CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210942Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	210942
Priority or Standard	Standard
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Division/Office	OND/ODEII/DPARP
Review Completion Date	January 29, 2019
Established Name	Colchicine oral solution
(Proposed) Trade Name	Gloperba
Pharmacologic Class	Tricyclic Alkaloid
Applicant	Romeg Therapeutics
Formulation(s)	Oral solution
Dosing Regimen	0.6 mg/5 mL
Applicant Proposed Indication(s)/Population(s)	Prophylactic treatment of gout flares in adults
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Prophylactic treatment of gout flares in adults

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

On March 30, 2018, Romeg Therapeutics submitted the original 505(b)(2) NDA 0.6 mg/5mL oral colchicine solution for the proposed indication of prophylaxis of gout flares in adults. 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 (ANDA 084279, Colchicine/Probenecid 0.5 mg/500 mg Tablet), and published literature for the efficacy and safety of colchicine for the proposed indication. The applicant conducted three clinical pharmacology studies: a relative bioavailability and food effect study using Col-Probenecid tablet (ANDA 084279) as the reference standard; and two drug interaction studies to support relevant dose modification recommendations for its product when used with concomitant medications. The proposed regulatory pathway and the submitted clinical pharmacology data to support this application are reasonable.

1.2. Conclusions on the Substantial Evidence of Effectiveness

As the Applicant has not conducted clinical trials to assess the safety and efficacy of their proposed colchicine product, the development program for this application is based on demonstration of bioequivalence (BE) to the reference standard (Col-probenecid tablet; ANDA 084279), and published literature. Two randomized, placebo-controlled, double-blinded studies from the published literature provided the principal evidence of the efficacy of colchicine by reproducibly demonstrating a reduction in the number of gout flares in adult patients with chronic gout compared to patients treated with placebo. The primary evidence was further supported by five open-label or retrospective studies from the literature. Each of the studies enrolled patients with chronic gout and represented the targeted patient population. Overall there was substantial evidence of sufficient quality to adequately assess the safety and efficacy of colchicine for use for prophylaxis of gout flares in patients with gout.

In this submission, the Applicant submitted one pivotal clinical pharmacology study (Study RMG-COL-PK001) to support BE of colchicine in their proposed product to the reference standard. The BE for colchicine was demonstrated (the 90% CI for the ratio of the geometric means of the test/reference products for the AUC and Cmax were within 80.00 – 125.00%) in Study RMG-COL-PK001, a single-dose, randomized, three-treatment crossover study under fasting condition in 34 male and female healthy volunteers aged 18 to 55 years. In this study, the dose-normalized geometric mean ratio (test/listed) of AUC0–∞, AUC0–t, and Cmax for colchicine were 100.5 (90% CI = 93.9, 107.6), 101.2 (90% CI = 94.1, 109.0) and 98.5 (90% CI = 88.5, 109.6), respectively. Food had no impact on the extent of absorption (AUC) for the proposed oral solution of colchicine. There was a slight decrease in Cmax (~19% lower Cmax) following administration with a high fat, high calorie meal.

The Applicant conducted two drug interactions studies - one with weak, moderate and strong CYP3A4 inhibitors (amlodipine, ciprofloxacin and posaconazole, respectively), and one with the P-gp inhibitor (carvedilol). These studies did not show a significant interaction with amlodipine, ciprofloxacin and carvedilol. The effect of posaconazole was clinically significant, with a 2.3-fold and 3.1-fold increase in Cmax and AUC of colchicine, respectively. Several published case reports indicate that colchicine toxicity can occur when it is co-administered with drugs that are potent inhibitors of both P-gp and CYP3A4 (e.g., clarithromycin, ketoconazole), strong to moderate inhibitors of CYP3A4 (e.g., erythromycin) as well as potent P-gp inhibitors (e.g., cyclosporine). Therefore, the Applicant's drug interaction study results are considered drug specific and should not be extrapolated to other inhibitors. Based on the published case reports, general cautionary language informing health care providers and patients about drug interaction potential of colchicine will be included in prescribing information along with recommendations for dose adjustment and close monitoring for colchicine toxicity. (see the clinical pharmacology section of the Unireview by Dr. Justin Penzenstadler for details).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Gout is a form of inflammatory arthritis that results from monosodium urate crystal deposition in synovial fluid and tissues. Gout causes acute, painful swelling of involved joints, but can also progress to a chronic inflammatory arthritis. Approximately 6 million adults in the United States suffer from the condition. Colchicine has been used in the US to treat gout since the early 19th century.

This is a 505(b)(2) application for an oral colchicine solution (0.6 mg/5 mL) drug product. The Applicant uses Col-Probenecid (ANDA 084279, Colchicine/Probenecid 0.5 mg/500 mg Tablet), and published literature to support efficacy and safety of colchicine for the prophylactic treatment of gout flares in adults. Two randomized, placebo-controlled, double-blinded studies from the published literature provided the principal evidence of the efficacy of colchicine by reproducibly demonstrating a reduction in the number of gout flares in adult patients with chronic gout compared to patients treated with placebo. The primary evidence was further supported by five additional studies from the literature. No clinical efficacy and safety studies were conducted or required under this application. The pivotal relative bioavailability study demonstrated BE for colchicine in the proposed drug product to the reference standard (Col-Probenecid tablet; ANDA 084279). The adverse events in the study were low and revealed no new safety signals. The safety of oral colchicine is further supported by the submitted literature review, and review of FDA and WHO post-marketing safety databases. The published literature is adequate to support the efficacy and safety of orally administered colchicine for prophylaxis of gout flares.

The overall risk-benefit profile of this colchicine drug product at up to 1.2 mg per day for prophylaxis of gout flares in adult patients is favorable. Gout flares cause significant pain and functional impairment. Treatment with colchicine has been demonstrated to reduce the number of gout flares in adult patients with chronic gout. The risk of colchicine at a dose of 0.6 mg once or twice daily is low, with appropriate precautions regarding interacting drugs and renal or hepatic impairment. A colchicine oral solution offers an alternative treatment option that may be preferable for some users.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Gout is a form of inflammatory arthritis that results from monosodium urate crystal deposition in synovial fluid and tissues. • Gout initially causes acute, painful swelling of involved joints, but can progress to become a chronic arthritis. • Approximately 6 million adults in the United States suffer from the condition.	• Gout is a serious disabling form of inflammatory arthritis with significant impact on quality of life for patients.
Current Treatment Options	• Currently approved treatment options for prophylaxis of gout flares include colchicine (available as oral tablets or oral capsules) and colchicine-probenecid combination products. • Non-steroidal anti-inflammatory drugs and corticosteroids may be used in the management of acute and chronic gout.	• Colchicine oral solution provides an additional therapeutic option for patients.
Benefit	• Based on the published literature, colchicine has been demonstrated to reduce the number of gout flares in adult patients with chronic gout compared to patients treated with placebo. • The pivotal relative bioavailability study demonstrated bioequivalence for Gloperba to the reference standard.	• The clinical benefit of Gloperba is based on the established efficacy of colchicine/probenecid (NDA 012383), review of the published literature, and the demonstration of bioequivalence to the reference standard.
Risk and Risk Management	• Colchicine is generally well tolerated when used in therapeutic doses and adjusted for patients with renal and/or hepatic insufficiency. • Risks associated with the use of colchicine include gastrointestinal toxicities, myelosuppression, and neuromuscular toxicity. • The safety profile observed in the studies conducted by the Applicant do not raise new safety concerns.	• The safety profile of colchicine is well established. • The studies conducted by the Applicant did not raise new safety concerns. • The potential for drug interactions with co-administration of CYP3A4 or P-gp inhibitors or inhibitors of both CYP3A4 and P-gp will be included in the product

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In drug interaction studies, the effect of posaconazole was clinically significant, with a 2.3-fold and 3.1-fold increase in Cmax and AUC of colchicine, respectively.	labeling.

