

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204820Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Update

Date	(electronic stamp)
From	Sarah Yim, M.D.
Subject	Cross-Discipline Team Leader Review 2 nd Cycle Update
NDA/BLA #	NDA 204820/
Supplement#	Original/Complete Response Submission
Applicant	Hikma/West-Ward
Date of Submission	March 28, 2014
PDUFA Goal Date	September 28, 2014
Proprietary Name / Established (USAN) names	Mitigare / Colchicine
Dosage forms / Strength	Capsules / 0.6 mg
Proposed Indication(s)	1. Prophylaxis of Gout Flares in Adults
Recommended:	<i>Approval</i>

1. Introduction

On October 5, 2012, Hikma Pharmaceuticals and their U.S. agent, West-Ward, submitted the original 505(b)(2) NDA for this 0.6 mg colchicine capsule, for the proposed indication of prophylaxis of gout flares. This 505(b)(2) NDA was acceptable for filing because, among other things, the proposed drug product was not a duplicate of Colcrys (the currently approved single-ingredient 0.6 mg colchicine tablet) given the difference in dosage form. In this 505(b)(2) NDA, the applicant proposed to rely on FDA's finding of safety and effectiveness for the combination product Col-Probenecid (colchicine 0.5 mg / probenecid 500 mg) and published literature for the efficacy and safety of colchicine for the proposed indication. In addition, the applicant performed four drug-drug interaction (DDI) studies with their colchicine capsules—one with the weak CYP3A4 inhibitor cimetidine, one with the moderate CYP3A4 inhibitor fluconazole, one with the strong CYP3A4 inhibitor voriconazole, and one with the P-gp inhibitor propafenone. All four DDI studies demonstrated no significant effect on the pharmacokinetics (PK) of the West-Ward colchicine capsule. The implications of these findings were the main focus of the original review and are discussed in detail in the CDTL and clinical pharmacology reviews from the first cycle.

The application received a Complete Response (CR) action in the first cycle due to unresolved deficiencies identified on inspection of the proposed drug product manufacturing facility (see Section 3 below). The applicant has corrected the manufacturing deficiencies and received a letter from the FDA New Jersey District Office acknowledging that the applicant has addressed the violation(s) contained in the Warning Letter 12-NWJ-10, dated February 3, 2012. The applicant has therefore submitted this CR resubmission, which contains labeling revised to reflect any comments previously communicated by FDA to the sponsor, and an updated review of the literature pertaining to colchicine. Updated stability data were also provided. No new data has otherwise been provided in this submission.

2. Background

The reader is referred to Section 2 in the original CDTL review for a background on colchicine and on the regulatory history of this application.

3. CMC/Device

CMC Reviewer: Craig Bertha, Ph.D.; Branch Chief: Prasad Peri, Ph.D.

ONDQA Biopharmaceutics Reviewer: Elsbeth Chikhale, Ph.D.;

Office of Compliance, Office of Medical Product Quality: Vipul Dholakia

- **General product quality considerations**

The drug product is an immediate-release gelatin capsule formulation containing 0.6 mg of colchicine, packaged in high density polyethylene bottles (100 and 1000 count). The formulation includes colchicine and the following excipients: anhydrous lactose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and colloidal silicon dioxide. The manufacturing process utilizes (b) (4) of the formulation. The stability data from the original submission supported a 24-month expiration dating period. Updated stability data were submitted in this resubmission. These were reviewed and determined not to alter the previous determination regarding the acceptability of the 24-month expiry.

The drug substance has the USAN name “colchicine” and a monograph appears in the current edition of the USP. Information about the drug substance is in the supplier’s master file (b) (4). Colchicine provided by (b) (4) is an (b) (4). The CMC information on the drug substance, as noted in the supplier’s master file, was reviewed and determined to be acceptable.

- **Facilities review/inspection**

The site proposed for manufacture of the 0.6 mg colchicine capsule final drug product is the Eatontown, New Jersey West-Ward facility. This site was inspected on multiple occasions over a period from 04/29/13 through 06/07/13. Twelve significant observations were noted, including four that specifically referenced the manufacture of colchicine capsules. Details of these deficiencies are listed in the original CDTL review and the Form 483. These deficiencies were considered “Official Action Indicated” (OAI), and resulted in a “Complete Response” (CR) action for the original application.

The applicant has corrected the manufacturing deficiencies and has been determined to be in compliance, as per the letter dated March 26, 2014, from the FDA New Jersey District Office acknowledging that the applicant has addressed the violation(s) contained in the Warning Letter 12-NWJ-10, dated February 3, 2012. This was confirmed, and an updated status of

“acceptable” was entered into the Establishment Evaluation System (EES) by the Office of Compliance on June 26, 2014. Therefore the CMC recommendation is now approval. No post-marketing commitments were recommended.

4. Nonclinical Pharmacology/Toxicology

Primary reviewer: L. Steve Leshin, D.V.M., Ph.D.; Supervisor: Marcie Wood, Ph.D.

The applicant submitted published nonclinical literature to support this 505(b)(2) NDA. No new nonclinical studies were conducted or required. No nonclinical deficiencies were identified in the original application for NDA 204820. The reader is referred to the first-cycle pharmacology-toxicology reviews by Dr. Leshin and Dr. Wood.

5. Clinical Pharmacology/Biopharmaceutics

Primary reviewer: Sheetal Agarwal, Ph.D.; 1st Cycle Supervisor: Suresh Doddapaneni, Ph.D.; 2nd Cycle Team Leader: Satjit Brar, Ph.D.

No new clinical pharmacology/biopharmaceutics data were required or submitted with this CR resubmission. No clinical pharmacology/biopharmaceutics deficiencies were identified in the original application for NDA 204820. In addition to drug-drug interaction (DDI) studies and a food effect study, the applicant submitted a comparative bioavailability study of the colchicine 0.6 mg capsules and Col-Probenecid, the colchicine 0.5/probenecid 500 mg combination product that is approved for the chronic treatment of gout and which serves as the listed drug for this NDA. The reader is referred to the first-cycle clinical pharmacology review by Dr. Agarwal and the first-cycle summary reviews.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Primary clinical reviewer: Keith Hull, M.D., Ph.D.

Primary statistical reviewer: Kiya Hamilton, Ph.D.; Statistical Team Leader: Joan Buenconsejo, Ph.D.

In addition to the comparative bioavailability study to support reliance on the efficacy of the listed drug Col-Probenecid, the applicant submitted published literature on the efficacy of colchicine for the prophylactic treatment of gout to support this 505(b)(2) NDA. No new clinical efficacy studies were conducted or required. No clinical deficiencies precluding approval were identified in the original application for NDA 204820. The reader is referred to

the first-cycle clinical and statistical reviews by Dr. Keith Hull and Dr. Kiya Hamilton, respectively; as well as my first-cycle CDTL review.

