adverse developmental effects when pregnant rats and rabbits were treated orally with amlodipine maleate during organogenesis at doses approximately 10 and 20-times the maximum recommended human dose (MRHD), respectively. However for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold). Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose [*see Data*]. The estimated background risk of major birth defects and miscarriage for the indicated population 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%-4% and 15%-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Data

Animal Data

⁶ Norvasc was updated to PLLR on October 30, 2017 and DPMH participated in this conversion and submitted a labelling review on November 14, 2016. See DARRTS consult of November 14, 2016, Reference ID: 4012763

⁷ Celebrex was updated to PLLR format on May 9, 2016. DPMH did not participate in this conversion

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (approximately 10 and 20 times the MRHD based on body surface area, respectively) during their respective periods of major organogenesis. However for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

8.2 Lactation

Risk Summary

Limited available data from a published clinical lactation study reports that amlodipine is present in human milk at an estimated median relative infant dose of 4.2%. No adverse effects of amlodipine on the breastfed infant have been observed. There is no available information on the effects of amlodipine on milk production.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m² basis, similar to the maximum recommended human dose of 10 mg amlodipine/day.^a For the rat, the highest dose was, on a mg/m² basis, about twice the maximum recommended human dose.^a Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times the maximum recommended human dose³ of 10 mg/day on a mg/m² basis).

a: Based on patient weight of 50 kg

Celebrex (celecoxib)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation (5.10, 8.1)

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

Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation (5.10, 8.1)

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of CELEBREX in women who have difficulties conceiving (8.3)

FULL PRESCRIBING INFORMATION: CONTENTS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential

FULL PRESCRIBING INFORMATION: CONTENTS

5 WARNINGS AND PRECAUTIONS

5.10 Premature Closure of Fetal Ductus Arteriosus

Celecoxib may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including CELEBREX, in pregnant women starting at 30 weeks of gestation (third trimester) [*see Use in Specific Populations (8.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Pregnancy category D from 30 weeks of gestation onward.

Risk Summary

Use of NSAIDs, including CELEBREX, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including CELEBREX, in pregnant women starting at 30 weeks of gestation.

There are no adequate and well-controlled studies of CELEBREX in pregnant women. Data from observational studies regarding 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, embryo-fetal deaths and an increase in diaphragmatic hernias were observed in rats administered celecoxib daily during the period of organogenesis at oral doses approximately 6 times the maximum recommended human dose of 200 mg twice daily. In addition, structural abnormalities (e.g., septal defects, ribs fused, sternbrae fused and sternbrae misshapen) were observed in rabbits given daily oral doses of celecoxib during the period of organogenesis at approximately 2 times the MRHD [*see Data*]. 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 celecoxib, resulted in increased pre- and post-implantation loss.

Clinical Considerations

Labor or Delivery

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

Data

Human Data

The available data do not establish the presence or absence of developmental toxicity related to the use of Celebrex.

Animal data

Celecoxib at oral doses ≥ 150 mg/kg/day (approximately 2 times the human exposure

at 200 mg twice daily as measured by AUC₀₋₂₄), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternbrae fused and sternbrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥ 30 mg/kg/day (approximately 6 times human exposure based on the AUC₀₋₂₄ at 200 mg twice daily for RA) throughout organogenesis. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses at oral doses ≥ 50 mg/kg/day (approximately 6 times human exposure based on the AUC₀₋₂₄ at 200 mg twice daily for RA).

Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by the AUC₀₋₂₄ at 200 mg twice daily). The effects of CELEBREX on labor and delivery in pregnant women are unknown.

8.2 Lactation

Risk Summary

Limited data from 3 published reports that included a total of 12 breastfeeding women showed low levels of CELEBREX in breast milk. The calculated average daily infant dose was 10-40 mcg/kg/day, less than 1% of the weight-based therapeutic dose for a two-year old-child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events. Caution should be exercised when CELEBREX is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CELEBREX and any potential adverse effects on the breastfed infant from the CELEBREX 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 CELEBREX, 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Celecoxib was not carcinogenic in Sprague-Dawley rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2-to 4-times the human exposure as measured by the AUC₀₋₂₄ at 200 mg twice daily) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC₀₋₂₄ at 200 mg twice daily) for two years.

Mutagenesis

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in vivo* micronucleus test in rat bone marrow.

Impairment of Fertility

Celecoxib had no effect on male or female fertility or male reproductive function in rats at oral doses up to 600 mg/kg/day (approximately 11 times human exposure at 200 mg twice daily based on the AUC₀₋₂₄). At ≥ 50 mg/kg/day (approximately 6-times human exposure based on the AUC₀₋₂₄ at 200 mg twice daily) there was increased preimplantation loss.

17 PATIENT COUNSELING INFORMATION

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including CELEBREX, 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 CELEBREX and other NSAIDs starting at 30 weeks of gestation because of the risk of the premature closing of the fetal ductus arteriosus [*see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)*].

REVIEW

Reviewer comment

The Norvasc and Celebrex labelings, in addition to NSAID class labeling, were adapted to create the applicant's proposed labeling text for the fixed dose combination product as no data from studies of the fixed dose combination product in pregnant women or animals are available. . DPMH in addition to the literature provided by the applicant, also relied on data in the Norvasc NDA and Celebrex NDA and the agency's findings of safety and effectiveness for Norvasc and Celebrex to support labeling sections of this fixed dose combination NDA. The cross-reference to the Norvasc consult for PLLR conversion is included to avoid duplicating the review (see PLLR labeling review by Dr. Dinatale M. in DARRTS, dated November 14, 2016, Reference ID: 4012763). DPMH did not participate in the Celebrex PLLR conversion. DPMH's recommendations for the fixed dose combination product labeling discussed below are based on information from literature provided by the applicant, Kitov, and literature which was independently located and considered for this application by DPMH.

Amlodipine

PREGNANCY

Animal Data

The applicant did not perform any studies on the fixed dose combination product NDA 210045 and relies on FDA's previous findings of safety and effectiveness for the reference listed drug (RLD): NDA 019787 for Norvasc (amlodipine besylate) tablets. As per the Norvasc labeling, studies did not reveal any teratogenicity or other embryo/fetal toxicity in rats and rabbits. No additional information was identified by the applicant.