1.4. Patient Experience Data

This 505(b)(2) NDA relies on FDA's finding of safety and effectiveness for the combination product Col-Probenecid (ANDA 084279, Colchicine/Probenecid 0.5 mg/500 mg Tablet), and published literature for the efficacy and safety of colchicine for the proposed indication. The Applicant has not conducted clinical trials to assess the safety and efficacy of the proposed colchicine oral solution. Patient experience data from studies with other colchicine products is included in some studies used in the literature review to support this application.

Bhawana Saluja
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Bhawana Saluja, Ph.D.
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Gout is a form of inflammatory arthritis that results from monosodium urate crystal deposition in synovial fluid and tissues. Gout typically occurs in patients with hyperuricemia, and although it is a necessary prerequisite, hyperuricemia in and of itself is not sufficient to induce the disease. Clinically, gout is classically described as having two phases. The first phase manifests as periodic acute attacks of arthritis that spontaneously resolve over 7-10 days if left untreated and patients are typically asymptomatic during intercritical periods. Patients with insufficiently treated hyperuricemia can progress to the second phase, referred to as chronic gout, which is characterized by periods of polyarticular arthritis which may remain symptomatic between acute exacerbations, urate crystal deposition into soft tissues (tophi), and formation of renal calculi. In general, gout becomes more prevalent with increasing age and is more common in men and post-menopausal women. Approximately 6 million adults in the United States are diagnosed with gout and the incidence is expected to rise due to the aging population, increasing levels of obesity, and American diet.

2.2. Analysis of Current Treatment Options

Definitive treatment of gout involves treatment of the hyperuricemia by lowering the serum uric acid concentration to a target that is usually defined as less than 6 mg/dL. If gout is not treated by lowering serum uric acid, patients will develop more frequent gout flares and are more likely to develop tophi. Initiation of urate-lowering therapy often precipitates gout flares as a result of the mobilization of uric acid stores causing inflammation. Consequently, prophylactic treatment with colchicine or non-steroidal anti-inflammatory drugs (NSAIDS) is often prescribed to prevent gout flares in patients with chronic gout who are initiating a urate-lowering drug, e.g., allopurinol or febuxostat.

Colchicine is a tricyclic alkaloid derivative originating from the plant *Colchicum autumnale*, more commonly known as “Autumn Crocus” or “Morning Saffron”. There is evidence that the bulb of the plant was used to treat pain and articular disease as early as the first century CE, and by the eighteenth century, colchicum was specifically used as a treatment for gout. The active ingredient, (-) colchicine, was isolated in 1821 by Pelletier and Caventou and has been used in the U.S. to treat disease since the early 19th century.

The exact mechanism whereby colchicine decreases inflammation is not fully understood, however, it has been long believed that colchicine disrupts the function of the cytoskeleton by interfering with microtubulin assembly; this in turn is thought to prevent the activation, degranulation, and migration of neutrophils to sites of inflammation. More recent evidence however now suggests that colchicine may derive its mechanism of action by interfering with

the intracellular assembly of the inflammasome complex found in neutrophils and monocytes that mediate IL-1β activation.

Colchicine is the only member of its pharmacologic class and has been used clinically as a single entity in the U.S. for over 70 years; consequently, its safety profile has been well-documented over this period of time. Colchicine is generally well-tolerated at normal therapeutic doses with the most common side effects related to gastrointestinal symptoms, e.g., diarrhea, nausea and vomiting. However, colchicine has a narrow therapeutic index and toxic levels can result in serious life-threatening adverse events and death. Oral administration of colchicine generally limits the majority of patients from achieving toxic serum levels since the gastrointestinal adverse effects become severe and consequently dose-limiting.

Currently available treatment for the prophylaxis of gout flares in patients with chronic gout includes NSAIDs and colchicine-containing products (Colcrys®, Mitigare® and colchicine/probenecid; Table 1). Although colchicine/probenecid was approved as a combination product by DESI review in 1972, it was not until July 2009 that colchicine was approved as a single active ingredient by the FDA for use in the treatment of gout flares under the trade name Colcrys. Treatments for acute flares of gout are typically treated using NSAIDs, colchicine, corticosteroids, and adrenocorticotropic hormone (ACTH). While most of the NSAIDs and corticosteroid formulations are approved as treatment for gout flares, ACTH is currently not an approved treatment. Colchicine 0.6 mg tablets are currently marketed in the United States under the trade name Colcrys® (Takeda Pharmaceuticals) for the treatment of familial Mediterranean fever (FMF), treatment of acute gout flares, and prophylaxis of gout flares in patients with chronic gout. Colchicine 0.6 mg capsules are also currently marketed in the United States under the trade name Mitigare® (Hikma Pharmaceuticals) for the prophylaxis of gout flares in adults. In this new drug application (NDA), Romeg has developed a Colchicine oral solution and is proposing dosing of 0.6 mg once or twice daily for the prophylaxis of gout flares in adult patients with chronic gout.

Table 1: Summary of Treatments for Prophylaxis of Gout Flares

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration
FDA Approved Treatments			
Colchicine 0.5mg/Probenecid 500 mg	• Prophylaxis of gout flares	1972	1 to 2 tablets QD
Colcrys (colchicine 0.6 mg tablet)	• Prophylaxis and treatment of gout flares • Familial Mediterranean Fever	2009	1 to 2 tablets QD
Mitigare (colchicine 0.6 mg capsules)	• Prophylaxis of gout flares	2014	1 to 2 capsules QD
Other Treatments			
NSAIDs			
Corticosteroids			

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

As discussed above, currently available colchicine-containing treatments for the prophylaxis of gout flares in patients with chronic gout include the products Colcrys®, Mitigare® and colchicine/probenecid. Although colchicine/probenecid was approved as a combination product by DESI review in 1972 (FR Vol.37, No.146), it was not until July 2009 that colchicine was approved as a single active ingredient by the FDA for use in the treatment of gout flares under the trade name Colcrys®. Colchicine 0.6 mg tablets are currently marketed in the United States under the trade name Colcrys® (Takeda Pharmaceuticals) for the treatment of familial Mediterranean fever (FMF), treatment of acute gout flares, and prophylaxis of gout flares in patients with chronic gout. Colchicine 0.6 mg capsules are also currently marketed in the United States under the trade name Mitigare® (Hikma Pharmaceuticals) for the prophylaxis of gout flares in adults. In this new drug application (NDA), Romeg has developed a colchicine oral solution and is proposing dosing of 0.6 mg once or twice daily for the prophylaxis of gout flares in adults.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Integrity and Surveillance (OSIS)

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) concluded that the clinical data from the audited study to be reliable and no significant deficiencies were observed. OSIS recommends that the data for the clinical portion of study submitted to NDA 208085 be accepted. [NDA 210942, MEMORANDUM, Srinivas R. Chennamaneni, PhD, Division of New Drug Bioequivalence Evaluation Office of Study Integrity and Surveillance (OSIS), 12/20/2018]. OSIS also recommends accepting the bioanalytical data from the audited study without an on-site inspection. [NDA 210942, MEMORANDUM, Shila Nkah, Division of New Drug Bioequivalence Evaluation Office of Study Integrity and Surveillance (OSIS), 06/12/2018].

