CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210942Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 11, 2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 210942
Product Name and Strength:	Gloperba (colchicine USP) Oral Solution, 0.6 mg/5 mL
Applicant/Sponsor Name:	Romeg Therapeutics, LLC
FDA Received Date:	January 7, 2019
OSE RCM #:	2018-700-1
DMEPA Safety Evaluator:	Melina Fanari, R.Ph
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised carton labeling and container label (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton labeling and container label for Gloperba are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Griffis, M. Label and Labeling Review for Gloperba (NDA 210942). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Aug 16. RCM No.: 2018-700.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JANUARY 7, 2019

Container labels

Carton labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MELINA N FANARI
01/11/2019 09:05:29 AM

SARAH K VEE
01/11/2019 09:20:44 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
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Division of Pediatric and Maternal Health Memorandum

Date: January 9, 2019 **Date Consulted:** April 18, 2018

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Lynne Yao, MD, Director
Division of Pediatric and Maternal Health (DPMH)

To: Susan Rhee, Regulatory Project Manager (RPM)
Division of Pulmonary and Rheumatology Products (DPARP)

Drug: Gloperba **(**Colchicine Oral Solution)

NDA: 210942

Indication: Prophylaxis of gout flares in adults

Applicant: Romeg Therapeutics

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- NDA 210942 submitted on March 30, 2018
- Applicant's response to the Filing Communication submitted June 18, 2018 including revised PLLR labeling and literature review

Consult Question: DPARP requests review of PLLR labeling for this new NDA

INTRODUCTION

On March 30, 2018, the applicant, Romeg Therapeutics, submitted an original new drug application (NDA) for Gloperba (Colchicine Oral Solution) via the 505 (b) (2) regulatory pathway. The Division of Pulmonary and Rheumatology Products (DPARP) consulted the Division of Pediatric and Maternal Health (DPMH) on April 18, 2018, to assist with the labeling review for the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- The applicant is relying on the FDA-approved drug Probenecid and Colchicine Tablets USP (ANDA 084279) as the listed drug relied upon.
- Colchicine received initial U.S. market approval in 1961 in a fixed-dose combination of probenecid and colchicine.
- The proposed indication for Gloperba is the prophylaxis of gout flares in adults.
- On June 9, 2018, the Agency sent the applicant a Filing Communication Letter requesting the prescribing information (PI) be submitted in PLLR format.
- On June 18, 2018, the applicant submitted revised labeling and literature review, which was found to be adequate for this PLLR review.

Colchicine Drug Characteristics[1]

- *Drug Class:* antigout
- *Molecular weight:* 399 Daltons
- *Bioavailability:* 45%
- *Protein binding:* 33-44%
- *Half-life:* 27-31 hours
- *Adverse reactions:* peripheral neuritis, muscle weakness, nausea, vomiting, abdominal pain, diarrhea, (b) (4) aplastic anemia, (b) (4), purpura, alopecia

Gout and Treatment Options

Gout is the most common form of inflammatory arthritis.[2] It affects more than 8 million people in the United States, approximately 9 million people in Europe, and more than 3 million in Japan.[3,4] Gout occurs more often in men, primarily because women tend to have lower uric acid levels. After menopause, however, women's uric acid levels approach those of men. Men also are more likely to develop gout earlier, usually between the ages of 30 and 50, whereas women generally develop signs and symptoms of gout after menopause.

[1] Probenecid and Colchicine Tablets USP (ANDA 084279) package insert last revised 2009.
[2] Doghramji PP, Wortmann RL. Hyperuricemia and gout: new concepts in diagnosis and management. Postgrad Med. 2012;124(6):98–109.
[3] de Oliveira EP, Burini RC. High plasma uric acid concentration: causes and consequences. Diabetol Metab Syndr. 2012;4:12.
[4] Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis. 2015;74(4):661–667.

Current State of the Labeling[1,5]

- Probenecid and Colchicine Tablet USP (ANDA 084279), the listed drug relied upon for this submission, currently approved labeling is neither in the Physicians Labeling Rule (PLR) format nor in the PLLR format.
  - (b) (4)