Review of Literature

Applicant's Review

On October 17, 2017, the applicant, Kitov, provided a review of the literature and summary of the available information to justify edits in subsections of labeling as per PLLR requirements. Kitov utilized the US National Library of Medicine National Center for Biotechnology Information PubMed database. Search terms included celecoxib and pregnancy, celecoxib and lactation, amlodipine and pregnancy and amlodipine and

lactation. All articles identified were reviewed to determine if they had relevance to the appropriate topics. In total, the applicant identified 5 publications with celecoxib in humans during pregnancy and 7 publications in animals during pregnancy, as well as 2 publications of use of amlodipine in humans and one publication in animals during pregnancy. The applicant also identified 4 publications of celecoxib use and two publications of amlodipine use in humans during breastfeeding/lactation.

Identified publications related to amlodipine exposure during pregnancy and lactation (by Ahn *et. al.*, Vigil-De Garcia *et. al.* and Naito *et. al.*) have been previously reviewed by Dr. Dinatale in 2016 and will not be further described in this review.

Pharmacovigilance Review

The applicant has provided no pharmacovigilance review because the FDCP is not marketed and the applicant does not have access to Pfizer's safety database.

DPMH Review

In addition to the search by the applicant, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for amlodipine and use in pregnancy. No publications were identified on human data in addition to the ones mentioned in the prior DPMH Norvasc PLLR review.

Studies performed on other calcium channel blockers used during pregnancy do not demonstrate an increased risk for major congenital malformations. A prospective, multicenter cohort study performed on calcium channel blocker (including nifedipine, verapamil, diltiazem, nimodipine, and felodipine) use during pregnancy does not demonstrate an increased risk of fetal malformations.⁸ A case-control study evaluating the exposure to calcium channel blockers (including verapamil, nifedipine, and felodipine) in early pregnancy showed no increased risk for limb defects or other major congenital abnormalities.⁹

Summary

There is no new animal safety data apart from what is currently reported in labeling for Norvasc. Review of the literature by the applicant and DPMH has failed to produce any new clinical literature on amlodipine use in pregnancy since the prior review from 2016, and therefore, no amlodipine-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes has been identified.

LACTATION

Two publications by Naito *et al*¹⁰ and Ahn *et al*¹¹ provided by the applicant have been previously reviewed and discussed in the prior DPMH Norvasc PLLR labeling review. No additional publications were identified by either the applicant or DPMH regarding amlodipine use during lactation.

⁸ Magee, et al. The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study. *Am J Obstet Gynecol* 1996; 174: 823–828

⁹ Sorensen, et al. The risk of limb deficiencies and other congenital abnormalities in children exposed in utero to calcium channel blockers. *Acta Obstet Gynecol Scand* 2001; 80: 397–401

¹⁰ Naito T, Kubono N, Deguchi S et al. Amlodipine passage into breast milk in lactating women with pregnancy-induced hypertension and its estimation of infant risk for breastfeeding. *J Hum Lact.* 2015;31:301-6.

¹¹ Ahn HK, Nava-Ocampo AA, Han JY et al. Exposure to amlodipine in the first trimester of pregnancy and during breastfeeding. *Hypertens Pregnancy.* 2007;26:179-87

Overall, only one lactation study (Naito *et al*) has been performed to assess the presence of amlodipine in human milk, and in that study the calculated median infant dosage was equivalent to a weight-adjusted maternal dosage of 4.2%. Although the safety data for amlodipine are limited, there have been no reported adverse events in any of the neonates/infants that have been exposed to amlodipine during lactation.

Summary

There are no new safety concerns about amlodipine use during breastfeeding since the last review by DPMH in 2016.

The following risk/benefit statement will be placed in section 8.2, Lactation (b) (4)

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

No additional information has been identified by the applicant or DPMH related to amlodipine and its effects on fertility. Because amlodipine is neither genotoxic nor mutagenic and no embryofetal toxicity was found, there is no need for contraception or pregnancy testing. Therefore, section 8.3, Females and Males of Reproductive Potential of the labeling, will not include any statement on amlodipine.

Celecoxib

PREGNANCY

Animal Data

The applicant did not perform any studies on the fixed dose combination product NDA 210045 and relies on the Agency's previous findings of safety and effectiveness for the RLDs: NDA 020998 for Celebrex (celecoxib) capsules. Celecoxib oral doses (b) (4) caused an increased incidence of ventricular septal defects and fetal alterations, such as ribs fused, sternbrae fused and sternbrae misshapen. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses. No additional new information was identified by the applicant.

Review of Literature

Applicant's Review

On October 17, 2017, the applicant, Kitov, provided a review of the literature and summary of the available information (b) (4)

Kitov utilized the US National Library of Medicine National Center for Biotechnology Information PubMed database. Search terms included celecoxib and pregnancy and celecoxib and lactation. All articles identified were reviewed to determine if they had relevance to the appropriate topics.

A summary table of the applicant's review of literature can be found in Appendix A. A summary of findings related to use of celecoxib use during pregnancy include:

- a nested case control study of data from the Quebec Pregnancy Registry that showed an increased association in pregnancies with the use of nonaspirin NSAIDs (adjusted OR 2.43), including celecoxib (adjusted OR 2.21), and spontaneous abortion outcomes when compared to unexposed pregnancies. The authors concluded that "Gestational exposure to any type or dosage of nonaspirin NSAIDs may increase the

- risk of spontaneous abortion” and to use the drugs with caution.
- randomized trials, comparing celecoxib to magnesium sulfate (MgSO₄) or indomethacin for the treatment of preterm labor, suggested a consideration of a tocolytic indication for celecoxib, and the drug’s effects on the duration of labor and delivery without observation of constriction of the fetal ductus arteriosus
 - in pregnant sheep, administration of celecoxib and indomethacin reduced the production of prostaglandins *in vitro* and *in vivo*. They both reduced blood flow through the fetal ductus arteriosus *in vivo*. However, indomethacin resulted in a more substantial reduction in blood flow than did celecoxib
 - an in-vitro study, when myometrial samples were incubated with celecoxib, decreased contractions in the uterine tissue was observed

Reviewer Comment

There has been inconsistency of study results associating nonaspirin NSAID use with spontaneous abortion. The published case-control study showed an increased association between celecoxib and spontaneous abortion but a causal relationship was not established. No dose–response effect was seen. There were methodological limitations with the study which include lack of adjustment to account for confounding by smoking or BMI, both of which have been associated with miscarriage. The authors also are referring to preconceptual use of nonaspirin NSAIDs including celecoxib. They excluded the patients who took these drugs close to the miscarriage because they considered that the miscarriage was underway and that is why they took the drugs.