4.2. Product Quality

General product quality considerations

The drug product is a non-sterile aqueous-based oral solution containing 0.6 mg/5 mL of colchicine packaged in 190 cc HDPE bottles with a child-resistant closure and foil liner. The formulation includes colchicine and the following excipients: benzyl alcohol, citric acid, dibasic sodium phosphate, glycerin, propylene glycol, sucralose, xanthum gum, FD&C Red No. (b) (4)

artificial cherry flavor and purified water. The drug product manufacturing process involves (b) (4) The stability data supports a 24-month expiration dating period.

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 provided separately in the drug substance supplier's master file (b) (4) Colchicine provided by (b) (4) is confirmed to have the same identity as the Colchicine, USP reference standard by infrared spectroscopy. The CMC information on the drug substance was reviewed and determined to be acceptable.

Facilities review/inspection

The site proposed for manufacture of the 0.6 mg/5 mL oral solution final drug product is Ferndale Laboratories Inc., Ferndale MI. Ferndale Laboratories Inc. is currently approved for U.S. distribution of multiple non-sterile OTC products and the manufacturing site is recommended for approval from the standpoint of facilities assessment. A detailed analysis of CMC issues can be found in Dr. Craig M. Bertha's review.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

The Applicant did not submit any nonclinical pharmacology or toxicology stud(y)ies to support this NDA. The Applicant relies on FDA's previous findings of safety for the colchicine/probenecid product under ANDA 084279. There are no outstanding nonclinical pharmacology and toxicology issues. The NDA is recommended for approval from the nonclinical pharmacology and toxicology perspective.

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Carol Galvis, Ph.D. signing for Anup Srivastava, Ph.D.
Primary Nonclinical Reviewer

Carol Galvis, Ph.D.
Nonclinical Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

On 30 March 2018, Romeg Therapeutics submitted NDA 210942 under Section 505(b)(2) of the FD&C Act, seeking approval of colchicine oral solution (0.6 mg/5 mL colchicine) for prophylaxis of gout flares. The proposed proprietary name for this product is Gloperba. This submission relies on the FDA's previous findings of safety and effectiveness established for colchicine in Col-Probenecid (Colchicine/Probenecid 0.5 mg/500 mg Tablet), and published literature for the efficacy and safety of colchicine for the proposed indication.

The clinical development for the drug product included one pivotal relative bioavailability study (Study RMG-COL-PK001) and two drug interaction studies (Study RMG-COL-PK002 and RMG-COL-PK003). In study RMG-COL-PK001, the relative bioavailability of the proposed colchicine oral solution was compared to the Reference Standard (Col-Probenecid; ANDA 084279) under fasted conditions in healthy subjects. The 90% confidence interval (CI) for the geometric mean ratios of the primary PK parameters (AUC0-∞, AUC0-last, Cmax) for the product comparisons were all within 80-125%.

The Office of Clinical Pharmacology has reviewed the clinical pharmacology studies submitted in NDA 210942. This NDA is approvable from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacology

Colchicine exhibits a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks, and to relieve the residual pain and mild discomfort of gout. The mode of action of colchicine in gout is unknown, however, has been postulated to be due to its ability to block neutrophil-mediated inflammatory responses induced by monosodium urate crystals in synovial fluid. Colchicine disrupts the polymerization of β-tubulin into microtubules, thereby preventing the activation, degranulation and migration of neutrophils to sites of inflammation. Colchicine also interferes with the inflammasome complex found in neutrophils and monocytes that mediates interleukin-1β (IL-1β) activation.

Clinical Pharmacokinetics

The comparability of the solution is supported by one pivotal relative bioavailability study (RMG-COL-PK001). Overall, the study was adequately designed to assess relative bioavailability. The key clinical pharmacology findings for Gloperba versus the reference standard (i.e., Colchicine and probenecid tablet) in Study RMG-COL-PK001 were confirmed by

the reviewer's independent analysis. Because different doses of colchicine were administered for the test and reference arms in Study RMG-COL-PK001, i.e., 0.6 mg and 0.5 mg colchicine for Gloperba and the reference standard, respectively, all pharmacokinetic parameters were dose-normalized. The proposed product, Gloperba (0.6 mg/5 ml), is bioequivalent to the corresponding dose-normalized reference standard for colchicine under fasted conditions (Table 2).

Table 2: Statistical Analysis for Primary Pharmacokinetic Parameters of Colchicine following Single Dose Administration of Gloperba or the Reference Standard in Healthy Subjects under Fasted Conditions (Study RMG-COL-PK001)

PK Parameter (Normalized by Dose)	Geometric Mean Ratio (Test/Reference) (%)	Lower Confidence Interval	Upper Confidence Interval
AUC0-∞ (hr.ng/mL/mg)	100.5	93.9	107.6
AUC0-last (hr.ng/mL/mg)	101.2	94.1	109.0
Cmax (ng/mL/mg)	98.5	88.5	109.6

Source: Adapted from NDA 210942, Module 5.3.1.2; rmg-col-pk0001-report-body-1.pdf, table 2-2

RMG-COL-PK001 also included a food-effect cross treatment period. Food had no impact on the extent of exposure (AUC) for the proposed oral solution of colchicine, however the Cmax was decreased by 19% following administration with a high fat, high calorie meal (Table 3). This difference is not expected to have any clinically meaningful impact on the safety and efficacy of colchicine, and the proposed product can be administered without regards to meals.

Table 3: Effect of Food on the Primary Pharmacokinetic Parameters of Colchicine for Gloperba in Healthy Subjects (Study RMG-COL-PK001)

PK Parameter (Normalized by Dose)	Geometric Mean Ratio (Fed/Fasted) (%)	Lower Confidence Interval	Upper Confidence Interval
AUC0-∞ (hr.ng/mL/mg)	92.8	86.7	99.3
AUC0-last (hr.ng/mL/mg)	92.4	85.8	99.5
Cmax (ng/mL/mg)	81.4	73.1	90.6

Source: Adapted from NDA 210942, Module 5.3.1.2; rmg-col-pk0001-report-body-1.pdf, table 2-3

6.2.2. Therapeutic Individualization

Two drug interaction studies were conducted by the Applicant, whereby strong, moderate, and weak CYP3A4 inhibitors and a P-gp inhibitor was co-administered with Gloperba. Overall, the studies were adequately designed to assess the drug interaction. The effect of amlodipine besylate 5 to 10 mg QD (a weak 3A4 inhibitor), ciprofloxacin 500 mg BID (a moderate 3A4 inhibitor), and carvedilol CR 20 to 40 mg QD (a P-gp inhibitor) are not clinically significant. The effect of posaconazole 300 mg was clinically significant, with a 281-340% increase in AUC[1] of colchicine. These results are drug specific and should not be extrapolated to other inhibitors.