- Colchicine Tablet USP (NDA 022352)[6] currently approved labeling is in the PLR but not the PLLR format.
  - *Highlights, Use in Specific Populations:*
    - *Pregnancy:* Use only if the potential benefit justifies the potential risk to the fetus.
    - *Nursing mothers:* Caution should be exercised when administered to a nursing woman.
  - *Pregnancy (8.1):* Category C
    - There are no adequate and well-controlled studies with colchicine in pregnant women. Colchicine crosses the human placenta. While not studied in the treatment of gout flares, data from a limited number of published studies found no evidence of an increased risk of miscarriage, stillbirth, or teratogenic effects among pregnant women using colchicine to treat familial Mediterranean fever (FMF).
    - Published animal reproduction and developmental studies indicate that colchicine causes embryofetal toxicity, teratogenicity, and altered postnatal development at exposures within or above the clinical therapeutic range.
  - *Labor and Delivery (8.2):* The effect of colchicine is unknown.
  - *Nursing mothers (8.3):* Colchicine is excreted into human milk. Limited information suggests that exclusively breastfed infants receive less than 10% of the maternal weight-adjusted dose. While there are no published reports of adverse effects in breastfeeding infants of mothers taking colchicine, colchicine can affect gastrointestinal cell renewal and permeability. Caution should be exercised, and breastfeeding infants should be observed for adverse effects when colchicine is administered to a nursing woman.
  - *Impairment of Fertility (13.1):* Case reports and epidemiology studies in human male subjects on colchicine therapy indicated that infertility from colchicine is rare. A case report indicated that azoospermia was reversed when therapy was

[5] Colchicine Tablet USP currently approved labeling from 2015. Drugs@FDA

[6] DPMH did not rely on data in the Colcrys NDA or the agency's finding of safety and effectiveness for Colcrys to support labeling sections of this labeling supplement. Rather, the cross-reference to the Colcrys labeling here is to describe how references to data from published literature appear in labeling for other colchicine products approved through the 505 (b)(2) pathway. DPMH's recommendations for the Gloperba labeling discussed below are based solely on information from literature that is not specific to a particular colchicine product, and which was independently located and considered for the Gloperba labeling supplement.

stopped. Case reports and epidemiology studies in female subjects on colchicine therapy have not established a clear relationship between colchicine use and female infertility. However, since the progression of FMF without treatment may result in infertility, the use of colchicine needs to be weighed against the potential risks.

REVIEW

PREGNANCY

(b) (4)[5]

Published animal reproduction and developmental studies indicate that colchicine causes embryofetal toxicity, teratogenicity, and altered postnatal development at exposures within or above the clinical therapeutic range. For more details, see the Nonclinical PLLR Review by Anup Srivastava, PhD.

Applicant's Review of Published Literature

The applicant performed a literature search but did not define the specific search criteria. The applicant referenced the following articles:

- Nonclinical data reporting a potential teratogenic effect of colchicine due to interference with microtubule formation, thereby affecting mitosis and other microtubule-dependent functions. Colchicine induced low frequencies of micronuclei in male rats which were centromere positive suggesting detached chromosomes.[7]

- Limited data from published observational cohort studies and meta-analyses indicate no apparent increased rate of congenital malformations or miscarriages in babies born to women with rheumatic diseases (such as rheumatoid arthritis, Behcet's disease, or FMF) who continued colchicine at therapeutic doses throughout pregnancy.[8,9,10,11]

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, Micromedex[12], TERIS[13], Reprotox[14], and Briggs[15] to find relevant articles not cited by the applicant. Search terms included: "colchicine" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," or "miscarriage."

- **Micromedex** states colchicine crosses the placenta. Cited studies are listed below:

[7] Kallio M, et al. Effects of vinblastin and colchicine on male rat meiosis in vivo: Disturbances in spindle dynamics causing micronuclei and metaphase arrest. Environ Mol Mutagen 1995; 25:106-117.
[8] Skorpen GC, et al. The EULAR points to consider for use of anti-rheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 2016; 75:795-810.
[9] Ben-Chetrit E, et al. Pregnancy outcomes in women with familial Mediterranean fever receiving colchicine: Is amniocentesis justified? Arthritis Care & Research 2010; 62 (2):143-8.
[10] Diav-Citrin O, et al. Pregnancy outcome after in utero exposure to colchicine. Am J Obstet Gynecol 2010; 203:144.e1-6.
[11] Indraratna PL, et al. Use of colchicine in pregnancy: a systematic review and meta-analysis. Rheumatology 2017; kex353 (Abstract only).
[12]Truven Health Analytics information, http://www.micromedexsolutions.com, Accessed 10/31/18.
[13]TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 10/31/18.
[14]Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 10/31/18
[15] Briggs GG, et al. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 9th Ed. 2011.