Celecoxib has been used successfully to prevent preterm labor. Possible mechanism is by reducing prostaglandin production. Celecoxib may cause constriction/closure of the fetal ductus arteriosus when used in third trimester, even though it may be less severe than other NSAIDs.

Pharmacovigilance Review

The applicant has provided no pharmacovigilance review because the FDCP is not marketed and the applicant does not have access to Pfizer’s safety database.

DPMH Review

In addition to the search by the applicant, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases and GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation, for celecoxib and use in pregnancy. No new safety data were identified.

No reports of placental transfer were identified. NSAIDs and specifically those with greater COX-2 affinity have a lower risk of developmental toxicity than high dose aspirin. As noted above, an association between celecoxib and spontaneous abortions has been reported in the literature.^{12,13}

Summary

Celecoxib is not associated with major birth defects. No new animal data is reported. Review of the literature has failed to produce any new safety human literature on celecoxib use in pregnancy, and therefore, no celecoxib-associated risk of major birth defects or adverse maternal or fetal outcomes has been identified. An association of spontaneous

¹² Tassinari MS, Cook JC, Hurt ME. NSAIDs and developmental toxicity: Birth defects. Res B. Dev Reprod Toxicol 2003;68:3-4

¹³ Nielsen GI, Sorensen HT, Larsen H, Pederson I. Risk of adverse birth outcomes and miscarriage in pregnant users of NSAIDs; population based observational study and case-control study. Br Med J 2001;322:266-70

abortions and use of celecoxib during pregnancy was identified from an epidemiologic study from Quebec, but no causal relationship was established. (b) (4)

Published literature reports that use of NSAIDs, including celecoxib, during the second and third trimesters of pregnancy increases the risk of oligohydramnios and premature closure of the fetal ductus arteriosus. (b) (4)

Language consistent with the current NSAID class labeling includes a Warning and Precaution on premature closure of the fetal ductus arteriosus and will be included in the amlodipine/celecoxib labeling. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first trimester of pregnancy are inconclusive.

DPMH has previously provided recommendations based on review of the NSAIDs data and literature described in prior DPMH reviews that are available in DARRTS (PMHS-MHT consult review dated April 10, 2013 and PMHS-MHT Memorandum dated August 21, 2014). 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.

LACTATION

Animal Data

No new animal safety data was identified by the applicant.

Review of Literature

Applicant's Review

The applicant's review of the literature identified the following publications presented in Appendix B:

Gardiner *et al*¹⁴- in a clinical lactation study in six volunteers administered a single oral dose of 200 mg celecoxib [median maternal celecoxib dose of 3.3 mg/kg (range of 2.3-3.7)] - found that celecoxib concentrations in breast milk are low relative to plasma, with a median milk/ plasma area under the concentration curve from time zero to infinity ($AUC_{0-\infty}$) ratio of 0.18 (range 0.15-0.26). The median time to maximum concentration (T_{max}) in plasma was 2.2 hours (range 1.0-4.0). The T_{max} in milk occurred during the 2-4 hour postdose expression. The median C_{max} of celecoxib in plasma and milk was 1.0 mg/L (range 0.4-1.2) and 0.20 mg/L (range 0.07-0.33), respectively. All subjects had quantifiable celecoxib in milk at the 8-12 hour expression, while two subjects had measurable celecoxib beyond this time. In these subjects, celecoxib could be quantified at the 32-36 hour expression, while one also had measurable concentrations at 36-48 hour (the final expression). The median total presence of celecoxib in milk was 0.011 mg (range 0.004-0.042) or 0.04% (range 0.01-0.15) of the maternal single dose (weight adjusted). The authors concluded that "the estimated daily infant dose was 0.013 mg/kg/day (range 0.011-0.021), which is 0.13 to 0.33% of the recommended celecoxib dose for pediatric patients and therefore, it should not represent a problem to infants being breast fed."-

¹⁴ Gardiner SJ, Doogue MP, Zhang M, Begg EJ. 2006. Quantification of infant exposure to celecoxib through breast milk. *Br J Clin Pharmacol*. 61(1):101-4.

Hale *et al.*¹⁵ 2004- performed a clinical lactation study to investigate the transfer of celecoxib to human milk.- Five women received 200mg once daily. -The milk/plasma ratio AUC ratio was 0.23The average concentration (AUC) in milk was 66 mcg/L. The absolute infant dose average was 9.8 mcg/kg/day. Plasma levels in 2 infants studied, were undetectable.¹⁶ As per Hale: the relative infant dose (RID): 0.3-0.7%.-

Kroppert- estimated from one woman who received 4 doses of celecoxib 100mg, twice daily- that the estimated maximum infant dose, using the maximum milk concentration reported for this patient (133 ng/ml) and a milk intake of 150 mL/kg/day for an average infant, that the absolute infant exposure to celecoxib to be approximately 20 mcg/kg/day. “They noted that milk concentrations of celecoxib obtained closer to the time of celecoxib administration would be expected to be higher, and that at double the concentration the estimated infant exposure would be 40 mcg/kg/day.¹⁷

Rhulen *et al* report on thirteen nonlactating women who took celecoxib 200 or 400 mg twice daily for 2 weeks followed by collection of nipple aspirate fluid. Two women taking 200 mg twice daily had celecoxib concentrations of 1.2 and 1.5 mg/L; 2 women taking 400 mg twice daily had celecoxib concentrations of 0.53 and 8.4 mg/L in the aspirate. Celecoxib was undetectable (lower limit of assay not stated) in the nipple aspirate fluid of the other 9 women. Collection times with respect to the doses were not stated.¹⁸

DPMH Review

In addition to the search by the applicant, DPMH also conducted a literature search in PubMed, Embase and the LactMed databases for celecoxib and use in lactation as well as in GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation and Hale TW Medications and Mother’s Milk.