The Applicant proposed following dose adjustment for the proposed product when co-administered with posaconazole: 0.24 mg once daily (2 mL) (b) (4); this dose adjustment is considered reasonable. Colchicine can be administered with amlodipine, ciprofloxacin and carvedilol without a need for dose adjustment.

Although colchicine did not interact to a significant extent with amlodipine, ciprofloxacin and carvedilol, several published case studies have reported colchicine toxicity when co-administered with drugs that are potent inhibitors of both P-gp and CYP3A4 (e.g., clarithromycin, ketoconazole), strong-to-moderate inhibitors of CYP3A4 (e.g., grapefruit juice, erythromycin) and P-gp inhibitors (e.g., cyclosporine). Therefore, colchicine's drug interaction potential with other P-gp and CYP3A4 inhibitors (dual inhibitors), and P-gp inhibitors and strong-to-moderate CYP3A4 inhibitors cannot be ruled out. Based on the available information, general cautionary language informing patients about drug interaction potential of colchicine will be included in the label along with the suggestion that colchicine daily dose may be reduced if co-administered with dual inhibitors of CYP3A4 and P-gp as well as with strong-to-moderate CYP3A4 inhibitors or P-gp inhibitors.

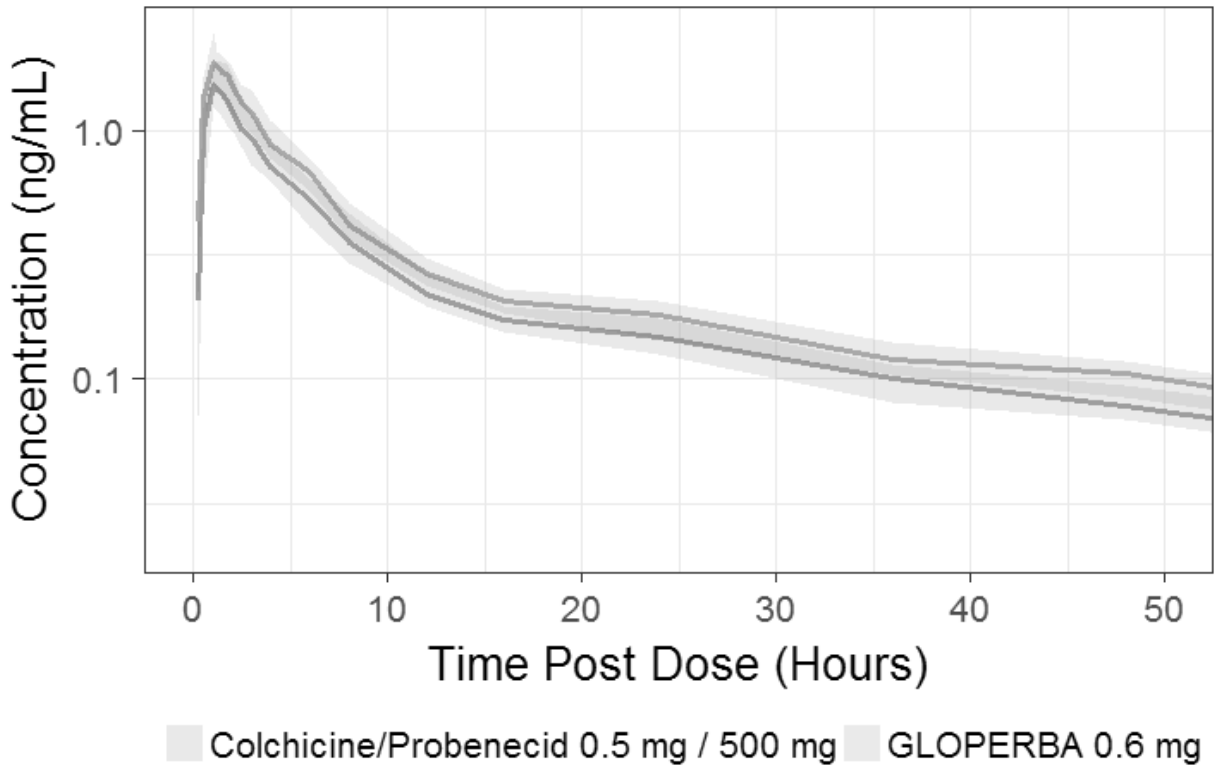
6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Colchicine oral solution reaches Cmax rapidly (1-2 hours under fasting conditions). It has a distribution phase of approximately 16 hours. The mean apparent volume of distribution (V_z/F) of Gloperba in healthy adults was approximately 1420 L. The terminal half-life is around 20-40 hours (Figure 1).

[1] Represents 90% CI for the geometric mean ratio for both AUC extrapolated to infinity and AUC, as determined by analysis of variance (ANOVA) analysis.

Figure 1: Concentration-time Profile of Colchicine following Single Dose Administration of Gloperba or the Reference Standard under Fasted Conditions (Study RMG-COL-PK001)



Source: Reviewer's supplementary analysis. Lines represent median value; shaded regions represent 25-75% quantiles of observed data.

Table 4: Pharmacokinetic Parameters for Colchicine under Fasted and Fed State for Gloperba (RMG-COL-PK001)