8. Safety

In addition to the comparative bioavailability study to support reliance on the safety of the listed drug Col-Probenecid, the applicant submitted published literature on the safety of colchicine for the prophylactic treatment of gout to support this 505(b)(2) NDA. Safety data from the applicant's six pharmacokinetic studies were also submitted in the original NDA. No new clinical safety studies were conducted or required. No clinical deficiencies precluding approval were identified in the original application for NDA 204820. The reader is referred to the first-cycle clinical review by Dr. Keith Hull, as well as my first-cycle CDTL review.

The toxicities of colchicine are manifold and are well known and described in the literature. These are described in detail in my first-cycle CDTL review. In the original submission, the applicant submitted 118 references to support the efficacy and safety of colchicine. In this resubmission, the applicant provided an additional 93 references from the worldwide literature (total of 211 references). These references include treatment guidelines and review articles, controlled trials evaluating the efficacy of colchicine in unapproved indications, and multiple case reports/case series of colchicine toxicity under various conditions and involving various toxicity management strategies. No previously unidentified toxicities or drug interactions were reported in these articles.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application—original or resubmission. No issues warranted discussion at advisory committee meeting.

10. Pediatrics

The applicant requested a full waiver from the requirements of the Pediatric Research Equity Act (PREA) on the basis that pediatric studies would be impossible or highly impracticable to conduct because gout does not occur in children. The review team and the Pediatric Review Committee (PeRC) agreed in the original submission that a full waiver is justified.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not applicable.
- **Exclusivity or patent issues of concern**

Colchicine is not a new molecular entity and there is no unexpired exclusivity covering the proposed indication for the prophylactic treatment of gout. The applicant has provided an

appropriate patent certification or statement for the listed drug relied upon (Col-Probenecid) pursuant to 21 CFR 314.50(i)(1)(ii).

- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues.
- **DSI audits**—No issues.
- **Other discipline consults**—Not applicable.
- **Any other outstanding regulatory issues**—No outstanding regulatory issues.

12. Labeling

- **Proprietary name**

The applicant proposed the tradename “Mitigare,” which was considered acceptable by the review team, the Office of Prescription Drug Promotion (OPDP) and the Office of Surveillance and Epidemiology (OSE) Division of Medication Error Prevention and Analysis (DMEPA).

- **Physician labeling**

The prescribing information for Mitigare 0.6 mg colchicine capsules will differ in the approach to drug-drug interactions and renal/hepatic impairment compared to the approved single-ingredient colchicine product, Colcris 0.6 mg tablets. The rationale for this was outlined in the first cycle CDTL review and is excerpted here:

Because of the uncertainty raised by the applicant’s DDI studies with respect to the generalizability and accuracy of detailed dose modification recommendations...the review team believes a less prescriptive approach to drug interaction- and organ dysfunction- related treatment recommendations is warranted. Because the interacting drugs of clinical significance appear to be inhibitors of both CYP3A4 and P-gp, concomitant use of these medications and colchicine should be avoided, if possible. However, because it may be difficult for a prescriber to be certain about which drugs are dual vs. single inhibitors of CYP3A4 and P-gp, the most conservative approach would be for a prescriber to avoid concomitant use of CYP3A4 or P-gp inhibitors with colchicine. If concomitant use is necessary, this should be done with caution, consideration of dose reduction, and close patient monitoring.

Because of the high risk of life-threatening drug-drug interaction with colchicine and dual inhibitors of CYP3A4 and P-gp in patients with renal or hepatic impairment, a contraindication against colchicine use in this scenario is justified.

Regarding dose-modifications due to renal or hepatic impairment, the review team concluded that the utility of the applicant’s proposed dose adjustments was questionable given the dose range of colchicine for the prophylactic gout indication (i.e., 0.6-1.2 mg daily), which is already less than or equal to half of the maximum dose of colchicine approved for chronic administration (Colcris, FMF indication), and thus would not be expected to produce serious toxicity, even if renal or hepatic impairment effectively doubled the concentration. However, in light of increased interindividual variability in the setting of severe hepatic or renal impairment, a general recommendation for avoidance or dose reduction and/or close monitoring in this setting is justifiable.

The prescribing information for Mitigare 0.6 mg colchicine capsules will also include a Limitations of Use statement that the safety and effectiveness of Mitigare for acute treatment of gout flares during prophylaxis has not been studied. It is well-recognized that recent colchicine use (i.e., for prophylaxis of gout flares) increases the susceptibility to toxicity related to additional doses of colchicine. Although the applicant is not seeking an indication for the treatment of acute gout flares, to the extent that a healthcare provider may be considering use of additional Mitigare for treatment of an acute gout flare in a patient receiving Mitigare for prophylaxis, the review team determined that it would be appropriate for the label to note that Mitigare should not be used in this way, as it has not been studied. Agreement on the final prescribing information for Mitigare was reached on September 11, 2014.

- **Carton and immediate container labels**

OPDP and DMEPA reviewed the carton and container labels. DMEPA recommended edits for standardization and clarity, which were accepted by the applicant.

- **Patient labeling/Medication guide**

The applicant submitted a proposed a Medication Guide, which was reviewed by OPDP and the Division of Medical Policy Programs (DMPP). OPDP and DMPP suggested edits to simplify or clarify proposed wording, remove redundancy, ensure consistency with the prescribing information, and that the medication guide meets the requirements of 21 CFR 208.20, and the applicant agreed to the proposed edits.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this application.

- **Risk Benefit Assessment**

The risk-benefit of colchicine at up to 1.2 mg per day for the prophylactic treatment of gout is favorable. Gout flares cause significant pain and functional impairment, and the risk of colchicine at a dose of 0.6 once or twice daily is low, with appropriate precautions regarding interacting drugs and renal or hepatic impairment.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

A Risk Evaluation and Mitigation Strategy (REMS) is neither necessary nor warranted. Colchicine has a long history of clinical use, and prescribers are aware of the potential for serious toxicity with colchicine.

- **Recommendation for other Postmarketing Requirements and Commitments**

No postmarketing requirements or commitments are warranted.

- **Recommended Comments to Applicant**

None.

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/s/

SARAH K YIM
09/11/2014

Cross-Discipline Team Leader Review

Date	July 15, 2013
From	Sarah Yim, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 204820/
Supplement#	original
Applicant	Hikma/West-Ward
Date of Submission	October 5, 2012
PDUFA Goal Date	August 5, 2013
Proprietary Name / Established (USAN) names	Mitigare / Colchicine
Dosage forms / Strength	Capsules / 0.6 mg
Proposed Indication(s)	1. Prophylaxis of Gout Flares in Adults
Recommended:	<i>Approval (or CR depending on CMC)</i>

1. Introduction

On October 5, 2012, Hikma Pharmaceuticals and their U.S. agent, West-Ward, submitted this 505(b)(2) NDA for a 0.6 mg colchicine capsule, for the proposed indication of prophylaxis of gout flares. In this 505(b)(2) NDA, the applicant proposes to rely on FDA's finding of safety and effectiveness for the combination product Col-Probenecid (colchicine 0.5 mg / probenecid 500 mg) and published literature for the efficacy and safety of colchicine for the proposed indication. In presubmission meetings with FDA, West-Ward was advised to conduct drug-drug interaction (DDI) studies to support any proposed dose modification recommendations. They performed four DDI studies with their colchicine capsules—one with the weak CYP3A4 inhibitor cimetidine, one with the moderate CYP3A4 inhibitor fluconazole, one with the strong CYP3A4 inhibitor voriconazole, and one with the P-gp inhibitor propafenone. Unexpectedly, all four DDI studies demonstrated no significant effect on the pharmacokinetics (PK) of the West-Ward colchicine capsule. The implications of these unexpected findings were the main focus of the review, although major deficiencies were identified on inspection of the proposed drug product manufacturing facility and may preclude an approval action.