No additional publications were identified. LactMed agrees with Gardiner *et al* and states “Because of the low levels of celecoxib in breastmilk, amounts ingested by the infant are small and would not be expected to cause any adverse effects in breastfed infants. No special precautions are required”.

Reviewer Comment

The celecoxib concentration in breast milk and the RID were notably low and as such it should not represent a problem to breastfed infants.

Summary

From the published human data, it appears that celecoxib is present in the breast milk but in small amounts, less than 1% of the recommended celecoxib dose for pediatric patients and therefore, it should not represent a problem to infants being breast fed. Plasma levels, in 2 infants studied, were undetectable. Therefore, DPMH recommends the following to be included in the labeling: (b) (4)

[Redacted text block]

¹⁵ Hale TW, McDonald R, Boger J. 2004. Transfer of celecoxib into human milk. J Human Lactation. 20(4):397-403.

¹⁶ Hale TW, McDonald R, Boger J. Transfer of celecoxib into human milk. J Hum Lact. 2004;20(4):397-403.

¹⁷ Knoppert DC, Stempak D, Baruchel S et al. Celecoxib in human milk: a case report. Pharmacotherapy. 2003;23(1):97-100.

¹⁸ Ruhlen RL, Chen YC, Rottinghaus GE, Sauter ER. RE: "Transfer of celecoxib into human milk". J Hum Lact. 2007;23:13-4.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Celecoxib is not mutagenic, genotoxic or clastogenic in Chinese hamster ovary cells. No new data was identified by the applicant or DPMH regarding celecoxib and potential effects on human 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.¹⁹ In women, ultrasound scans of follicular development showed a fivefold increase in the incidence of this syndrome in the presence of some NSAIDs.^{20,21} 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 (PMHS-MHT consult review dated April 10, 2013 and PMHS-MHT Memorandum dated August 21, 2014). 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.

Summary

Celecoxib is not mutagenic, genotoxic or clastogenic in Chinese hamster ovary cells, and is not associated with major birth defects. Therefore, there is no need for pregnancy testing or contraception during treatment with celecoxib.

DPMH proposes the following language regarding 8.3 Females and Males of Reproductive Potential, Infertility, Females: “Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including celecoxib 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. (b) (4)

Consider withdrawal of NSAIDs, including celecoxib in women who have difficulties conceiving or who are undergoing investigation of infertility”.

The above statement on Infertility should be included in the combination drug product labeling, Subsection 8.3 as per the current template for NSAIDs labeling.

CONCLUSIONS

Amlodipine and celecoxib fixed dose combination 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 (see below).

DPMH refers to the final NDA action for final labeling.

The *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections of

¹⁹ Armstrong DT, Grinwich DL: Blockade of spontaneous and LH-induced ovulation in rats by indomethacin, an inhibitor of prostaglandin synthesis. *Prostaglandins* 1972;1:21.

²⁰ Marik J, Hulka J: Luteinized unruptured follicle syndrome: a subtle cause of infertility. *Fertil Steril* 1978; 29:270.

²¹ Killick S, Elstein M: Pharmacological production of luteinized unruptured follicles by prostaglandin synthetase inhibitors. *Fertil Steril* 1987;47:773-7.

the fixed dose combination drug product (FDCP) labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Subsection 8.1**
 - The “Pregnancy” subsection of the FDCP labeling was formatted in the PLLR format to include: “Risk Summary”, “Clinical Considerations” and “Data” headings.
- **Lactation, Subsection 8.2**
 - The “Lactation” subsection of FDCP labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” headings.
- **Females and Males of Reproductive Potential, Subsection 8.3**
 - Females and Males of Reproductive Potential subsection of the FDCP labeling was formatted in the PLLR format to include the “Infertility” subheading.
- **Section 17 PATIENT COUNSELING INFORMATION**

RECOMMENDATIONS

DPMH has the following recommendations for the FDCP tablets labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks of gestation (5.12, 8.1).

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

Infertility: NSAIDs are associated with reversible infertility. (b) (4)
(8.3)

FULL PRESCRIBING INFORMATION: CONTENTS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential

FULL PRESCRIBING INFORMATION: CONTENTS

5 WARNINGS AND PRECAUTIONS

5.12 Premature Closure of Fetal Ductus Arteriosus
Avoid use of NSAIDs, in pregnant women starting at 30 weeks of gestation [see *Use in Specific Populations (8.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including BRANDNAME, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including BRANDNAME, in pregnant women starting at 30 weeks of gestation (third trimester). There are risks to the mother and fetus associated with poorly controlled hypertension in pregnancy (see *Clinical Considerations, Data*). There is no published literature of BRANDNAME in pregnant women. No animal reproductive toxicity studies have been conducted with the combination of celecoxib and amlodipine.

Celecoxib

The available published data and case reports did not identify a risk of major birth defects, miscarriage or adverse maternal outcomes (b) (4) Published literature reports that use of NSAIDs, including celecoxib, during the third trimesters of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimester of pregnancy are inconclusive (see *Clinical Considerations, Data*). In animal reproduction studies, embryo-fetal deaths and an increase in diaphragmatic hernias were observed in rats administered celecoxib daily during the period of organogenesis at oral doses approximately 6 times the maximum recommended human dose of 200 mg twice daily. In addition, structural abnormalities (e.g., septal defects, ribs fused, sternbrae fused and

sternebrae misshapen) were observed in rabbits given daily oral doses of celecoxib during the period of organogenesis at approximately 2 times the MRHD. 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 celecoxib, resulted in increased pre- and post-implantation loss, and decreased uterine decidualization (*see Data*).

Amlodipine

The available data from post-marketing reports and a small study with Norvasc use in pregnant women with mild to moderate chronic hypertension did not identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, there was no evidence of adverse developmental effects when pregnant rats and rabbits were treated orally with amlodipine maleate during organogenesis at doses approximately 10 and 20-times the MRHD, respectively. However, in rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold). Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population 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 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal Adverse Reactions

Avoid use of NSAID's in pregnant women in the third trimester because NSAIDs, including celecoxib, can cause premature closure of the fetal ductus arteriosus (*see Data*).