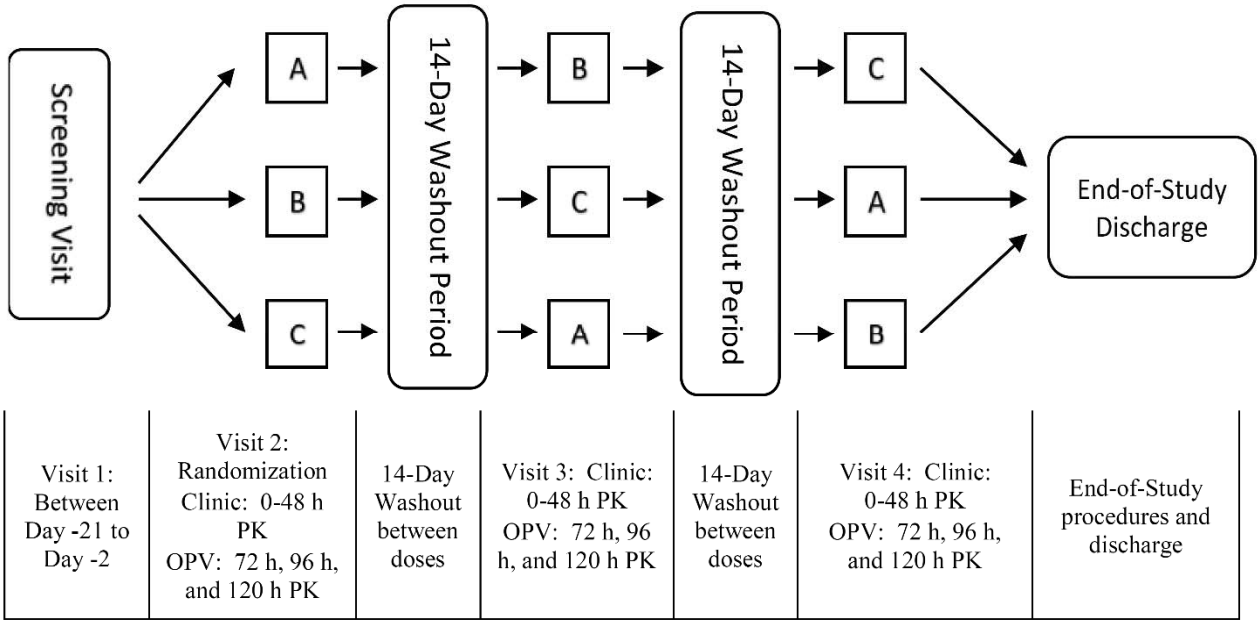
Arithmetic Mean Parameter	GLOPERBA Fasted (N=34)	GLOPERBA Fed (N=34)
Cmax (ng/mL) Mean (SD)	2.16 (0.87)	1.68 (0.39)
AUC0-last (h·ng/mL) Mean (SD)	18.59 (4.64)	17.20 (4.23)
AUC0-∞ (h·ng/mL) Mean (SD)	19.90 (4.74)	18.47 (4.29)
Tmax (h) Median (Min-Max)	1.00 (0.50: 2.00)	2.00 (1.00: 4.00)
t1/2 (h) Mean (SD)	31.04 (5.99)	30.54 (5.22)

Source: Adapted from NDA 210942, Module 5.3.1.2; rmg-col-pk001-report-body-1.pdf, table 2-1

6.3.2. Clinical Pharmacology Assessment for Pivotal Relative Bioavailability and Food Effect Study (RMG-COL-PK001)

The pivotal relative bioavailability study was an open-label, randomized, single-dose, three-treatment, three-way crossover study enrolling thirty-six subjects, thirty-four of which completed the study per protocol. Two subjects discontinued prematurely from the study for reasons unrelated to the study drug. Three treatments were administered: 5 mL (0.6 mg colchicine) of the test oral solution under fasting conditions, 5 mL (0.6 mg colchicine) of the test oral solution under fed conditions, and one probenecid and colchicine (500 mg/0.5 mg) tablet (Reference Standard). During each of the 3 study periods, confinement began at approximately 1400 hours on the day prior to dosing and continued until after the 24-hour PK post-dose sampling and safety assessments. Subjects could exit the clinical facility and then return on an outpatient basis for the 48, 72, 96, 120 and 144-hour PK sampling and safety assessments. Pharmacokinetic sampling occurred every 15 minutes for the first 2 hours, at 2.5 hours, 3, 4, 6, 8, 12, 16, and 24 hours, and 1.5, 2, 3, 4, and 5 days post-dose. The PK sampling and between treatment washout was adequate to ensure proper PK characterization.

Figure 2: Study Schematic for RMG-COL-PK001



Source: Adapted from NDA 210942, Module 5.3.1.2; rmg-col-pk001-report-body-1.pdf, figure 2-1

Subjects enrolled were non-smokers and medically healthy, as determined by medical history, physical, and laboratory results. The subjects were 75% male, with a mean age of 41.1 years, ranging from 21 to 55 years. The mean BMI was 26.78. Nineteen subjects were African American, 16 were white, and 1 was Asian. The primary PK endpoints were plasma colchicine AUC0-last, AUC0-inf, and Cmax. Secondary PK endpoints were tmax, Vz/F, CL/F, Kel, and t½.

In each cohort, log-transformed PK parameters AUC0-last, AUC0-∞, and Cmax were analyzed using an analysis of variance (ANOVA) model including treatment as a fixed effect, and subject as a random effect. The two subjects with incomplete data were excluded from the reviewer's analysis. Because the doses were different, statistical analysis was performed on exposure parameters that were dose-normalized. The reviewer used subject level colchicine concentration versus time data to perform non-compartmental analysis in R using the package PKNCA[2]. Resulting PK parameters (Cmax, AUC0-last, AUC0-∞) were log-transformed, and the

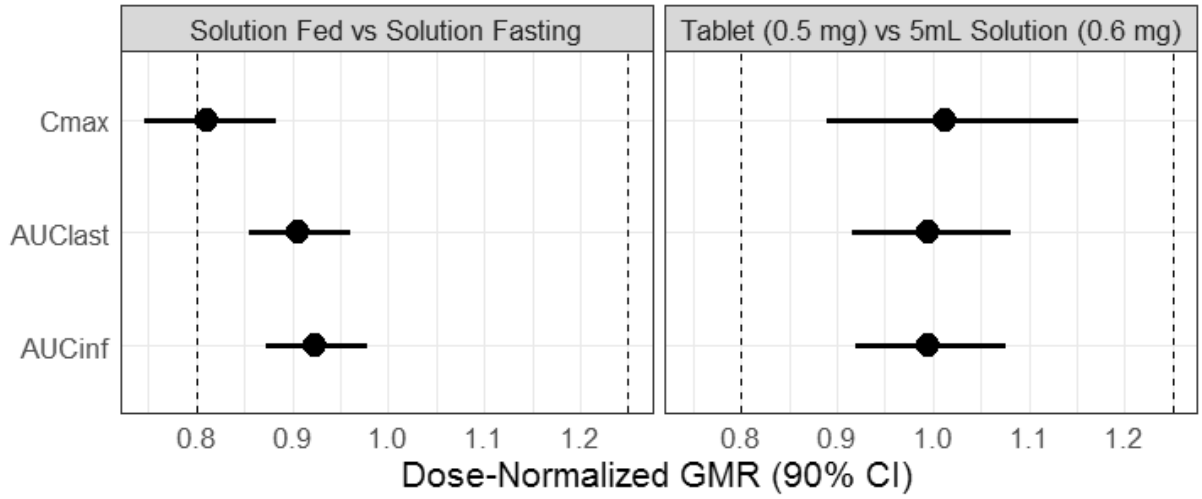
[2] Denney W, Duvvuri S and Buckeridge C (2015). "Simple, Automatic Noncompartmental Analysis: The PKNCA R Package." Journal of Pharmacokinetics and Pharmacodynamics, *42*(1), pp. 11-107,S65. ISSN 1573-8744, doi: 10.1007/s10928-015-9432-2 (URL: http://doi.org/10.1007/s10928-015-9432-2), R package version 0.8.4, <URL:https://github.com/billdenney/pknca>.

[3] Pinheiro J, Bates D, DebRoy S, Sarkar D and R Core Team (2017). nlme: Linear and Nonlinear Mixed Effects Models. R package version 3.1-131, <URL: https://CRAN.R-project.org/package=nlme>.

geometric mean ratio was determined ANOVA in R using the package nlme[3]. The results presented by the Applicant (below) are consistent with the results of the reviewer.