- In a prospective observational study from 1994 to 2006 in Israel, the rate of major congenital anomalies was not significantly affected in neonates who were exposed to colchicine in utero (n=238) versus those who were unexposed (n=964). The median daily colchicine dose was 1 mg (range 1 to 1.5 mg) and most women were being treated for familial Mediterranean fever. First trimester exposure was reported in 97% of the colchicine exposed group and 80% of mothers took colchicine throughout pregnancy. Major anomalies occurred in 4.5% (10/221) of the colchicine exposed pregnancies and 3.9% (35/908) of the unexposed pregnancies (p=0.648).[10]

- One study reported colchicine crosses the placenta and was present in the umbilical cord blood taken from a newborn.[16]

- Case series in patients with FMF suggest colchicine does not cause harm to the fetus (birth defects, growth or development disorders) or mother.[17]

- A long-term study of 45 females of reproductive potential with FMF who took colchicine for many years concluded colchicine is safe for use during pregnancy.[18]

- Another study reported 55 pregnancies during colchicine therapy for FMF. One pregnancy ended by therapeutic abortion due to trisomy 23. The remainder of the pregnancies resulted in normal live infants.[19]

- **Reprotox** states "colchicine treatment increased the incidence of congenital malformations in experimental animals. By contrast, human experience with this medication does not suggest an increase in adverse pregnancy outcome."
  - Human pregnancy -- uncontrolled reports:
    - A case report from France in which a 25-year-old woman inadvertently took colchicine during the 1st trimester and had an infant with vertebral malformations.[20] Colchicine dosage, duration, and gestational age at exposure were not reported.
    - In contrast, several case reports describe normal pregnancy outcomes (approximately 22 generally FMF-related) after treatment with colchicine with or without other drugs.[21,22,23,24,25,26,27,28,29,30,31]

[16] Amoura Z, et al. Transplacental passage of colchicine in familial Mediterranean fever. J Rheumatol 1994; 21:383.
[17] Rabinovitch O, et al. Colchicine treatment in conception and pregnancy: two hundred thirty-one pregnancies in patients with familial Mediterranean fever. Am J Reprod Immunol 1992; 28:245-246.
[18] Ben-Chetrit E & Levy M: Colchicine prophylaxis in familial Mediterranean fever: reappraisal after 15 years. Semin Arthritis Rheum 1991; 20:241-246.
[19] Pras M, et al. Recent advances in familial Mediterranean fever. Adv Nephrol 1984; 13:261-270.
[20] Dudin A, et al. Colchicine in the first trimester of pregnancy and vertebral malformations. Arch Fr Pediatr 46:627-628. 1986.
[21] Deuschle KW, et al. The use of nitrogen mustard in the management of two pregnant lymphoma patients. Blood 8:576-9, 1953.
[22] Tanchev S, et al. A rare combination of pregnancy and periodic disease treated wtih colchicine. Akush Ginekol Sofiia 1993; 32:41-2.

- A retrospective study of 36 women with FMF on long-term colchicine treatment did not suggest an increased incidence of miscarriage or infertility compared to women with FMF not on colchicine therapy. All 16 infants born to mothers on colchicine therapy during pregnancy were healthy.[32]
- One study evaluated the records of 326 couples between 1973-2003 in which one of the partners had FMF. A total of 901 pregnancies (628 females with FMF and 273 female partners of males with FMF) were reviewed. There were 777 viable pregnancies treated with colchicine, in which all but 3 were conceived while using colchicine. No increase in chromosomal abnormalities was observed in the study population compared to the number expected based on maternal age. There were fewer birth defects than expected.[33]
- A case report of a trisomic infant born to a man treated with colchicine for gout.[34,35,36]
- There was no increase in adverse outcomes in 222 pregnancies fathered by men with FMF, most of whom took colchicine at conception.[37]

o Human pregnancy -- controlled studies
- A retrospective study read in abstract based on 46 pregnant patients with FMF showed that of 9 patients who did not receive colchicine therapy in current or previous pregnancies, 4 (44%) had a history of two or more previous miscarriages. Two or more miscarriages occurred among 3 patients receiving colchicine (8.1%), a decrease that

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[23] Mordel N, et al. Successful full-term pregnancy in FMF complicated with amyloidosis: a case report and review of the literature. Fetal Diagn Ther 1993; 8:129-34.
[24] Vergoulas G, et al. Renal transplantation and pregnancy in a patient with FMF amyloidosis taking triple-drug immunosupression and colchicine. Nephrol Dial Transplant 1992; 7:273-4.
[25] Cousin C, et al. Periodic disease and pregnancy. J Gynecol Obstet Biol Reprod Paris. 1991; 20:554-61.
[26] Shimoni Y, et al. Pregnancy and complicated FMF. Int J Gynaecol Obstet 1990; 33:165-9.
[27] Ditkoff EC, et al. Successful pregnancy in FMF patient following assisted reproduction. J Assist Reprod Genet 1996; 13:684-5.
[28] Michael O, et al. Safety of colchicine therapy during pregnancy. Can Fam Physician 2003; 29:967-9.
[29] Cohen MM, et al. A cytogenetic evaluation of long-term therapy in the treatment of FMF. Am J Med Sci 1977; 274:147-152.
[30] Kosmidis C, et al. Episode of FMF-related periotonitis in the second trimester of pregnancy followed by acute cholecystitis: dilemmas and pitfalls. Am J Case Rep 17:115-119.
[31] Duman NC, et al. Assessment of colchicine use during pregnancy and breastfeeding in a University Hospital Repro Toxicol, 60: 179. 2016.
[32] Ehrenfeld M, et al. Fertility and obstetric history in patients with FMF on long-term colchicine therapy. BJOG 94:1186-1191, 1987.
[33] Berkenstadt M, et al. Chromosomal abnormalities and birth defects among couples with colchicine treated FMF. AJOG 2005; 193:1513-1516.
[34] Ferreira NR. Trisomy after colchicine therapy. Lancet 2: 1304, 1968.
[35] Walker FA: Trisomy after colchicine therapy (letter). Lancet 1:257, 1969.
[36] Joefnagel D: Trisomy after colchicine therapy (letter). Lancet 1:1160, 1969.
[37] Ben-Chetrit E, et al. The outcome of pregnancy in the wives of men with FMF treated wtih colchicine. Semin Arthritis Rheum. 2004 Oct; 34 (2):549-52.