Data

Human Data

Celecoxib

Published literature has concluded that the use of NSAIDs during the third trimester of pregnancy may cause constriction of the patent ductus arteriosus and premature closure of the fetal ductus arteriosus.

Animal Data

Celecoxib

Celecoxib at oral doses ≥ 150 mg/kg/day (approximately 2 times the human exposure at 200 mg twice daily as measured by AUC_{0-24}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternbrae fused and sternbrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥ 30 mg/kg/day (approximately 6 times human exposure based on the AUC_{0-24} at 200 mg twice daily for RA) throughout organogenesis. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses at oral doses ≥ 50 mg/kg/day (approximately 6 times human exposure based on the AUC_{0-24} at 200 mg twice daily for RA).

Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by the AUC_{0-24} at 200 mg twice daily).

Amlodipine

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (approximately 10 and 20 times the MRHD based on body surface area, respectively) during their respective periods of major organogenesis. However, for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

8.2 Lactation

Risk Summary

The available published literature report the individual components of BRANDNAME (celecoxib, amlodipine) are present in human breast milk at low levels. Data from 3 published reports that included a total of 12 breastfeeding women calculated the average daily infant dose of celecoxib as 10-40 mcg/kg/day, less than 1% of the weight-based therapeutic dose for a two-year old-child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events with maternal use of celecoxib. Data from a published observational clinical lactation study reports that amlodipine is present at an estimated median relative infant dose of 4.2%, approximately 1.7 to 3.3% of the recommended dose for an average 6-year old (20 kg) (*see Data*). No adverse effects of amlodipine were observed in the breastfed infants. There is no available information on the effects of celecoxib or amlodipine on milk production. (b) (4)

Data

Celecoxib

A clinical lactation study in 6 volunteers administered a single oral dose of 200 mg celecoxib [median maternal celecoxib dose of 3.3 mg/kg (range of 2.3-3.7)] at 6.5 to 15 months postpartum (mean 11 months) and in the final stage of weaning showed that the median total amount of celecoxib present in milk was 0.011 mg (range 0.004-0.042) or 0.04% (range 0.01-0.15) of the maternal single dose (weight adjusted). The estimated daily infant dose was 0.013 mg/kg/day (range 0.011-0.021), which is 0.13 to 0.33% of the clinically used celecoxib dose for pediatric patients.

A clinical lactation study in 3 breastfeeding mothers who had been taking 200 mg celecoxib orally once daily for many weeks and who were at steady state (group 1) and 2 breastfeeding mothers administered a single 200-mg oral dose of celecoxib (group 2) averaging 12 months post-partum (range 3-22 months). The mean average concentration of celecoxib in milk during the 8-hour interval following administration of celecoxib for all five mothers was 66 mcg/L (95% CI: 41-89). The estimated mean absolute infant dose was 9.8 mcg/kg/day (95% CI: 6.2-13.4), which is 0.1 to 0.25% of the dose clinically used for pediatric patients. Comparison of this to the weight-normalized maternal dose yields an estimated mean relative infant dose of 0.30% (95% CI: 0.19-0.39).



Amlodipine

An observational clinical lactation study of 31 lactating women who were receiving amlodipine within 3 weeks after delivery for pregnancy-induced hypertension showed a median concentration of amlodipine in milk 24 hours after a mean maternal oral dose of approximately 6 mg/day for 7 to 9 days of 11.5 ng/mL (interquartile range of 9.84-18.0 ng/mL). The mean maternal body weight-adjusted dose was 0.0987 ± 0.0366 mg/kg. The median plasma concentration of amlodipine was 15.5 (interquartile range of 12.0-22.8 ng/mL). The median amlodipine concentration ratio of milk to plasma was 0.85 (interquartile range of 0.743-1.08). The median estimated infant daily dose was 4.17 mcg/kg/day (interquartile range of 3.05 to 6.32 mcg/kg/day), approximately 1.7 to 3.3% of the recommended dose for an average 6-year old (20 kg). The median relative infant daily dose was 4.18% (interquartile range of 3.12%-7.25%).

8.3 Females and Males of Reproductive Potential

Celecoxib

Infertility

Females:

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including celecoxib, 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. Consider withdrawal of NSAIDs, including celecoxib, in women who have difficulties conceiving or who are undergoing investigation of infertility.

17 PATIENT COUNSELING INFORMATION

Fetal Toxicity

Advise pregnant women to avoid use of BRANDNAME starting at 30 weeks of gestation because of the risk of the premature closing of the fetal ductus arteriosus. Advise females of reproductive potential to contact their healthcare provider with a known or suspected pregnancy [*see Warnings and Precautions (5.12) and Use in Specific Populations (8.1)*].

Female Fertility

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

Appendix A.

Table 1: Applicant’s Summary of Published Literature for celecoxib use in pregnancy

Authors	Country, Study, Period Data Source, Population	Study Design	Exposure Type /Exposure Time	Treatment	OR (95% CI)	Conclusion
Nakhai-Pour, 2011 ²²	North America/ Canada 1997-today The Quebec Pregnancy Registry. Data from 4705 women with abortion (spontaneous) 1-20 weeks. Control: randomly selected 10 controls from the remaining women in the registry with matching index date (date of spontaneous abortion) and gestational age, for a total of 47,050 controls. Used filled prescription data on all NSAID use.	Nested case control study	Use of NSAIDs during pregnancy. 352 (7.5%) with Ab had filled Rx for NSAIDs vs 1213 (2.6%) with no AB who used NSAIDs.		For all NSAIDs OR 2.43 (CI: 2.12-2.79) For Celecoxib OR 2.21 (CI 1.42-3.45)	Increased association between celecoxib and spontaneous Ab (not a causal relationship)
Saadati 2014 ²³	Ahvaz Educational Hospitals (Iran) from March to August 2013. 600 pregnant women in total	Single blinded randomized clinical trial/ study	Celecoxib vs MgSO ₄ Gestational age: >24 weeks and <34 weeks	Given 4 grams of MgSO ₄ intravenously or 100mg of celecoxib	Preterm labor was prevented in 75.7% of subjects who	Celecoxib was similar to MgSO ₄ as a medication to prevent preterm labor.