Dosing in the fasted state met the bioequivalence (BE) criteria (i.e., 90% confidence interval (CI) of 80-125%) for both dose-adjusted Cmax and dose-adjusted AUC for the proposed product as compared to the Reference Standard (Figure 3, Table 2). Similarly, dosing under the fed state met the BE criteria for AUC, however, the 90% CI for Cmax were outside the BE limit (i.e., 90% CI of 73.1-90.6%). The difference in Cmax is not expected to have any clinically meaningful impact on the safety and efficacy of colchicine.

Figure 3: Forest Plots for Study Results of RMG-COL-PK001



Source: Reviewer's supplementary analysis

6.3.3. Clinical Pharmacology Assessment for CYP3A4 Inhibitor Study (RMG-COL-PK003)

RMG-COL-PK003 was a three-independent cohort, open-label, two-period study to assess the effects of three different hepatic CYP3A4 inhibitors at steady state on the pharmacokinetics of a single oral dose of Gloperba. The study used Norvasc (amlodipine), Cipro (ciprofloxacin), and Noxafil (posaconazole) as weak, moderate, and strong inhibitors, respectively. Twenty to twenty-one subjects were enrolled for each drug interaction study. The study was designed such that the enrollment of the three cohorts was independent of each other. Subjects received a single oral colchicine dose alone in Period 1. The CYP3A4 inhibitor was then dosed to steady-state, and a single oral colchicine dose was co-administered on the last day of the study in Period 2.

The perpetrators (i.e., CYP3A4 inhibitors) were dosed according to approved labeling. Run-in length of the perpetrators was adequate to obtain steady state exposures at the time of the second period, and for complete washout of colchicine (Table 5).

Table 5: Study Design for RMG-COL-PK003

Period, Day	**Cohort 1**	**Cohort 2**	**Cohort 3**
Period 1, Day 1	Single oral dose of Colchicine Oral Solution 0.6 mg (0.6 mg/5 mL, 5 mL) at approximately 08:00 hours administered 30 minutes following a light breakfast for Cohort 1 and following an overnight fast in Cohorts 2 and 3, such that dosing conditions relative to fed or fasted state are identical within a cohort for Periods 1 and 2		
Period 1, Days 2-10	Washout period between treatments		
Period, Day	**Cohort 1**	**Cohort 2**	**Cohort 3**
Period 2, Days 11-16 for Cohorts 1 and 2, Days 11-19 for Cohort 3	On Day 11, each subject received 300 mg Noxafil (posaconazole) (100 mg×3) delayed-release tablets at 8:00 a.m. and 6:00 pm, then on Days 12-16, each subject received a 300 mg Noxafil (posaconazole) dose at 8:00 a.m. following a light breakfast.	On Days 11-16, each subject received one 500 mg Cipro (ciprofloxacin hydrochloride) tablet at 8:00 a.m. in the fasted state, following an overnight fast of at least 10 hours. And a second dose was given at 8:00 p.m. following dinner.	On Days 11-13, each subject received a 5 mg Norvasc (amlodipine besylate) tablet at 8:00 a.m. in the fasted state following an overnight fast of at least 10 hours. Then, if tolerated based on vital signs assessments and overall safety and tolerability assessments, on Days 14-19, subjects received a 10 mg Norvasc (amlodipine besylate) tablet in the fasted state following an overnight fast of at least 10 hours.

Period 2, Day 17 for Cohorts 1 and 2, Day 20 for Cohort 3	On Day 17, each subject received both one dose of 0.6 mg colchicine oral solution and a 300 mg Noxafil (posaconazole) (100×3) dose following a light breakfast.	On Day 17, each subject received both one dose of 0.6 mg colchicine oral solution and a 500 mg Cipro® (ciprofloxacin hydrochloride) at 8:00 a.m. following an overnight fast of at least 10 hours and a final dose of Cipro 500 mg at 8:00 p.m. (without colchicine) following dinner.	On Day 20, each subject received both one dose of 0.6 mg colchicine oral solution and a 10 mg Norvasc (amlodipine besylate) tablet dose at 8:00 a.m. in the fasted state following an overnight fast of at least 10 hours.
Period 2, serial PK sampling following last dose of Colchicine + CYP3A4 inhibitor	Serial PK samples for plasma colchicine concentration determination were obtained following Day 17 dosing	Serial PK samples for plasma colchicine concentration determination were obtained following Day 17 dosing	Serial PK samples for plasma colchicine concentration determination were obtained following Day 20 dosing

Source: Adapted from NDA 210942, Module 2.7.2.5, Table 2.7.2-6

During each study period, confinement began at approximately 1400 hours on the day prior to dosing and continued until after the 24-hour PK post-dose sampling and safety assessments. Subjects took colchicine after a 10 hour fast, except for those taking posaconazole. Subjects taking posaconazole were given a light breakfast. Subjects could exit the clinical facility and then return on an outpatient basis for the 48, 72, 96, 120 and 144-hour PK sampling and safety assessments.

In Study RMG-COL-PK001, a high fat, high calorie meal was found to slightly affect the Cmax of colchicine. Since the meal administered with posaconazole was lighter, and a crossover design was employed, the GMR results are considered valid.

Twenty-two subjects completed Cohort 1 (Norvasc cohort), 20 subjects completed Cohort 2 (Cipro cohort), and 21 subjects completed Cohort 3 (Noxafil cohort). No subject discontinued from the study due to an AE, and there were no SAEs or deaths reported during the study.

Subjects enrolled were non-smokers and medically healthy, as determined by medical history, physical, and laboratory results. The cohorts were majority male (range: 79.2 – 83.3% male). The mean age ranged from 36.8 – 40.3 years of age (range: 18-53). Sixty to seventy percent of the subjects were Black/African-American, 25-40% of the subjects were white. There were 2 subjects that were not African-American or Caucasian.

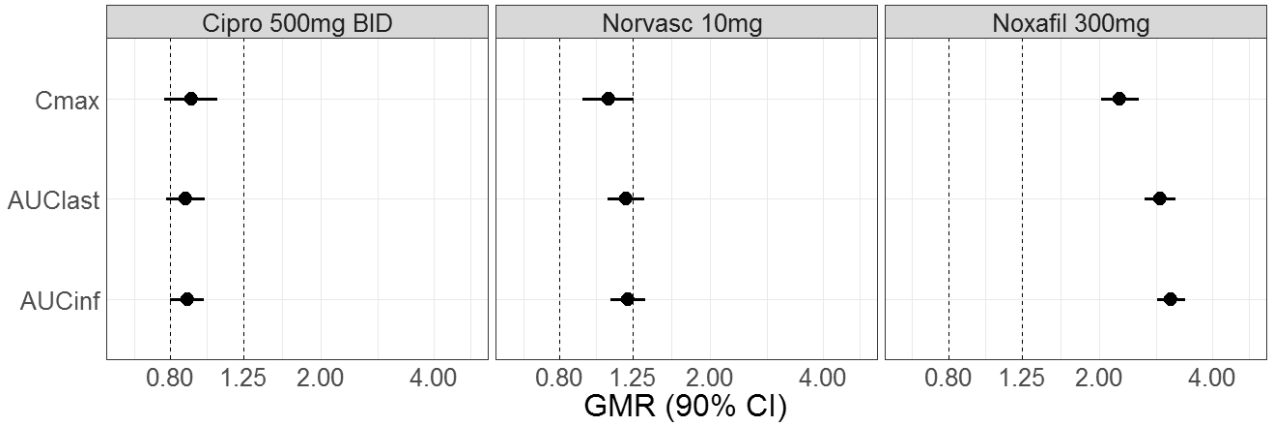
Concurrent dosing with amlodipine (weak CYP3A4 inhibitor) resulted in a point estimate increase (90% CI) for Cmax of 109% (94-128%), AUC0-∞ of 122% (109-136%), and AUC0-last of 123% (111-137%).