2. Background

Colchicine, an alkaloid originally derived from the autumn crocus (*Colchicum autumnale*), has a long history of medicinal use, dating back to its first use as a purgative agent in ancient Egypt and Greece, more than 3000 years ago. Its first use as a selective treatment for gout dates back to 6 A.D. Colchicine is well known to have dose-related toxicity. The most common toxicity of colchicine is gastrointestinal (with nausea, vomiting, abdominal pain, and diarrhea), which is reversible with discontinuation of colchicine. Although gastrointestinal toxicity does not necessarily indicate an overdose of colchicine, it may be the first sign of

more serious toxicity to follow, particularly with oral administration. Overdose toxicity can include electrolyte imbalance, bone marrow suppression, cardiovascular collapse, renal failure, rhabdomyolysis, seizures, mental status changes and death. Colchicine is estimated to be effective at doses of approximately 0.015 mg/kg, toxic in doses greater than 0.1 mg/kg, and typically lethal at doses of approximately 0.8 mg/kg. In the therapeutic range, plasma levels are approximately 0.5 to 3 ng/ml.¹

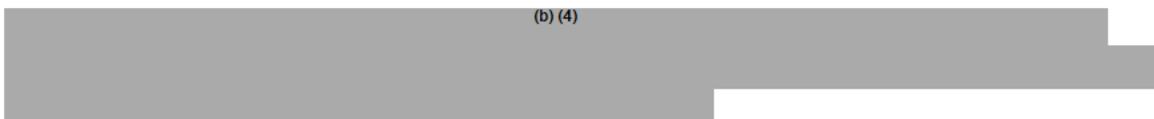
Colchicine was first isolated from colchicum in 1820 and made available in oral dosage forms during the 19th century. It has been used in small doses for gout prophylaxis since the 1930s. However, colchicine was first approved by the FDA in 1961 as part of combination with probenecid for the chronic treatment of gout (ColBenemid—colchicine 0.5 mg/probenecid 500 mg). ColBenemid underwent review in the Drug Efficacy Study Implementation (DESI) process (FR Vol.37, No.146, 28 July 1972), which deemed the combination effective for “chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout,” or essentially, prophylactic treatment of gout flares.

Single-ingredient colchicine tablets were available for decades as marketed but unapproved products, in 0.6 mg strength. The first approved single-ingredient oral colchicine product was Mutual Pharmaceutical’s colchicine 0.6 mg tablets (Colcrys), which was approved in July 2009 for treatment of familial Mediterranean fever (FMF) and treatment of acute flares of gout; approval for the prophylactic treatment of gout was given in October 2009. Approval of Colcrys for prophylactic treatment of gout was based primarily on published literature and FDA’s finding of safety and effectiveness for the colchicine-probenecid combination product. Hikma/West-Ward’s approach for this NDA for the prophylactic treatment of gout is also based on the published literature and FDA’s finding of safety and effectiveness for the colchicine-probenecid combination product.

Colchicine’s drug-drug interaction potential, as a P-gp² and cytochrome P450³ substrate (specifically CYP3A4⁴), has long been reported in the literature. Historically, there were no widely-accepted specific recommendations for dose reduction in the setting of potential concomitant use of drugs with known interactions, other than avoidance when possible and caution when necessary, with vigilant monitoring for clinical signs of toxicity. With the approval of Colcrys in 2009, specific dose modification recommendations were provided in the label on the basis of DDI studies.

Regulatory History

(b) (4)



¹ E Niel and JM Scherrmann, “Colchicine Today” *Joint Bone Spine* 2006; 73:672-678.

² AR Safa, ND Mehta, M Agresti, “Photoaffinity labeling of P-glycoprotein in multidrug resistant cells with photoactive analogs of colchicine.” *Biochem and Biophys Res Com*, 1989; 162(3):1402-1408

³ AL Hunter, CD Klassen, “Biliary excretion of colchicine.” *J Pharmacol Exp Ther*, 1974; 192:605-17

⁴ T Tateiski, et al. “Colchicine biotransformation by human liver microsomes: identification of CYP3A4 as a major isoform responsible for colchicine demethylation.” *Biochem Pharmacol*, 1997; 10:111-16

In November 2010, Mutual filed a Citizen Petition requesting, among other things, that any single-ingredient oral colchicine product must reference Colcris and include all drug-drug interaction information in Colcris labeling, including relevant dose adjustments needed to prevent unnecessary toxicity. Mutual's citizen petition was granted in part, and denied in part. FDA disagreed that any single-ingredient oral colchicine product submitted through the 505(b)(2) pathway must necessarily cite Colcris as its listed drug, irrespective of whether the proposed product shares the same strength, PK profile, or other characteristics such as dosage form or conditions of use. With respect to drug-drug interaction labeling, FDA agreed that product labeling for any single-ingredient oral colchicine product needs to include adequate information on drug-drug interactions, including relevant dose adjustments needed to prevent unnecessary toxicity.

In November 2011, FDA met with West-Ward to discuss their development plan, and agreement was reached on a program that included 4 DDI studies—one each with a strong, moderate, and weak CYP3A4 inhibitor and a P-gp inhibitor. The protocols were not reviewed by the FDA, and the data were not discussed with FDA before submission; however, this is not typically expected for DDI studies.

On October 5, 2012, Hikma Pharmaceuticals and their U.S. agent, West-Ward, submitted this 505(b)(2) NDA for a 0.6 mg colchicine capsule, for the proposed indication of prophylaxis of gout flares. Because, as a capsule, this dosage form is not a duplicate of Colcris, this application was considered acceptable for filing as a 505(b)(2) NDA. As noted in section 1, the applicant is relying on FDA's finding of safety and effectiveness for Col-Probenecid and published literature for the efficacy and safety of colchicine for the proposed indication. However, to support any dose-modification recommendations, West-Ward performed four DDI studies with their colchicine capsules—one with the weak CYP3A4 inhibitor cimetidine, one with the moderate CYP3A4 inhibitor fluconazole, one with the strong CYP3A4 inhibitor voriconazole, and one with the P-gp inhibitor propafenone. Unexpectedly, all four DDI studies demonstrated no significant effect on the pharmacokinetics of the West-Ward colchicine capsule. Inspection of the DDI study sites did not identify concerns with study conduct or other explanations for the unexpected study results. Further details are described in the Clinical Pharmacology section below.

In addition, major deficiencies have been identified with the chemistry, manufacturing, and controls (CMC) of the product. Further details are described in section 3 below.