²² Nakhai-Pour HR, Broy P, Sheehy O, Bérard A. 2011. Use of nonaspirin nonsteroidal antiinflammatory drugs during pregnancy and the risk of spontaneous abortion. CMAJ. 183(15):1713-20.

²³ Saadati N, Moramezi F, Cheraghi M, Sokhray L. 2014. Using celecoxib for the suppression of preterm labor instead of magnesium sulfate. Journal of Pregnancy. Vol. 2014:ID 869698,4 pages.

Authors	Country, Study, Period Data Source, Population	Study Design	Exposure Type /Exposure Time	Treatment	OR (95% CI)	Conclusion
Borna S, 2007 ²⁴	104 pregnant women with preterm labor (52 per arm)	Blinded randomized clinical trial/	Celecoxib vs MgSO ₄ Gestational age: >24 weeks and <34 weeks	orally every 12 hours for at least 2 days. Given 4-6 grams of MgSO ₄ intravenously or 100mg of celecoxib orally every 12 hours for at least 2 days.	Delivery was delayed for 48 hours in 42 (81%) and 45 (87%) patients in the celecoxib and MgSO ₄ groups, respectively (p = 0.298).	Celecoxib was similar to MgSO ₄ as a medication to prevent preterm labor. The only reported adverse reactions were headache, lethargy, and palpitations in the MgSO ₄ treatment arm. No adverse reactions were reported in the celecoxib arm. There were no drug related severe maternal or neonatal complications reported for either group.
Stika CS, 2002 ²⁵	US, (Barnes-Jewish Hospital, Washington University School	Blinded randomized clinical trial/	Randomized to tocolytic therapy with either celecoxib or indomethacin	Given celecoxib 100-mg twice daily (48 hours)		Celecoxib was as effective as a tocolytic as indomethacin, but

²⁴ Borna S and Saeidi FM. 2007. Celecoxib versus magnesium sulfate to arrest preterm labor: randomized trial. *J Obstet Gynaecol Res.* 33(5):631-4.

²⁵ Stika CS, Gross GA, Leguizamon G, Gerber S, Levy R, Mathur A, Bernhard LM, Nelson DM, Sadovsky Y. 2002. A prospective randomized safety trial of celecoxib for treatment of preterm labor. *Am J Obstet Gynecol.* 187:653-60.

Authors	Country, Study, Period Data Source, Population	Study Design	Exposure Type /Exposure Time	Treatment	OR (95% CI)	Conclusion
	of Medicine, St Louis, Mo, and Northwestern Memorial Hospital, Northwestern University Medical School, Chicago, Ill) 24 women (12 per arm)		Gestational age: >24 weeks and <34 weeks	Or indomethacin 100-mg followed by indomethacin 50 mg orally every 6 hours for 7 additional doses (48 hours of therapy).		without the detrimental constriction of the fetal ductus arteriosus observed for indomethacin
Kuc P, 2011 ²⁶	Poland, Medical University of Bialystok, Bialystok, Poland	In Vitro study. Two groups of patients who delivered by cesarean section were involved in the study: 36 patients who delivered preterm between the 24th and 34th week of pregnancy and 40 patients who delivered at term	Myometrial samples were obtained from the lower uterine segment during cesarean sections.	Drug combinations: atosiban/nifedipine; atosiban/celecoxib, nifedipine/celecoxib. Tocolytic efficiency of the drug combinations was assessed		The atosiban/nifedipine combination has additive tocolytic effect on myometrial strips contractility in preterm and term patients. The other combinations: atosiban /celecoxib and nifedipine/celecoxib presented only antagonistic effects in both studied groups.

²⁶ Kuc P, Laudański P, Pierzyński P, Laudański T. 2011. The effect of combined tocolysis on *in vitro* uterine contractility in preterm labour. Adv Med Sci. 56(1):88-94.

Authors	Country, Study, Period Data Source, Population	Study Design	Exposure Type /Exposure Time	Treatment	OR (95% CI)	Conclusion
Takahashi ²⁷	USA and Canada Cardiovascular Research Institute and Departments of Pediatrics and Pharmacy, University of California, San Francisco, and Research Center, Hospital Sainte-Justine, Montreal, Quebec.	They studied thirteen pregnant sheep at between 127–131 days gestation (full term is approximately 145 days).		Single 200 and 400 mg celecoxib (0.7 and 1.4 µg/ml, respectively), vs indomethacin. <i>In vitro</i> studies were also performed on ductus arteriosus tissue dissected free from untreated fetal lambs that were delivered by cesarean section.		Celecoxib and indomethacin reduced the production of prostaglandins <i>in vitro</i> and <i>in vivo</i> . Both indomethacin and celecoxib constricted the isolated ductus <i>in vitro</i> . Celecoxib reduced the flow less

Appendix B

Table 2: Applicant’s Summary of Published Literature for celecoxib use in breastfeeding/lactation

Author	Study	Study design	Findings	RID	Comment
Gardiner <i>et al</i> ²⁸	A clinical lactation study	In six volunteers administered a single oral dose of 200 mg celecoxib [median maternal celecoxib dose of 3.3 mg/kg (range of 2.3-3.7)]	Celecoxib concentrations in breast milk were low relative to plasma, with a median milk/ plasma area under the concentration curve from time zero to infinity (AUC _{0-∞}) ratio of 0.18 (range 0.15-0.26). All subjects had quantifiable celecoxib in	The authors concluded that “the estimated daily infant dose was 0.013 mg/kg/day (range 0.011-0.021), which is 0.13 to 0.33% of the recommended celecoxib dose for	It should not represent a problem to infants being breast fed

²⁷ Takahashi Y, Roman C, Chemtob S, Tse MM, Lin E, Heymann MA, Clyman RI. 2000. Cyclooxygenase-2 inhibitors constrict the fetal lamb ductus arteriosus both *in vitro* and *in vivo*. *Am J Physiol Regul Integr Comp Physiol*. 278:R1496-505.