was statistically significant. The study authors noted that colchicine appears to be safe for use in pregnancy.[38]
    - Additional studies already discussed above.[9,10]

- "Because of the reassuring human reports and the importance of continuing treatment for FMF during pregnancy, colchicine use has been regarded by commentators as acceptable in spite of its interference with cell division and effects in experimental animals."

- **Briggs** pregnancy recommendation is "Compatible: although colchicine is teratogenic in animals, the human pregnancy experience suggests the embryo-fetal risk is low, if it exists at all. The use of colchicine by the father before conception does not appear to represent a significant reproductive risk, but azoospermia may be a rare complication. Because some reports suggest a risk of chromosome abnormalities, routine amniocentesis was recommended in cases of FMF treated with colchicine[33]; however, data that are more recent suggest routine amniocentesis is not justified.[10,9]

Reviewer's Comment
The applicant's search for reported pregnancy cases in the published literature appears adequate. Available human data from prospective and retrospective observational studies, case series, and case reports have not identified any drug-associated risks for miscarriage, birth defects, or adverse maternal or fetal outcomes. Limitations of the available human pregnancy data include the lack of randomization and the inability to control for confounders such as underlying maternal disease and maternal use of concomitant medications.

LACTATION

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(b) (4)

Applicant's Review of Published Literature
The applicant performed a literature search but did not define the specific search criteria. The applicant noted limited published data suggest that breast-fed infants receive <10% of the maternal weight-adjusted dose, although one report estimated breastfed infants may receive up to 31.5% of the maternal dose.[8,39] The European League Against Rheumatism (EULAR) task force found colchicine compatible with pregnancy and breastfeeding. The EULAR performed a systemic literature review and reported no adverse effects in 149 breastfed children The EULAR advised to reconsider breastfeeding if the infant has diarrhea.[8] In another study, no gastrointestinal or other symptoms were reported in 38 colchicine-exposed breastfed infants.[39]

DPMH's Review of Published Literature
This Reviewer performed a search in *Medications and Mother's Milk*[40], LactMed[41],

[38] Yasar O, Iskender C, Kaymak O, Taflan Yaman S, Uygur D, Danisman N. 2014. Retrospective evaluation of pregnancy outcomes in women with familial Mediterranean fever. J Matern Fetal Neonatal Med 27(7): 733-736
[39] Herscovici T, et al. Colchicine use during breastfeeding. Breastfeeding Medicine 2015; 10 (2).
[40] Hale, Thomas (2017) Medications and Mother's Milk. Amarillo, Texas. Hale Publishing.

Micromedex[12], Reprotox[14], Briggs[15], PubMed, and Embase using the terms "colchicine" AND "lactation" OR "breastfeeding."

- *Medications in Mother's Milk* lactation rating is "L3-Limited Data-Probably Compatible"
  - "No consistent data on colchicine concentrations in breastmilk are available."
    - The milk concentration of colchicine varied from 1.2 to 2.5 mcg/L in a lactating woman on postpartum days 16-21 treated with 0.6 mg twice daily. No adverse events were reported in the breastfed infant.[42]
    - In another study, a lactating woman taking 1 mg once daily had average milk concentrations of 30 mcg/L at 8 hours post therapy. The maximum infant daily dose was 31% of the weight-adjusted maternal dose.[43]
    - In a third study, four women took 1 mg of colchicine daily during pregnancy and lactation with varying levels of colchicine in breastmilk (maximum concentration 1.98 to 8.6 mcg/L occurred within 3 hours).[44] The breastfed infants ranged from 4 to 58 days of life and no adverse events were reported at 10 months follow-up. The authors reported 6 additional infants breastfed up to 3 months with no adverse effects noted during the 2 years of follow-up.
    - A prospective observational cohort study of 38 mother-infant pairs who breastfed (average 9.1 months) while taking colchicine (average 2.4 mg/day) found no increase in adverse developmental outcomes or infant side effects (such as gastrointestinal symptoms).[39]
  - Overall, the author Thomas Hale concludes, "colchicine is not a preferred medication in breastfeeding mothers as we have many other analgesics and anti-inflammatories that are superior in breastfeeding for the treatment of gouty symptoms. However, if this medication is required then the infant should be monitored closely, as the relative infant doses vary from 2.1-31%." Infant monitoring for vomiting and diarrhea are recommended.