3. CMC/Device

CMC Reviewer: Craig Bertha, Ph.D.; Branch Chief: Prasad Peri, Ph.D.

ONDQA Biopharmaceutics Reviewer: Elsbeth Chikhale, Ph.D.;

Office of Compliance, Office of Medical Product Quality: Vipul Dholakia

- **General product quality considerations**

The drug product is an immediate-release gelatin capsule formulation containing 0.6 mg of colchicine, packaged in high density polyethylene bottles (100 and 1000 count). The formulation includes colchicine and the following excipients: anhydrous lactose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and colloidal silicon dioxide. The manufacturing process utilizes (b) (4) of the formulation. One of the primary stability batches of the drug product was also used in the bioequivalence study supporting the application and has the (b) (4).

Based on the stability data for the registration batches and those for the supportive tablet batch with the (b) (4), a 24-month expiration dating period is supported.

The drug substance has the USAN name “colchicine” and a monograph appears in the current edition of the USP. Information about the drug substance is in the supplier’s master file (b) (4) (b) (4). Colchicine provided by (b) (4) is an (b) (4). The CMC information on the drug substance, as noted in the supplier’s master file, is acceptable, and the supplier has an acceptable recent inspection from (b) (4).

The applicant’s dissolution data and methodology were reviewed by Dr. Elsbeth Chikhale and were considered acceptable.

- **Facilities review/inspection**

The site proposed for manufacture of the 0.6 mg colchicine capsule final drug product is the Eatontown, New Jersey West-Ward facility. This site was inspected on multiple occasions over a period from 04/29/13 through 06/07/13. Twelve significant observations were noted, including four that specifically reference the manufacture of colchicine capsules (**bolded**):

1. The responsibilities and procedures applicable to the quality control unit are not fully followed.
2. There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has been already distributed.
 - **This deficiency includes a failure to adequately evaluate and address metal contamination found in some drug product batches, including colchicine 0.6 mg capsules, batch (b) (4).**
3. Procedures describing the handling of all written and oral complaints regarding a drug product are not followed.
4. Samples of representative units were not collected and visually examined for correct labeling at the completion of finishing operations.
5. There is a lack of written procedures describing in sufficient detail the handling and examination of labeling and packaging materials.
6. Reserve drug product samples are not representative of each lot or batch of drug product.
7. Input to and output from the computer, related systems of formulas, and records or data are not checked for accuracy.

8. Equipment used in the manufacture, processing, packing, or holding of drug products is not of appropriate design to facilitate operations for its intended use and cleaning and maintenance.
9. Written procedures are not followed for evaluations conducted at least annually to review records associated with a representative number of batches, whether approved or rejected.
10. **There is no test or specification established for the visual appearance of the colchicine capsule fill for release or stability testing.**
11. **There is no development data to support the parameters established for the (b) (4) process of the colchicine active pharmaceutical ingredient (API) and (b) (4) established at (b) (4) (b) (4).**
12. **Colchicine API (b) (4) however there is no development data to support the (b) (4) used during the manufacturing of the colchicine capsule product. Additionally there is no assurance that (b) (4) to conduct the manufacturing of colchicine 0.6 mg capsules.**

Additional details of these deficiencies are listed in the Form 483. These deficiencies were considered “Official Action Indicated” (OAI) and had not been adequately addressed at the time of the writing of this review. Presuming an OAI designation remains, a “complete response” (CR) action would be warranted on the basis of these deficiencies.

- **Other notable issues (resolved or outstanding)**

See above.

4. Nonclinical Pharmacology/Toxicology

*Primary reviewer: L. Steve Leshin, D.V.M., Ph.D.; Supervisor: Marcie Wood, Ph.D.
This section is largely excerpted from Dr. Leshin’s review.*

- **General nonclinical pharmacology/toxicology considerations**

The applicant submitted published nonclinical literature to support this 505(b)(2) NDA. No new nonclinical studies were conducted or required. The reader is referred to Dr. Leshin’s pharmacology/toxicology review for details and references.

Pharmacology: Colchicine binds to the intracellular protein tubulin, preventing its alpha and beta forms from polymerizing into microtubules. This disruption of the microtubular network results in impaired protein assembly in the Golgi apparatus, decreased endocytosis and exocytosis, altered cell shape, depressed cellular motility, and arrest of mitosis. Colchicine also interferes with the formation of the inflammasome, a cellular structure involved in the production of inflammatory-related cytokines. In addition, colchicine also prevents neutrophil

migration from the vasculature into tissue by preventing the expression of cell surface adhesion-related molecules E- and L-selectins.

General toxicology: Historical information provided by the applicant from published animal and clinical studies indicated similar toxicities in animals and humans with increasing doses. The published nonclinical literature does not contain adequate long-term toxicology studies. Almost all the studies were conducted prior to GLP regulations and lack much of the information now routinely assessed, such as clinical pathology and histopathology findings. A direct NOAEL comparison could not be conducted, since nonclinical studies were not conducted with the goal of identifying a NOAEL. Rather, the studies were conducted to identify toxicities or underlying biological mechanisms of colchicine action. In general, the acute toxic signs in animals (rats, dogs, rabbits, cats) with short-term colchicine administration are gastrointestinal tract-related and include emesis, distended intestines, diarrhea (bloody in more severe cases), lack of appetite, and lethargy. With increasing doses these signs become more severe, and there is a loss of body tone, abnormal gait and hindlimb paralysis and wasting atrophy, ascites and eventually death.

- **Carcinogenicity**

Genetic Toxicology: Colchicine was negative for mutagenicity in the bacterial reverse mutation assay. In a chromosomal aberration assay in cultured human white blood cells, colchicine treatment resulted in the formation of micronuclei. However, published studies demonstrated these micronuclei were formed by mitotic nondisjunction without structural DNA changes, and therefore, colchicine is not considered clastogenic.

Carcinogenicity: There are no adequate studies of colchicine's carcinogenicity potential. Due to the long history of clinical experience with colchicine, carcinogenicity studies were not requested for this application.

- **Reproductive toxicology**

Reproduction and Developmental Toxicology: The nonclinical literature indicates that colchicine has detrimental effects on reproduction and development due to its inhibition of microtubule formation and cell division. This adversely affects germ cell development by meiosis and subsequent fertility in males and females, as well as interfering with mitosis and subsequent early embryonic development and implantation, and organogenesis. The effects are species and dose dependent, with the timing of exposure also critical for the effects on embryonic development.

Though nonclinical literature indicates that colchicine has detrimental effects on reproduction and development in animals, published clinical epidemiology studies in patients with familial Mediterranean fever found that colchicine therapy during pregnancy was compatible with normal reproduction and developmental in the therapeutic dose range. It is not known if a similar risk-benefit profile would apply for female patients taking colchicine for chronic prophylactic treatment of gout, as colchicine has a non-essential role in patients with gout.