²⁸ Gardiner SJ, Doogue MP, Zhang M, Begg EJ. 2006. Quantification of infant exposure to celecoxib through breast milk. *Br J Clin Pharmacol*. 61(1):101-4.

Hale <i>et al.</i> ²⁹ 2004	a clinical lactation study	Five women received 200mg once daily	milk at the 8-12 hour expression, while two subjects had measurable celecoxib beyond this time (32-36 hours) The median total presence of celecoxib in milk was 0.011 mg (range 0.004-0.042) or 0.04% (range 0.01-0.15) of the maternal single dose (weight adjusted). The milk/plasma ratio AUC ratio was 0.23. The average concentration (AUC) in milk was 66mcg/L. The absolute infant dose average was 9.8 mcg/kg/day. Plasma levels in 2 infants studied, were undetectable.³⁰	milk at the 8-12 hour expression, while two subjects had measurable celecoxib beyond this time (32-36 hours) The median total presence of celecoxib in milk was 0.011 mg (range 0.004-0.042) or 0.04% (range 0.01-0.15) of the maternal single dose (weight adjusted).	pediatric patients and therefore.” -	RID below 10% is not of concern
Kroppert	Estimation	One woman who received 4 doses of celecoxib 100mg, twice daily	Maximum milk concentration reported for this patient (133 ng/ml)	The absolute infant exposure to celecoxib estimated to be approximately 20 mcg/kg/day	They noted that milk concentrations of celecoxib obtained closer to the time of celecoxib administration would be expected to be higher, and that	

²⁹ Hale TW, McDonald R, Boger J. 2004. Transfer of celecoxib into human milk. *J Human Lactation.* 20(4):397-403.

³⁰ Hale TW, McDonald R, Boger J. Transfer of **celecoxib** into human milk. *J Hum Lact.* 2004;20(4):397-403.

Rhulen <i>et al</i> ³²		Thirteen nonlactating women who took celecoxib 200 or 400 mg twice daily for 2 weeks followed by collection of nipple aspirate fluid.	Celecoxib concentrations were 1.2, 1.5, 0.53 and 8.4 mg/L in the aspirate. In the remaining 9, the concentration of celecoxib was undetectable.		at double the concentration the estimated infant exposure would be 40 mcg/kg/day. ³¹

³¹ Knoppert DC, Stempak D, Baruchel S et al. **Celecoxib** in human milk: a case report. *Pharmacotherapy*. 2003;23(1):97-100.

³² Ruhlen RL, Chen YC, Rottinghaus GE, Sauter ER. RE: "Transfer of **celecoxib** into human milk". *J Hum Lact*. 2007;23:13-4.

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

/s/

CHRISTOS MASTROYANNIS
05/04/2018

TAMARA N JOHNSON
05/07/2018

**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: May 3, 2018

To: Norman Stockbridge, MD
Director
**Division of Cardiovascular and Renal Products
(DCaRP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Zarna Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): BRANDNAME (amlodipine and celecoxib)

Dosage Form and Route: tablets, for oral administration

Application Type/Number: NDA 210045

Applicant: Kitov Pharmaceuticals

1 INTRODUCTION

On July 31, 2017, Kitov Pharmaceuticals submitted for the Agency's review an original 505(b)(2) New Drug Application (NDA) 210045 for BRANDNAME (amlodipine and celecoxib) tablets. The reference listed drugs for this submission are NDA 020998 CELEBREX (celecoxib) capsules held by G.D. Searle, LLC and NDA 019787 NORVASC (amlodipine besylate) tablets, held by Pfizer Inc. The proposed indication for BRANDNAME is for patients who require (b) (4) treatment (D) (+) of osteoarthritis and who also require the treatment of hypertension, to lower blood pressure.

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 Cardiovascular and Renal Products (DCaRP) on October 25, 2017 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BRANDNAME (amlodipine and celecoxib) tablets.

2 MATERIAL REVIEWED

- Draft BRANDNAME (amlodipine and celecoxib) tablets MG received on July 31, 2017, and received by DMPP and OPDP on April 23, 2018.
- Draft BRANDNAME (amlodipine and celecoxib) tablets Prescribing Information (PI) received on July 31, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 23, 2018.

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 APFont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial 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)

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.

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

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

/s/

MORGAN A WALKER
05/03/2018

ZARNA PATEL
05/03/2018

BARBARA A FULLER
05/03/2018

LASHAWN M GRIFFITHS
05/03/2018

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

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

Memorandum

Date: May 2, 2018

To: Sabry Soukehal, Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

Michael Monteleone, Associate Director for Labeling, (DCRP)

From: Zarna Patel, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for celecoxib and amlodipine besylate tablets

NDA: 210045

In response to DCRP consult request dated August 10, 2017, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for celecoxib and amlodipine besylate tablets.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DCRP on April 23, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 25, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Zarna Patel at (301) 796- 3822 or zarna.patel@fda.hhs.gov.

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

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

/s/

ZARNA PATEL
05/02/2018

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:	January 29, 2018
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 210045
Product Name and Strength:	Consensi (Celecoxib/Amlodipine Besylate) Tablets, 200 mg/2.5 mg, 200 mg/5 mg, 200 mg/10 mg
Product Type:	Multi-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Kitov Pharmaceuticals Ltd. (Kitov)
Submission Date:	July 31, 2017, October 20, 2017, and December 8, 2017
OSE RCM #:	2017-1605
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As a part of the NDA review process, this review evaluates the proposed Consensi container labels, as well as the proposed Prescribing Information (PI) and Medication Guide (MG) for areas of vulnerability that could 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-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the materials identified some undefined abbreviations, contradictory and misleading statements, and missing descriptive information (e.g., NDC numbers, route of administration, etc.) on the container labels or in the PI or MG.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Consensi container labels, PI, and MG can be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