- **LactMed** states, "long-term prophylactic maternal doses of colchicine up to 1.5 mg daily in patients with FMF produced levels in milk that result in the infant receiving less than 10% of the maternal weight-adjusted dosage. The highest milk levels occur 2 to 4 hours after a dose, so avoiding breastfeeding during this time can minimize the infant dose, although some clinicians simply recommend taking the drug after nursing. No adverse effects in breastfed infants have been reported in case series and a case-control study and

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[41] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 10/31/18

[42] Milunsky JM. Breastfeeding during colchicine therapy for familial Mediterranean fever. J Pediatr 1991; 119:164.

[43] Guillonnea M, et al. Colchicine is excreted at high concentrations in human breast milk. Eur J Obstet Gynaecol Reprod Biol 1995; 61:177-178.

[44] Ben-Chetrit E, et al. Colchicine in breast milk of patients with familial mediterranean fever. Arthritis & Rheumatism 1996; 39 (7):1213-1217.

some authors consider colchicine safe during breastfeeding in women being treated for familial Mediterranean fever or rheumatic conditions."[44,45]

- *Maternal levels:* same studies cited as referenced above by Hale.

- *Infant levels:* Colchicine was undetectable (<5 mcg/L) in 12-hour urine samples taken from a breastfed infant at 5 and 15 days of age whose mother was taking 1 mg of colchicine once daily (same study as discussed above by Hale where RID estimated at 31%).[43]

- *Effects in breastfed infants:*
  - In a study of 181 women who took colchicine during pregnancy, 111 women reported breastfeeding (extent not stated) with no colchicine-related adverse effects in the infants.[10]
  - Another study reported 10 lactating women treated with colchicine with no adverse effects on the breastfed infant reported.[46]

- *Effects on lactation and breastmilk:* no data

- **Micromedex** states, "infant risk is minimal. The weight of an adequate body of evidence and/or expert consensus suggests this drug poses minimal risk to the breastfed infant."

  - American Academy of Pediatrics Rating: compatible with breastfeeding.[47]
  - World Health Organization Rating: compatible with breastfeeding.
  - Clinical management: "colchicine has been shown to be excreted into human breast milk in high concentrations. Studies have reported that exclusively breast-fed infants receive less than 10% of the maternal weight-adjusted dose. Colchicine may affect gastrointestinal cell renewal and permeability; therefore, breastfed infants should be observed for adverse effects.

- **Reprotox** states "because colchicine is rapidly metabolized and eliminated, milk concentrations would be expected to vary widely with changing concentrations in the blood. Despite concerns expressed by one group of authors that colchicine from milk might accumulate and cause hematologic and digestive toxicity in neonates, several cases are reported in which continued breastfeeding while taking colchicine was not associated with adverse effects on exposed neonates."

- **Briggs** breastfeeding recommendation is "Limited human data-Probably Compatible"

Reviewer's Comment
The applicant's search of the published literature for relevant lactation data appears adequate.

[45] Dotters-Katz S, et al. The impact of familial Mediterranean fever on women's health. Obestet Gynecol Surv. 2012; 67:357-64.
[46] Duman NC, et al. Assessment of colchicine use during pregnancy and breastfeeding in a university hospital. Reprod Toxicol. 2016; 60:179.
[47] Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human breast milk. Pediatrics 108: 776-789, 2001.

Available data suggest colchicine is present in human milk. The reported RID varied from 2 to 31%. Generally, a RID of <10% is considered compatible with breastfeeding.[47] *DPMH discussed the available lactation data with the Clinical Pharmacology Review team who recommended the 31% RID not be included in labeling because this data is based on a single case report from 1995 and insufficient to justify inclusion in the labeling. Overall, no adverse effects have been reported in the breastfed infant. There are no data on the effects of colchicine on milk production.*

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

(b) (4)[5]

Published nonclinical studies demonstrated that colchicine-induced disruption of microtubule formation affects meiosis and mitosis. Animal reproductive studies also reported abnormal sperm morphology and reduced sperm counts in males, and interference with sperm penetration, second meiotic division, and normal cleavage in females when exposed to colchicine.