- **Other notable issues (resolved or outstanding)**

There are six known impurities: (b) (4)

The levels of impurities are within the applicant's proposed limits. With the exception of the (b) (4)

all of the individual specified impurities are limited to the International Conference on Harmonization (ICH) Q3A qualification threshold of 0.15%, which was considered acceptable by the pharmacology/toxicology and CMC review teams.

Other known impurities of colchicine include 2 (b) (4)

. The applicant's proposed acceptance criteria for (b) (4) is NMT (b) (4), which was considered acceptable by the pharmacology/toxicology and CMC review teams.

5. Clinical Pharmacology/Biopharmaceutics

*Primary reviewer: Sheetal Agarwal, Ph.D.; Supervisor: Suresh Doddapaneni, Ph.D.
This section is largely adapted/excerpted from Dr. Agarwal's review.*

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.**

Absorption

In healthy adults, Colchicine Capsules, when given orally, reached a mean C_{max} of 3 ng/mL in 1.3 h (range 0.7 to 2.5 h) after 0.6 mg single dose administration. Absolute bioavailability is reported to be approximately 45%. The relative bioavailability of West-Ward's 0.6 mg capsule product was compared to Col-Probenecid (colchicine 0.5 mg/probenecid 500 mg, ANDA 084729, Watson Labs). West-ward's product showed a slightly higher C_{max} (~17% higher C_{max}) and equivalent AUC compared to dose-normalized C_{max} and AUC parameters of Col-Probenecid.

A food effect assessment was conducted with a previous West-Ward 0.6 mg tablet formulation of colchicine and not with the 0.6 mg Colchicine Capsules. The presence of a high-fat, high-calorie meal did not have much effect on colchicine PK (~11% lower C_{max}, 12% lower AUC). This food effect assessment was considered acceptable for the current 0.6 mg capsule formulation because (a) the colchicine 0.6 mg tablet formulation and the proposed-to-be-marketed capsule formulation are qualitatively and quantitatively similar (the main difference being (b) (4)); and (b) the applicant provided dissolution data for both tablet and capsule

formulation indicating that dissolution profiles of the tablet and capsule formulations are similar.

Distribution

Colchicine has a mean apparent volume of distribution in healthy young volunteers of approximately 5 to 8 L/kg. Colchicine binding to serum protein is about 39%, primarily to albumin. Colchicine crosses the placenta and distributes into breast milk.

Metabolism

A published *in vitro* human liver microsome study showed that about 16% of colchicine is metabolized to 2-O-demethylcolchicine and 3-O-demethylcolchicine (2- and 3-DMC, respectively) by CYP3A4.⁵ Glucuronidation is also believed to be a metabolic pathway for colchicine.

Excretion

In a published study in healthy volunteers, 40 to 65% of the total absorbed dose of colchicine (1 mg administered orally) was recovered unchanged in urine. Enterohepatic recirculation and biliary excretion are also believed to play a role in colchicine elimination. Colchicine is a substrate of P-gp and P-gp efflux is postulated to play an important role in colchicine disposition. Elimination half-life in humans was found to be 31 h (range 21.7 to 49.9 h).

- **Drug-drug interactions**

Although this application relies on the FDA's finding of efficacy and safety for Col-Probenecid and the published literature for colchicine in the prophylactic treatment of gout, the applicant was advised to conduct drug-drug interaction (DDI) studies to support any dose-modification recommendations that might be needed for labeling. The applicant conducted four drug-drug interaction studies:

- 1) Weak CYP3A4 inhibitor—cimetidine
Design: Day 1: 0.6 mg colchicine single dose; Days 4-8: 800 mg cimetidine BID for 5 days; Day 9: 0.6 mg colchicine + 800 mg cimetidine
- 2) Moderate CYP3A4 inhibitor—fluconazole
Design: Day 1: 0.6 mg colchicine single dose; Day 4: 2 X 200 mg (400 mg) fluconazole (loading dose); Days 5-8: 200 mg fluconazole QD for 4 days; Day 9: 0.6 mg colchicine + 200 mg fluconazole
- 3) Strong CYP3A4 inhibitor—voriconazole
Design: Day 1: 0.6 mg colchicine single dose; Days 4-8: 200 mg voriconazole BID for 5 days; Day 9: 0.6 mg colchicine + 200 mg voriconazole
- 4) P-glycoprotein (P-gp) inhibitor—propafenone
Design: Day 1: 0.6 mg colchicine single dose; Days 4-8: 225 mg propafenone BID for 5 days; Day 9: 0.6 mg colchicine + 225 mg propafenone

⁵ Tateishi T et al., 1997, *Biochemical Pharmacology*, 53, 111:116

Results of these studies are summarized in Table 1, below:

Table 1: PK Parameters of Colchicine in the Presence or Absence of the Selected Inhibitors

	- VCZ	+ VCZ	-FCZ	+FCZ	-CMN	+CMN	-PFN	+PFN
Cmax (pg/mL)	2663	2058	1926	2299	2997	2109	2118	2206
AUC (pg.h/mL)	19605	20731	14939	21270	20382	18082	16626	16777
CLtot/F (L/h)	33	28	37	26	28	34	34	33
T1/2el (h)	30	31	34	35	35	32	30	28
Kel (1/h)	0.02	0.02	0.02	0.02	0.02	0.02	0.024	0.026

VCZ=voriconazole; FCZ=fluconazole; CMN=cimetidine; PFN=propafenone
Source: Table 8 of Dr. Agarwal’s Clinical Pharmacology Review

With the exception of fluconazole, which was associated with modest increase primarily in the AUC of colchicine, there were no significant changes in the PK of colchicine in the applicant’s DDI studies. These results were unexpected, given that colchicine’s drug-drug interaction potential, as a P-gp⁶ and cytochrome P450⁷ substrate (specifically CYP3A4⁸), has long been reported in the literature.

The review team carefully considered possible explanations for these unexpected DDI study findings:

- The PK study site underwent inspection, which did not identify any issues.
- The formulation was not considered likely to cause the apparent difference, as the (b) (4) associated with production of the colchicine capsules did not appear to change the dissolution characteristics of colchicine, which were appropriate for an immediate-release formulation.
- The selected probe inhibitors were considered to be the likely explanation.
 - Dr. Agarwal did an extensive search of published literature and found no reports of colchicine drug-drug interaction with the inhibitors selected (cimetidine, fluconazole, voriconazole, and propafenone). Although these inhibitors were selected as representative of weak, moderate, and strong CYP3A4 inhibitors, and a P-gp inhibitor, no inhibitors that had been previously reported to interact with colchicine were used in the West-Ward DDI studies.