Concurrent dosing with ciprofloxacin (moderate CYP3A4 inhibitor) resulted in a point estimate decrease (90% CI) for Cmax of 88% (74-104%), AUC0-∞ of 88% (79-98%), and AUC0-last of 87% (78-97%).

Concurrent dosing with posaconazole (strong CYP3A4 inhibitor) resulted in an estimated increase for Cmax of 227% (202-256%), AUC0-∞ of 309% (281-339%), and AUC0-last of 311% (284-340%). The reviewer independently confirmed these results, as described above. These results are displayed graphically in Figure 4 below.

The Applicant proposed a dose adjustment of 0.24 mg once daily (2 mL) (b) (4) (b) (4) for Gloperba when co-administered with posaconazole. This dose adjustment is considered reasonable. Colchicine can be administered with amlodipine and ciprofloxacin without a need for dose adjustment.

Figure 4: Forest Plots for Study Results of RMG-COL-PK003



Source: Reviewer's supplementary analysis

6.3.4. Clinical Pharmacology Assessment for P-gp Inhibitor Study (RMG-COL-PK002)

RMG-COL-PK002 was an open-label, two-period, sequential study to assess the effects of multiple oral doses of carvedilol CR, a P-gp inhibitor, on the pharmacokinetics of a single oral dose of Gloperba. Twenty-four healthy, non-smoking, adult, male and female subjects were enrolled. Twenty-one subjects (87.5%) completed the study per protocol. Three subjects discontinued prematurely from the study due to drug screening, non-compliance, or withdrawal of consent.

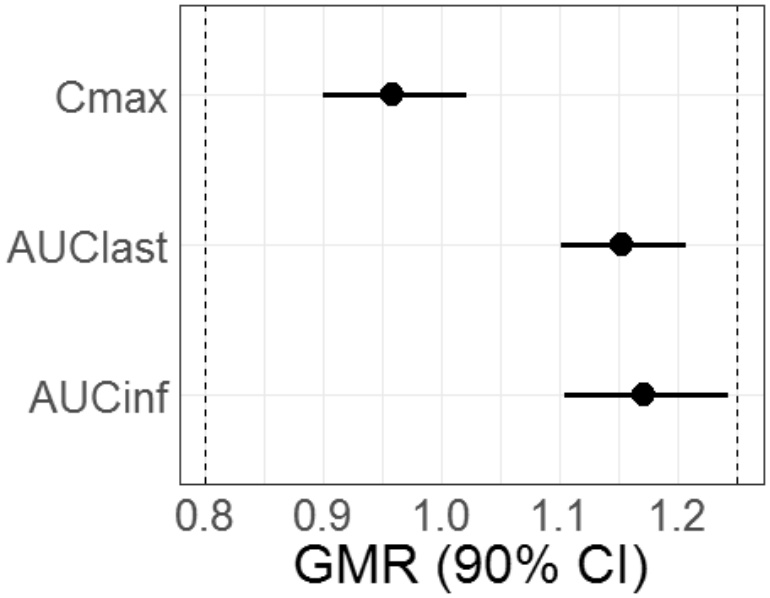
Subjects were representative of a healthy adult male (n=19, 79.2%) and female (n=5, 20.8%) population ranging from 18 to 55 years of age. Overall mean (SD) age was 38.9 (10.05) years and mean (SD) BMI was 26.01 (2.598) kg/m^2. Racial composition was 14 (58.3%) Black/African-American, 9 (37.5 %) White, and 1 (4.2 %) Asian.

In the first period, colchicine oral solution was administered alone. Following a 10-day washout period, carvedilol CR was dosed according to approved labeling, which included a two-day titration period of carvedilol CR at 20 mg. After safety and tolerability assessment, carvedilol was titrated to 40 mg for 5 days. On the last day, colchicine oral solution was co-administered. The run-in length was adequate to obtain steady state exposures of the perpetrator (i.e., P-gp inhibitor). The wash-out period was adequate for colchicine.

All drug administrations in RMG-COL-PK002 were given within 30 minutes of a light breakfast, per COREG CR labeling. During each study period, confinement began at approximately 1400 hours on the day prior to dosing and continued until after the 48-hour PK post-dose sampling and safety assessments. Subjects could exit the clinical facility and then return on an outpatient basis for the 48, 72, 96, 120 and 144-hour PK sampling and safety assessments.

Concurrent dosing with carvedilol (P-gp inhibitor) resulted in a point estimate increase (90% CI) for AUC0-∞ of 118% (112-124%), an increase in AUC0-last of 118 % (112-124%), and a decrease in Cmax to 96% (90-102%). The reviewer independently confirmed these results, as described above. These results are visually displayed in Figure 5.

Figure 5: Forest Plot for Study Results of RMG-COL-PK002



Source: Reviewer's supplementary analysis

6.3.5. Bioanalytical Assay Validation

The colchicine bioanalytical assay was conducted at (b) (4). Concentrations of colchicine in human serum samples were determined using a liquid chromatography MS/MS method. Calibration was performed using a linear model with a proportional ($1/x^2$) weighting factor, over an assay range of 0.02 – 20 ng/mL. The precision and accuracy of the assay, as determined from the analysis of quality control samples ranged from 1.1% to 4.8% (precision) and from 99.1-110.0% (accuracy). The bioanalytical PK assay met the regulatory criterion for acceptable performance during sample analysis. The bioanalytical method validation of colchicine, used in all three pharmacokinetic studies (RMG-COL-PK001, RMG-COL-PK002, RMG-COL-PK003), is summarized in Table 6.