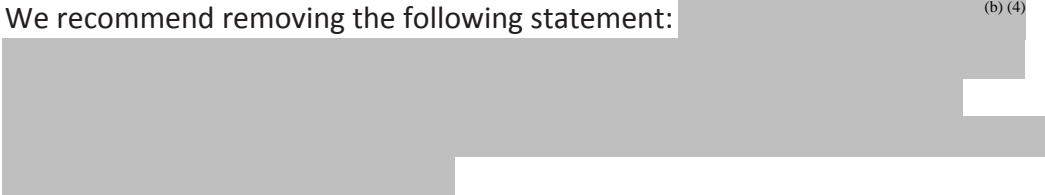
Based on our review, we recommend the following changes to the PI be implemented prior to the approval of this NDA:

- A. Prescribing Information (PI) and Medication Guide (MG)
1. In the MG and the Patient Information section at the end of the full PI, we recommend spelling out “SSRIs or SNRIs” the first time that the abbreviations are used.^a
- B. Prescribing Information
1. We note that the statements in section 2.3 of the full PI are contradictory (b) (4) and therefore request clarification from the Applicant.
 - i. Based on the Applicant’s clarification, at a minimum, in the Highlights Dosage and Administration Section, we recommend relocating the statement (b) (4) to the bullet containing the statement (b) (4). This will inform the prescriber that Consensi can be substituted, (b) (4)
 2. Provide the route of administration as follows in the PI:^b
 - i. Highlights, Dosage and Administration Section- (b) (4)
 - ii. Section 2.1: (b) (4)
 3. We note the placeholder “XXXX-XXXX-XX” for the NDC numbers in Section 16 of the PI. Provide the actual NDC numbers in Section 16 of the PI as well as on the container labels.
 4. In Section 16 of the full PI, we recommend providing descriptive information for the tablets related to scoring and coating.
 5. In Section 17 of the full PI under the heading “Avoid Concomitant Use of NSAIDs,” we recommend defining the abbreviations “NSAIDs” and “GI” the first time the abbreviations are used.

^a ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2017 DEC 20]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

^b Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

C. Medication Guide

1. We recommend removing the following statement: (b) (4)

2. Provide the route of administration as follows in the MG:^c
 - i. Under section titled, “How should I take BRANDNAME?” as a part of the following phrase: “Take 1 BRANDNAME tablet **orally** each day.”

4.2 RECOMMENDATIONS FOR KITOV

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

A. Container Labels

1. Revise the container labels by using different colors, boxing, or some other means to provide adequate differentiation between the three strengths.^d As currently presented, there is inadequate differentiation between the three proposed strengths.
2. Provide the actual NDC numbers on the container labels as well as in Section 16 of the PI.
3. We note the format for the expiration date on the container labels is “MM/YYYY”. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend using a format like either MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017).^e
4. Add the statement “Dispense the enclosed Medication Guide to each patient” or a similar statement prominently on the principal display panel (PDP) per 21 CFR 208.24(d).
5. Consider revising the statement  (b) (4)
 ” to the following: “Usual Dose: See prescribing information.”

^c Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

^d Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

^e Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

6. Decrease the size of the “Kitov Pharmaceutical” company logo on the PDP so that it doesn’t distract the user from other important information on the labels (e.g., Proprietary and established names, strength).^f
7. We note the placeholder for the barcode on the container labels. When printed, ensure the barcode is positioned vertically^g and with enough white space surrounding it^h so that it is able to be scanned.

^f Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

^g Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. *Am J Health Syst Pharm.* 2003 Apr 15;60 (8):768-79.

^h Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Consensi that Kitov submitted on October 20, 2017.

Table 2. Relevant Product Information for Consensi (Celecoxib and Amlodipine Besylate)	
Initial Approval Date	N/A
Active Ingredient	Celecoxib and Amlodipine Besylate
Indication	Patients who require (b) (4) treatment (b) (4) of osteoarthritis and who also require the treatment of hypertension, to lower blood pressure.
Route of Administration	Oral
Dosage Form	Tablets
Strength	200 mg/2.5 mg, 200 mg/5 mg, 200 mg/10 mg
Dose and Frequency	○ Adult recommended starting dose (celecoxib/amlodipine): 200 mg/5 mg once daily with maximum dose 200 mg/10 mg once daily. ○ Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 200 mg/2.5 mg once daily and this dose may be used when adding BRANDNAME to other therapy. ○ (b) (4) Monitor blood pressure carefully (b) (4) ○ Celecoxib should be used at the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. BRANDNAME is not available in lower strengths of celecoxib, is only to be taken once daily, and is only for patients who require chronic treatment of osteoarthritis. Consider individual components for: ○ Hepatic Impairment: Reduce daily dose of celecoxib by 50% in patients with moderate hepatic impairment (Child-Pugh Class B). ○ Poor Metabolizers of cytochrome P450 (CYP) 2C9 Substrates: Consider a celecoxib dose reduction by 50% in patients known or suspected to be CYP2C9 poor metabolizers. ○ Short term or intermittent treatment of osteoarthritis. ○ Administration of celecoxib as divided dose. ○ BRANDNAME may be substituted for its individual components.
How Supplied	Tablets are supplied in 100 count and 500 count bottles
Storage	Store bottles at room temperature 20°C to 25°C (68°F to 77°F); (b) (4) [see USP Controlled Room Temperature] and dispense in tight, light-resistant containers (USP).

Container Closure	100-count packaging size: 100-mL HDPE white bottle, with an induction seal liner, 38-mm (b) (4) child-resistant white cap 500-count packaging size: 400-mL HDPE white bottle, with an induction seal liner, 53-mm (b) (4) white cap

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 18, 2017, we searched DMEPA's previous reviews using the terms, NDA number "210045", "Consensi", "Amlodipine Besylate and Celecoxib", and "Celecoxib and Amlodipine Besylate" to identify reviews previously performed by DMEPA and related to this labels and labeling review. Our search identified no previous reviews relevant to this labels and labeling review.

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,ⁱ along with postmarket medication error data, we reviewed the following Consensi labels and labeling submitted by Kitov on July 31, 2017, October 20, 2017, and December 8, 2017.

- Container labels submitted on July 31, 2017
- Medication Guide submitted on December 8, 2017 (Image not shown)
- Prescribing Information submitted on October 20, 2017 (Image not shown)

G.2 Labels and Labeling Images

Container Labels



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

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

/s/

SARAH E THOMAS
01/29/2018

CHI-MING TU
01/29/2018