⁶ AR Safa, ND Mehta, M Agresti, “Photoaffinity labeling of P-glycoprotein in multidrug resistant cells with photoactive analogs of colchicine.” Biochem and Biophys Res Com, 1989; 162(3):1402-1408

⁷ AL Hunter, CD Klassen, “Biliary excretion of colchicine.” J Pharmacol Exp Ther, 1974; 192:605-17

⁸ T Tateiski, et al. “Colchicine biotransformation by human liver microsomes: identification of CYP3A4 as a major isoform responsible for colchicine demethylation.” Biochem Pharmacol, 1997; 10:111-16

- The inhibitors selected for the West-Ward DDI studies are considered to inhibit only the CYP3A4 pathway or the P-gp pathway, not both; whereas the interacting drugs of clinical significance (e.g., clarithromycin, erythromycin, azithromycin, and cyclosporine) appear to have effects on both pathways.
- The dose of propafenone used in the West-Ward DDI study is lower than the dose of propafenone reported to result in interactions with digoxin.
- There is uncertainty regarding the consistency of CYP3A4 inhibition by voriconazole, e.g., it does not increase systemic exposure of indinavir, a well-known CYP3A4 substrate, in humans.⁹
- Fluconazole is considered a moderate CYP3A4 inhibitor, but is also known to inhibit uridine-5'-diphospho-glucuronosyltransferase (UGT), so the 40% increase in AUC of colchicine observed could be due to inhibition of either or both pathways, as colchicine is also known to be glucuronidated from animal studies.

Although there are uncertainties with the specific probe inhibitors selected, the clinical pharmacology team concluded that the data from these studies were interpretable and conformed to the recommendations in the draft Guidance for Industry: Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.¹⁰ However, the West-Ward DDI studies also raise important new questions about the sensitivity of colchicine to interaction with drugs that inhibit either the CYP3A4 or P-gp pathway alone; particularly as the interacting drugs of clinical significance, which have been reported to cause life-threatening or fatal toxicity with colchicine, actually interact with both pathways. Of the drugs which could be considered to significantly interact with colchicine (as indicated by > 20% inhibition in the University of Washington drug-interaction database¹¹), the drugs that have been reported more than once to interact with colchicine in a clinically significant manner are clarithromycin, erythromycin, cyclosporine, and azithromycin. Clarithromycin is considered a strong CYP3A4 inhibitor and a potent P-gp inhibitor, and cyclosporine is considered a potent P-gp inhibitor and a weak CYP3A4 inhibitor. Erythromycin and azithromycin are considered moderate to weak CYP3A4 inhibitors with some P-gp inhibition potential.¹⁰

The West-Ward DDI study results suggest that it may not be appropriate to extrapolate drug-interaction potential (and thus dose modification recommendations) from one CYP3A4 inhibitor to another, or one P-gp inhibitor to another, as individual drugs may have different overall interaction potential with colchicine depending on the degree to which they interact with multiple pathways. On top of the wide interindividual variability already in play for colchicine (see next section), this extra variability adds to the uncertainty regarding whether specific dose modifications may be applicable for a given scenario, and whether they would

⁹ Purkins L et al., Br J Clin Pharmacol 2003;56 (Suppl 1):62-68

¹⁰ Draft Guidance for Industry: Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

¹¹ <http://www.druginteractioninfo.org/>

result in improved safety over simpler recommendations for close monitoring and dose adjustment based on clinical judgment.

- **Demographic interactions/special populations**

Dedicated PK studies were not conducted by the applicant to address the influence of age, race, body mass, pregnancy and organ dysfunction on the pharmacokinetics of colchicine. Colchicine is known to be excreted in urine. Ben-Chetrit et al.¹² published a report on PK of colchicine in patients with FMF (Familial Mediterranean Fever) with and without severe renal impairment who were on dialysis. Using data from this study, West-Ward created PK simulation models which were then used with the known PK data with Colchicine Capsules. They proposed (b) (4) in dose for mild renal impairment (creatinine clearance [CrCl] 60-89 mL/min), a (b) (4) % dose reduction in the setting of moderate renal impairment (CrCl, 30-59 mL/min) and a (b) (4) % dose reduction for severe renal impairment (CrCl 15-29 mL/min). For patients on dialysis, the applicant proposed (b) (4); or reduction to (b) (4) of the normal dose if colchicine therapy is necessary. These recommendations include a caveat for close monitoring of the patient.

The review team determined that the available PK data from the published study does not suggest the fine dose adjustment proposed by the applicant for the different renal impairment categories is needed. The utility of such finely-tuned dose adjustment is also questionable given the dose range of colchicine for the prophylactic gout indication (i.e., 0.6-1.2 mg daily), which is already less than or equal to half of the maximum dose approved for the chronic administration of colchicine in FMF.

It should be noted that the approved label for Colcris (colchicine), 0.6 mg tablet, recommends a starting dose of 0.3 mg per day for patients with severe renal impairment (CrCl less than 30 mL/min) taking colchicine for prophylaxis of gout flares, and a starting dose of 0.3 mg twice a week for patients on dialysis. Both recommendations include a caveat for close monitoring of the patient. Acknowledging these already-approved recommendations for another colchicine product, it has been historically accepted that there is wide interindividual variability in responses to colchicine, which more recently has been postulated to be related to P-gp and CYP3A4 effects at multiple body sites.¹³ Adding in the variability associated with organ dysfunction, it is difficult to be certain that a given dose modification recommendation would be necessary or adequate for a given individual. Thus the review team has concluded that the most justifiable recommendation is to avoid using colchicine in patients with severe renal or hepatic impairment; or if avoidance is not possible, consideration should be given to dose reduction and the patient should be closely monitored.

- **Thorough QT study or other QT assessment**

A Thorough QT study or other QT assessment was not conducted or required.

- **Other notable issues (resolved or outstanding)**

¹² Ben-Chetrit et al., 1994, J. Rheumatology, 21(4): 710

¹³ E. Niel, J.-M. Scherrmann, "Colchicine Today." Joint Bone Spine 73 (2006) 672-678

See above.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Primary clinical reviewer: Keith Hull, M.D., Ph.D.

Primary statistical reviewer: Kiya Hamilton, Ph.D.; Statistical Team Leader: Joan Buenconsejo, Ph.D.

• Clinical and Statistical Review of Efficacy

The primary evidence of the efficacy of colchicine for the prophylactic treatment of gout is derived from two randomized controlled trials in the published literature—Paulus et al.¹⁴ in 1974, and Borstad et al.¹⁵ in 2004.

Paulus, 1974

Paulus et al. conducted a six-month, randomized, double-blind, placebo controlled study of colchicine for the prevention of gout flares in patients with gout starting on urate-lowering therapy with the uricosuric drug, probenecid. A total of 52 male patients with a confirmed diagnosis of gout and serum uric acid level greater than 7.5 mg/dL were randomized to receive probenecid 500 mg + placebo or probenecid 500 mg + colchicine 0.5 mg three times daily. Differences in the administration of probenecid occurred at the two different study sites. Patients at the Los Angeles site had urate-lowering drugs discontinued two weeks prior to beginning study treatment, while patients at the Kansas City site were allowed to continue on stable doses of probenecid for the two weeks before beginning study treatment.

Patients reported gout flares on a monthly basis, and flares were recorded as mild, moderate, or severe by the investigator based on the degree of pain and accompanied swelling and tenderness described by the patient. Only moderate and severe flares were included in the analysis. Prior to the unblinding of data, the investigators reviewed the serum urate levels to determine whether the urate-lowering therapy was successful. Only those patients who successfully lowered their levels of serum uric acid were included in the analysis.