Colchicine administered to pregnant animals resulted in fetal death and teratogenicity. These effects were dose-dependent, with the time of exposure critical for the effects on embryofetal development. The nonclinical doses evaluated were generally higher than an equivalent human therapeutic dose, but safety margins for reproductive and developmental toxicity could not be determined. For more details, see the Nonclinical PLLR Review by Anup Srivastava, PhD .

Applicant's Review of Published Literature

The applicant performed a literature search but did not define the specific search criteria. The applicant stated limited published data suggest that colchicine may rarely result in low or absent sperm counts in men, which could result in male infertility.[48]

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, and Reprotox[14] using the terms "colchicine" AND "fertility," "contraception," "oral contraceptives," OR "infertility."

- **Briggs** describes the following studies related to colchicine and fertility:
  - One study observed azoospermia in a 36-year-old patient induced by 1.2 mg/day of colchicine, but not with 0.6 mg/day.[49]
  - Another study using 1.8-2.4 mg/day in 7 healthy men (age 20-25 years) observed no effect on sperm production or serum levels of testosterone, luteinizing hormone, or follicle-stimulating hormone.[50] The authors could not exclude that some men may be unusually sensitive to colchicine resulting in testicular toxicity.
  - A review article concluded that colchicine by itself may not have a significant direct adverse effect on sperm production or function.[51]

[48] Ben-Chetrit and Levy. Reproductive system in familial Mediterranean fever: an overview. Ann Rheum Dis 2003; 62:916-9.
[49] Merlin HE. Azoospermia caused by colchicine-a case report. Fertil Steril 1972; 23:180-1.
[50] Bremer WJ, et al. Colchicine and testicular function in man. NEJM 1976; 294:1384-5.
[51] Haimov-Kochman R, et al. The effect of colchicine treatment on sperm production and function: a review. Human Reprod. 1998; 13:360-2.

- **Reprotox** states "colchicine was associated with sperm abnormalities (including azoospermia) in some, but not all, treated men.[49,52,53,] A review of the literature reported that while colchicine might have the ability to affect sperm motility and production, these complications are expected to be rare at therapeutic dose levels.[48]

Reviewer's Comment
The applicant's review of the published literature for infertility cases related to colchicine use appears adequate. Available data in the published literature are conflicting regarding the effects of colchicine on male fertility, with case reports indicating a potential risk for azoospermia.

DISCUSSION and CONCLUSIONS

Pregnancy

DPMH recommends subsection 8.1 of labeling include a Risk Summary that describes the available human data regarding colchicine use during pregnancy. Overall, available data from published literature (observational studies, case series, case reports) have not identified any drug-associated risks for miscarriage, birth defects, or adverse maternal or fetal outcomes. However, published animal data do suggest colchicine causes embryofetal toxicity and teratogenicity.

Lactation

DPMH recommends subsection 8.2 of labeling state colchicine is present in human milk. No adverse effects have been reported in the breastfed infants of women taking colchicine. There are no data on the effects of colchicine on milk production. The AAP and WHO consider colchicine compatible with breastfeeding. Therefore, DPMH recommends the risk/benefit statement for lactation be included in colchicine labeling. In addition, a human data section should be included to describe the available lactation data.

Females and Males of Reproduction Potential

DPMH recommends subsection 8.3 of labeling describe the limited available data suggesting a potential risk for azoospermia related to colchicine use by males. Providers must consider potential risk for infertility related to untreated underlying disease (such as with FMF) when weighing the risks and benefits of colchicine therapy.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2 and 8.3 of labeling for compliance with the PLLR (see below). The recommendations reflect input from the Clinical Pharmacology and Nonclinical Review Teams. DPMH discussed our labeling recommendations with the Division at the November 20, 2018 labeling meeting. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Colchicine Oral Solution Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

- Females and Males of Reproductive Potential: Advise males that Gloperba may rarely and transiently impair fertility (8.3).

[52] Buchanan JF, et al. Drug-induced fertility. Drug Intell Clin Pharm 18:122-132, 1984.
[53] Ehrenfeld M, et al. The effects of long-term colchicine therapy on male fertility in patients with FMF. Andrologia 18:42906, 1986.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available human data from published literature on colchicine use in pregnancy over several decades have not identified any drug associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data).* Animal reproduction and developmental studies were not conducted with Gloperba. Published animal reproduction and development studies indicate that colchicine causes embryofetal toxicity and altered postnatal development at exposures within or above the clinical therapeutic range.

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

Data

Human Data

Available data from published observational studies, case series, and case reports over several decades do not suggest an increased risk for major birth defects or miscarriage in pregnant women with rheumatic diseases (such as rheumatoid arthritis, Behcet's disease, or familial Mediterranean fever (FMF)) treated with colchicine at therapeutic doses during pregnancy. Limitations of these data include the lack of randomization and inability to control for confounders such as underlying maternal disease and maternal use of concomitant medications.