A single patient from each study arm was excluded from the final analysis. A total of 12 of 15 (80%) colchicine-treated patients completed all six months with the remaining three patients dropping out at three and four months. In the placebo-treated arm, 8 of 11 (73%) patients completed all six months of the study; three patients dropped out after one, two, and four

¹⁴ Paulus HE et al. *Arthritis Rheum* 1974; 17(5):609-14.

¹⁵ Borstad GC et al. *J Rheumatol* 2004; 31(12):2429-32.

months, respectively. Of note, an additional patient from the colchicine treatment arm was excluded from the analysis because they developed an adverse reaction of alopecia.

The number of acute gout flares per month was used as the primary endpoint to assess the efficacy of colchicine to prevent gout flares. As shown in Table 2 below, colchicine-treated patients reported fewer moderate to severe gout flares compared with patients treated with placebo (0.19 attacks/month vs. 0.48 attacks/month, respectively).

Table 2: Primary Efficacy Results in the Paulus Study

Treatment Group	Serum Urate mg/100 ml \pm SE		Attacks of Gouty Arthritis per Patient per Month \pm SE	No. of Patients with (Drug-related) Side Effects
	Before	After		
Colchicine-Probenecid	8.4 \pm 0.4	6.3 \pm 0.4†	0.19 \pm 0.05*	15
Placebo-Probenecid	9.2 \pm 0.6	6.2 \pm 0.4†	0.48 \pm 0.12*	8‡

* $P < 0.05$

† $P < 0.01$

‡0.1 $> P > 0.05$ (chi square analysis)

*Source: Table 2 from Paulus et al., 1974

The data from this study had several major shortcomings including:

- Differences between study sites regarding the pre-study period handling of urate-lowering drugs. One could postulate that patients at the Los Angeles site might be more prone to flare if their previous urate-lowering therapy was discontinued prior to the study. Unless the majority of patients at the Los Angeles site were randomized to placebo, it is unlikely that this would have resulted in a treatment effect in favor of colchicine if there was not one. However, since the original data are not available, it is not possible to explore this further.
- The authors did not use the intent-to-treat population in their analysis as they excluded patients who did not demonstrate a reduction in serum uric acid levels, and thus, introduced the potential for bias.
- The publication does not describe how missing data (from patients discontinuing from the study) was handled with respect to the final analysis.
- The primary endpoint was suboptimal, as it involved investigator interpretation of patient-reported flares, which in turn were based on patient recall.

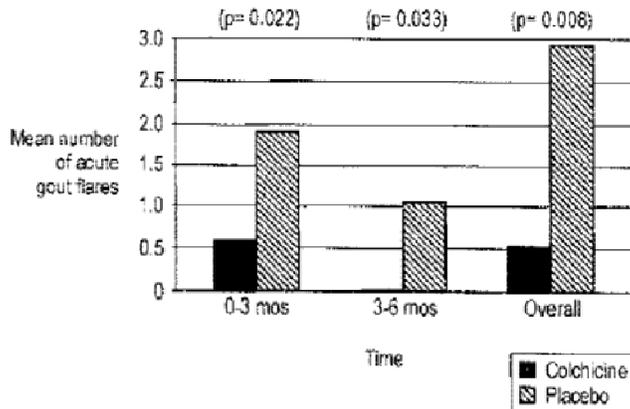
Borstad, 2004

Borstad et al. reported the results from a randomized, placebo-controlled study that enrolled patients with confirmed gouty arthritis and who met criteria for initiating allopurinol. A total of 43 patients were randomized to receive colchicine 0.6 mg twice daily or placebo. Patients with renal insufficiency received colchicine 0.6 mg once daily. Baseline demographics and disease characteristics of the two groups reflected a typical gout population and were generally similar between treatment arms; however a greater percentage of patients in the colchicine-treatment arm used diuretics compared to the placebo treatment arm, 57% versus 27%, respectively. This imbalance would not be expected to bias results in favor of colchicine, as patients on diuretics would be expected to be more susceptible to gout flares.

A total of 51 patients were initially enrolled in the study but eight discontinued prior to beginning the blinded study drug. Patients from both treatment arms started allopurinol therapy at a dose of 100 mg daily and increased as necessary by 100 mg/d increments until serum uric acid levels were less than 6.5 mg/dL, at which time patients were given blinded study drug for three months. The primary analysis population was all patients who had received at least one dose of study medication. The primary efficacy endpoint was the mean number of flares at three and six months.

Colchicine-treated patients reported fewer acute gout flares in the 0-3 month and 3-6 month time periods, on average, compared to placebo-treated patients (see Figure 1 below). In addition, fewer colchicine-treated patients (33%) reported gout flares compared with placebo-treated patients (77%); and fewer colchicine-treated patients experienced multiple flares, 14% vs. 63% of placebo patients.

Figure 1: Primary Efficacy Results in the Borstad Study



*Source: Figure 1 from Borstad et al., 2004

Caveats with this study include:

- The trial was not truly blinded as the colchicine tablets and placebo tablets differed in appearance.
- The article did not explain how the primary analysis accounted for patients who had multiple flares and for patients who discontinued from the study.

Efficacy Summary

Using studies from the published literature is problematic, as the description of the studies is intentionally limited for purposes of brevity, and the study datasets are not available to allow for confirmation and sensitivity analyses. If, as in the case with the Paulus and Borstad studies, there are concerns about potential sources of bias, the lack of ability to evaluate the raw study data is particularly problematic. For these reasons, the statistical review team could not confirm the adequacy of the efficacy results from these studies.

However, in this case, the uncertainties raised by the limitations of the individual studies are ameliorated by the fact that the study results corroborate each other. Additionally, a gout flare

is a distinct and discrete episode that tends to be consistent and readily identifiable by individual gout patients; this would make the outcome less susceptible to bias from unblinding. Finally, the estimated treatment effect in favor of colchicine was large in both studies.

Data from these two studies is supported by a number of other published studies and a long history of clinical use of colchicine for the prophylactic treatment of gout. These older studies were the basis for the DESI review of ColBenemid, and were determined to provide adequate evidence of the benefit of colchicine and probenecid for the treatment of chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout (37 FR 15189, July 28, 1972).

Based on the totality of the evidence, I concur with Dr. Hull that these data provide adequate evidence of the benefit of colchicine in the prophylactic treatment of gout.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

See above.

8. Safety

- **Adequacy of the database, major findings/signals**

The safety profile of colchicine is well known and extensively described in the literature. The applicant submitted a wide array of published articles to support the proposed dose and indication. The applicant also submitted the limited safety data available from their clinical development program, which is comprised of short term colchicine exposures in their PK studies, and did not reveal new safety concerns.

Colchicine is well known to have dose-related toxicity. The most common toxicity of colchicine is gastrointestinal (with nausea, vomiting, abdominal pain, and diarrhea). Although gastrointestinal toxicity does not necessarily indicate an overdose of colchicine, it may be the first sign of more serious toxicity to follow, particularly with oral administration.

A wide variety of adverse reactions have been reported with colchicine. The following adverse reactions are considered generally reversible by interrupting treatment or lowering the dose of colchicine:

- Gastrointestinal: abdominal cramping, abdominal pain, diarrhea, lactose intolerance, nausea, vomiting
- Nervous System: sensory motor neuropathy
- Dermatological: alopecia, maculopapular rash, purpura, rash
- Hematological: leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, aplastic anemia
- Hepatobiliary: elevated AST, elevated ALT
- Musculoskeletal: myopathy, elevated CPK, myotonia, muscle weakness, muscle pain, rhabdomyolysis

- Reproductive: azoospermia, oligospermia

Colchicine overdose toxicity generally follows a characteristic pattern. In the first stage, which occurs in the first 24 hours after ingestion, gastrointestinal symptoms predominate, and include abdominal pain, nausea, vomiting and diarrhea of sufficient severity to potentially cause volume depletion and leukocytosis. From 24 to 72 hours after ingestion, multi-organ failure predominates, and may include bone marrow failure, renal failure, adult respiratory distress syndrome, arrhythmias, disseminated intravascular coagulation (DIC), metabolic and electrolyte disturbances, rhabdomyolysis, convulsions and coma. If the patient survives, rebound leukocytosis and alopecia may be observed during the recovery phase.¹⁶ Colchicine is estimated to be effective at doses of approximately 0.015 mg/kg, toxic in doses greater than 0.1 mg/kg, and typically lethal at doses of approximately 0.8 mg/kg. In the therapeutic range, plasma levels are approximately 0.5 to 3 ng/ml.¹⁷

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

A total of 107 AEs were reported in 56 patients from the applicant's PK studies. No deaths or serious adverse events were reported. The most commonly reported AEs among the 112 healthy volunteers exposed to at least one oral dose of colchicine 0.6 mg were headache (10%) and nausea (10%). All of the AEs were of mild to moderate severity and none of the AEs required discontinuation from the study. No new safety signals for colchicine were identified in these limited data.

- **Immunogenicity**—Not applicable
- **Special safety concerns**—See sections 6 and 8 above.
- **Discussion of primary reviewer's comments and conclusions**

Dr. Hull has concluded that the safety profile of colchicine in the prophylactic treatment of gout is favorable, based on information available in the published literature and from its long history of clinical use. The applicant's data from the 6 pharmacokinetic studies conducted to support this NDA are limited and did not reveal any new safety signals. I concur with Dr. Hull's conclusions.

- **Discussion of notable safety issues (resolved or outstanding)**

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application.

¹⁶ Ben-Chetrit and Levy, "Colchicine: 1998 Update." *Semin Arthritis Rheum* 28:48-59.

¹⁷ E Niel and JM Scherrmann, "Colchicine Today" *Joint Bone Spine* 2006; 73:672-678.

10. Pediatrics

The applicant requested a full waiver from the requirements of the Pediatric Research Equity Act (PREA) on the basis that pediatric studies would be impossible or highly impractical to conduct because gout does not occur in children. The review team and the Pediatric Review Committee (PeRC) agreed that a full waiver is justified.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not applicable.
- **Exclusivity or patent issues of concern**

Colchicine is not a new molecular entity and there is no unexpired exclusivity covering the proposed indication for the prophylactic treatment of gout. The applicant has provided an appropriate patent certification or statement for the listed drug relied upon (Col-Probenecid) pursuant to 21 CFR 314.50(i)(1)(ii).

- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues.
- **DSI audits**—No issues.
- **Other discipline consults**—Not applicable.
- **Any other outstanding regulatory issues**—No outstanding regulatory issues.

12. Labeling

- **Proprietary name**

The applicant proposed the tradename “Mitigare,” which was considered acceptable by the review team, the Office of Prescription Drug Promotion (OPDP) and the Office of Surveillance and Epidemiology (OSE) Division of Medication Error Prevention and Analysis (DMEPA).

- **Physician labeling**

Because of the uncertainty raised by the applicant’s DDI studies with respect to the generalizability and accuracy of detailed dose modification recommendations (see section 5 above for details), the review team believes a less prescriptive approach to drug interaction- and organ dysfunction- related treatment recommendations is warranted. Because the interacting drugs of clinical significance appear to be inhibitors of both CYP3A4 and P-gp, concomitant use of these medications and colchicine should be avoided, if possible. However, because it may be difficult for a prescriber to be certain about which drugs are dual vs. single inhibitors of CYP3A4 and P-gp, the most conservative approach would be for a prescriber to avoid concomitant use of CYP3A4 or P-gp inhibitors with colchicine. If concomitant use is

necessary, this should be done with caution, consideration of dose reduction, and close patient monitoring.

Because of the high risk of life-threatening drug-drug interaction with colchicine and dual inhibitors of CYP3A4 and P-gp in patients with renal or hepatic impairment, a contraindication against colchicine use in this scenario is justified.

Regarding dose-modifications due to renal or hepatic impairment, the review team concluded that the utility of the applicant's proposed dose adjustments was questionable given the dose range of colchicine for the prophylactic gout indication (i.e., 0.6-1.2 mg daily), which is already less than or equal to half of the maximum dose of colchicine approved for chronic administration (Colcrys, FMF indication), and thus would not be expected to produce serious toxicity, even if renal or hepatic impairment effectively doubled the concentration. However, in light of increased interindividual variability in the setting of severe hepatic or renal impairment, a general recommendation for avoidance or dose reduction and/or close monitoring in this setting is justifiable.

- **Carton and immediate container labels**

OPDP and DMEPA reviewed the carton and container labels. DMEPA recommended edits for standardization and clarity. Final agreement on the carton and container labels is pending at the time of this review.

- **Patient labeling/Medication guide**

The applicant submitted a proposed a Medication Guide, which was reviewed by OPDP and the Division of Medical Policy Programs (DMPP). OPDP and DMPP suggested edits to simplify or clarify proposed wording, remove redundancy, ensure consistency with the prescribing information, and that the medication guide meets the requirements of 21 CFR 208.20. Final agreement on the medication guide with the applicant is pending at the time of this review.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this application, provided that the CMC deficiencies can be satisfactorily addressed. The CMC deficiencies may preclude approval.

- **Risk Benefit Assessment**

The risk-benefit of colchicine at up to 1.2 mg per day for the prophylactic treatment of gout is favorable. Gout flares cause significant pain and functional impairment, and the risk of

colchicine at a dose of 0.6 once or twice daily is low, with appropriate precautions regarding interacting drugs and renal or hepatic impairment.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

A Risk Evaluation and Mitigation Strategy (REMS) is neither necessary nor warranted. Colchicine has a long history of clinical use, and prescribers are aware of the potential for serious toxicity with colchicine.

- **Recommendation for other Postmarketing Requirements and Commitments**

No postmarketing requirements or commitments are warranted.

- **Recommended Comments to Applicant**

Pending final disposition of the CMC deficiencies identified on drug product manufacturing site inspection.

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

/s/

SARAH K YIM
07/15/2013