8.2 Lactation

Risk Summary

Colchicine is present in human milk *(see Data).* Adverse events in breastfed infants have not been reported in the published literature after administration of colchicine to lactating women. There are no data on the effects of colchicine on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Gloperba and any potential adverse effects on the breastfed infant from Gloperba or from the underlying maternal condition.

Data

Limited published data from case reports and a small lactation study demonstrate colchicine is present in breastmilk. A systematic review of literature reported no adverse effects in 149 breastfed children and advised to reconsider breastfeeding if the infant has diarrhea. In a prospective observational cohort study, no gastrointestinal or other symptoms were reported in 38 colchicine-exposed breastfed infants.

8.3 Females and Males of Reproductive Potential

Infertility

Case reports and epidemiology studies in human male subjects on colchicine therapy indicate that infertility from colchicine is rare and may be reversible.

17 PATIENT COUNSELING

Infertility

Advise males of reproductive potential that Gloperba may rarely and transiently impair fertility *[see Use in Specific Populations (8.3)]*.

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/s/

KRISTIE W BAISDEN
01/09/2019 11:55:33 AM

TAMARA N JOHNSON
01/10/2019 01:22:55 PM

LYNNE P YAO
01/10/2019 01:27:57 PM

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

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

Memorandum

Date: December 31, 2018

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

From: Adewale Adeleye, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for GLOPERBA (colchicine) Oral Solution

NDA: 210942

In response to DGIEP consult request dated April 19, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for GLOPERBA (colchicine) Oral Solution.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DPARP (Susan Rhee) on December 3, 2018 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on December 14, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 30, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

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/s/

ADEWALE A ADELEYE
12/31/2018 02:45:07 PM

M E M O R A N D U M

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

DATE: December 20, 2018

TO: Sally Seymour, MD
Director (Acting)
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Office of Drug Evaluation II
Office of New Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles R. Bonapace, Pharm.D.
Director
DNDBE
OSIS

SUBJECT: Routine inspection of Frontage Clinical Services, Inc., Secaucus, NJ.

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study Rmg-col-pk001 (NDA 210942) conducted at Frontage Clinical Services, Inc., Secaucus, NJ.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I conclude the data from the audited study are reliable. Thus, I recommend that the data from study Rmg-col-pk001 and other studies of similar design be accepted for further Agency review.

2 Inspected Studies:

NDA 210942

Study Number: Rmg-col-pk001

Study Title: "A Randomized, Open-Label, Single-Dose, 3-Way, Relative Bioavailability Study of Colchicine Oral Solution 0.6 mg (0.12 mg/mL, 5 mL) under Fed and Fasted Conditions and Probenecid and Colchicine Tablets, USP (500 mg/0.5 mg) under Fasted Conditions in Healthy Adult Volunteers"

Dates of conduct: 1/4/2017 – 2/21/2017

Clinical site: Frontage Clinical Services, Inc.
200 Meadowlands Parkway
Secaucus, NJ 07094

ORA investigator Peter R. Lenahan (BIMOE) inspected Frontage Clinical Services, Inc., Secaucus, NJ from October 15–19, 2018.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance including protocol deviations, institutional review board approvals, sponsor and monitor correspondence, randomization, adverse events, case report forms, dosing records, blood sample collection times and test article accountability and storage.

3 Inspectional Findings

At the conclusion of the inspection, investigator Lenahan did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

4. Conclusion:

After reviewing the inspectional findings, I conclude the data from the audited study are reliable. Therefore, I recommend that the data from study Rmg-col-pk001 (NDA 210942) be accepted for further review.

Based on the inspectional findings, studies of similar design conducted between the previous inspection (10/2016) and the end of the current surveillance interval should be accepted for review by the Agency without an inspection.

Srinivas R. Chennamaneni, Ph.D.
Staff Fellow

Final Classification:

NAI- Frontage Clinical Services, Inc.
Secaucus, NJ 07094
FEI#: 3005134380

cc:
OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Chennamaneni
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au
OND/ODEII/DPARP/Seymour/Rhee
ORA/OMPTO/OBIMO/ORABIMOE.Correspondence@fda.hhs.gov

Draft: SRC 12/17/2018
Edit: GB 12/18/2018; CRB 12/19/2018

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Frontage Clinical Services, Inc., Secaucus, NJ, USA/FY18:First Day of Inspection/Pre-Inspection Folder/Background Folder/RMG-COL-PK001

OSIS File #: BE 8102

FACTS: (b) (4)

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/s/

SRINIVAS RAO N CHENNAMANENI
12/20/2018

GOPA BISWAS
12/20/2018

CHARLES R BONAPACE
12/20/2018

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:	December 14, 2018
To:	Sally Seymour, MD Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	GLOPERBA (colchicine)
Dosage Form and Route:	Oral Solution
Application Type/Number:	NDA 210942
Applicant:	B&H Consulting Services, Inc., regulatory agent for Romeg Therapeutics, LLC

1 INTRODUCTION

On March 30, 2018, B&H Consulting Services, Inc., regulatory agent for Romeg Therapeutics, LLC submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) for GLOPERBA (colchicine) Oral Solution. The proposed indication for GLOPERBA (colchicine) Oral Solution is prophylaxis of gout flares in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on April 19, 2018 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for GLOPERBA (colchicine) Oral Solution.

2 MATERIAL REVIEWED

- Draft GLOPERBA (colchicine) Oral Solution MG received on March 30, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 4, 2018.
- Draft GLOPERBA (colchicine) Oral Solution Prescribing Information (PI) received on March 30, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 4, 2018.
- Approved MITIGARE (colchicine) comparator labeling dated September 24, 2014.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We 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)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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/s/

KELLY D JACKSON
12/14/2018

ADEWALE A ADELEYE
12/14/2018

MARCIA B WILLIAMS
12/14/2018

LASHAWN M GRIFFITHS
12/14/2018

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:	8/16/2018
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 210942
Product Name and Strength:	Gloperba (colchicine USP) Oral Solution, 0.6 mg/5 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Romeg Therapeutics, LLC
FDA Received Date:	March 30, 2018
OSE RCM #:	2018-700
DMEPA Safety Evaluator:	Melina Griffis, RPh
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

As part of the approval process for Gloperba (colchicine USP) Oral Solution, 0.6 mg/5 mL the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)requested that we review the proposed label and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-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

We performed a risk assessment of the proposed label and labeling for Gloperba for areas of vulnerability that may lead to medication errors and determined the label and labeling could be revised to improve clarity and prominence of information and to promote safe use of the proposed product.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. We provide the recommendations in section 4.1 and 4.2 below and recommend that they are implemented prior to approval.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
    1. Dosage Forms and Strength
        i. The product strength should be specified as an amount per 5 mL (e.g. 0.6 mg/5 mL) since the recommended dose of Gloperba will be 5 mL.

2. How Supplied/Storage and Handling Section
    i. This section should be revised to include the product strength, a description of the 150 mL container and a numerical NDC number.

4.2 RECOMMENDATIONS FOR ROMEG THERAPEUTICS, LLC

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

A. General Comments (Container labels & Carton Labeling)
    1. The product strength should be revised to specify an amount per 5 mL (e.g. 0.6 mg/ 5 mL) since the recommended dose of Gloperba will be 5 mL.

    2. The place holder NDC number in all locations should be updated to reflect the actual numerical NDC number.

    3. The lot number and expiration date should be relocated away from the bar code to avoid being mistaken as the bar code numbers.[a]

    4. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format for the expiration date you intend to use (see below for examples):
        a. DDMMMYYYY (e.g., 31JAN2013)
        b. MMMYYYY (e.g., JAN2013)
        c. YYYY-MMM-DD (e.g., 2013-JAN-31)
        d. YYYY-MM-DD (e.g., 2013-01-31)

B. Container Labels
    1. Increase the prominence of the product strength to improve its readability.

    2. The net quantity statement should be relocated to the bottom of the principle display panel.

[a] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Gloperba received on March 30, 2018 from Romeg Therapeutics, and the listed drug (LD).

Table 2. Relevant Product Information for Gloperba and the Listed Drug		
Product Name	Gloperba	Colchicine
Initial Approval Date	N/A	1961
Active Ingredient	Colchicine	Colchicine
Indication	For the prophylaxis of gout flares in adults	For the prophylaxis of gout flares in adults
Route of Administration	Oral	Oral
Dosage Form	Solution	Tablet
Strength	0.6 mg/ 5 mL	0.6 mg
Dose and Frequency	0.6 mg (5 mL) once or twice daily	0.6 mg once or twice daily
How Supplied	150 mL container	30, 100 and 1000 count bottles
Storage	20° C to 25° C (68° to 77° F). (b) (4)	20° C to 25° C (68° to 77° F). Protect from light and moisture.
Container Closure	N/A	N/A

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 15, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, colchicine. Our search did not identify any relevant previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following labels and labeling for Gloperba submitted by Romeg Pharmaceuticals Inc.

- Container label received on March 30, 2018
- Carton labeling received on March 30, 2018
- Prescribing Information and Med Guide (Image not shown) received on June 18, 2018

G.2 Label and Labeling Images

Container Label

Carton Label

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/s/

MELINA N GRIFFIS
09/05/2018

SARAH K VEE
09/05/2018

M E M O R A N D U M

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

DATE: 6/21/2018

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

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

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

RE: NDA 210942

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

Rationale

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

Inspection Site

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

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/s/

SHILA S NKAH
06/21/2018