Table 6: Bioanalytical Assay Summary

Report location	Central Data Room at (b) (4)
Method description	Method BTM-1206-R0 is an LC/MS/MS method for the determination of colchicine in human plasma using colchicine-d_3 as the internal standard (IS). Colchicine and the IS were extracted by liquid-liquid extraction from human plasma. Reversed-phase HPLC separation was achieved with a Synergi Polar-RP column (50 X 2.0 mm, 4 µ). MS/MS detection was set at mass transitions of 400.2→310.1 m/z for colchicine and 403.1→310.1 m/z for colchicine-d_3 (IS) in TIS positive mode.
Sample volume	100 µL
Regression	Linear Regression
Weighting factor	$1/x^2$
Dynamic range	0.02-20 ng/mL
QC concentrations	0.06 ng/mL, 3.8 ng/mL, and 15 ng/mL
Analyte	Colchicine
Internal standard	Colchicine-d_3
Linearity	r^2 ≥0.9966
Lower limit of quantitation (LLOQ)	0.02 ng/mL
Average recovery of Colchicine (%)	45.7
Average recovery of colchicine-d_3 (IS) (%)	42.9
QC Intraday precision range (%CV)	Day 1: 1.1-4.8
	Day 2: 2.0-4.7
	Day 3: 2.1-3.0
QC Intraday accuracy range (%Nominal)	Day 1: 100.8-105.0
	Day 2: 99.1-106.7
	Day 3: 99.6-110.0
QC Interday precision range (%CV)	1.8-4.7
QC Interday accuracy range (%Nominal)	100.1-106.7
QC sample bench-top stability	At least 6 hours at room temperature
Stock solution stability	To be determined (refer to section 7)
Processed sample stability	At least 119 hours at room temperature
QC sample freeze/thaw stability	3 freeze (-20 °C)/thaw cycles
QC sample long-term storage stability	To be determined (refer to section 7)
Dilution integrity	200 ng/mL diluted 20 times for colchicine
Selectivity	No interfering peaks were detected at the retention times of colchicine or the IS in blank human plasma.

Source: NDA 210942, Module 5.3.1.4; mut-r126-study-report.pdf, page 6, "Validation Summary Table for the Determination of Colchicine"

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Justin Penzenstadler, Pharm.D.
Primary Clinpharm Reviewer

Bhawana Saluja, Ph.D.
Clinpharm Team Leader

7 Sources of Clinical Data and Review Strategy

7.1. Tables of Clinical Studies

Table 7: Articles from the Public Literature to Support the Efficacy and Safety of Colchicine for Prophylaxis of Gout Flares in Subjects with Chronic Gout

Reference	N	Study Design	Treatment Dose & Duration	Primary Efficacy Outcome
Randomized, Controlled Studies				
Borstad et al., 2004	43	R, PC, DB	Colchicine 1.2 mg QD + Allopurinol	Mean number of gout flares
Paulus et al., 1974	38	R, PC, DB	Colchicine 0.5 mg TID + Probenecid	Attack rate (# gout flares/time) for subjects with sUA<6.5 mg/dL
Non-Randomized, Open-Label Trials				
Becker et al., 2005a	153	Open-label	Colchicine 0.6 mg BID + febuxostat	Incidence of gout flares
Yu et al., 1982	540	Retrospective	Colchicine 0.5-0.6 mg QD	Number of gout flares
Karimzadeh et al., 2005	190	Open-label	Colchicine 1 mg QD + allopurinol	Probability of recurrence of gout flare
Schumacher et al., 2008	772	Open-label	Colchicine 0.6 mg QD or naproxen 250 mg BID + febuxostat	Incidence of subjects requiring treatment of gout flares
Becker et al., 2005b	729	Open-label	Colchicine 0.6 mg QD or naproxen 250 mg BID + febuxostat	Incidence of subjects requiring treatment of gout flares
Submitted but not reviewed				
Wortmann et al., 2010	4,101	Post-hoc reanalysis of 3 Trial	Colchicine, NSAIDs, febuxostat	Incidences of gout flares based on prophylactic treatment

R: randomized; PC: placebo-controlled; DB: double blind; sUA: serum uric acid

Table 8: Applicant-initiated Pharmacokinetics Studies

Study	N	Study Design	Primary Outcome
RMG-COL-PK001	34	R, OL, SD, 3-Way, bioavailability study comparing colchicine oral solution 0.6 mg vs. colchicine & probenecid tablets (0.5 mg/500 mg) under fed/fasted conditions in healthy adult volunteers	Relative bioavailability
RMG-COL-PK002	24	OL, 2-period, sequential studying multiple doses of carvedilol phosphate extended-release capsules on the PK of a single dose of oral colchicine solution in healthy adult volunteers	Drug-Drug interaction
RMG-COL-PK003	24	OL, 2-period, sequential study to assess the effects of multiple oral doses of posaconazole delayed release tablets, ciprofloxacin hydrochloride tablets and amlodipine besylate tablets on the PK of single dose colchicine oral solution in healthy adult volunteers	Drug-Drug interaction
OL: open-label; PK: pharmacokinetics; R: randomized; SD: single-dose			

7.2. Review Strategy

The Division agreed in principle to allow the Applicant to submit the current NDA under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act relying on the Agency's previous findings of clinical safety and efficacy for colchicine in the combination product (probenecid and colchicine), as well as publicly available information as the primary source of data necessary to demonstrate the clinical safety and efficacy of colchicine for the prophylaxis of gout flares in patients with chronic gout. Consequently, the majority of data in this application is derived from the scientific literature provided by the Applicant and supplemented by additional literature researched by this reviewer. Additionally, the Applicant has submitted data from two Applicant-initiated pharmacokinetic (PK) studies. These studies will be reviewed briefly in the Clinical Section of the current review for purposes of safety data analyses. The PK results are discussed in the Clinical Pharmacology Section.

Eight published articles were included in the Applicant's submission to contribute information supporting the clinical efficacy of colchicine for the prophylaxis of gout flares in patients with chronic gout; however, only seven of the eight publications are considered to be of adequate quality or relevance to be used for the purposes of this review. Table 7**Error! Reference source not found.** outlines the studies used to support the efficacy of colchicine in descending order of strength of evidence.

The primary efficacy data are derived from two randomized, placebo-controlled trials using the incidence of gout flares as their primary efficacy endpoints in subjects with chronic gout who were undergoing urate-lowering therapy (Borstad et al, 2004; Paulus, et al, 1974). Further supportive evidence comes from five additional trials. Three of these trials studied colchicine prophylaxis of gout flares as a secondary endpoint in subjects who were receiving febuxostat

for treatment of hyperuricemia (Becker et al., 2005a, Becker et al,, 2005b, Schumacher et al, 2008), one trial was a long-term retrospective study in patients with chronic gout receiving colchicine (Yu et al., 1982), and one was an open-label study in subjects with gout and hyperuricemia designed to evaluate the optimal duration of prophylactic colchicine for prevention of gout arthritis in patients being treated with allopurinol (Karimzadeh et al, 2005).

The eighth study (Wortmann et al., 2010) submitted by the Applicant was an investigator-initiated, post-hoc reanalysis of data on gout flares from the three randomized, placebo-controlled, phase 3 trials with febuxostat that evaluated the proportion of patients requiring treatment for gout flares at 4-week intervals based on mean postbaseline serum uric acid concentrations (<6 mg/dL and ≥6 mg/dL). Subjects received either febuxostat, allopurinol or placebo for six-months or one-year and flare prophylaxis with colchicine 0.6 mg/d or naproxen 250 mg BID for eight-weeks or six-months. The prophylactic regimen was chosen at the discretion of the investigator based on renal function and known intolerance to either drug. Given that this review is based on post-hoc analysis of three varied large studies with differences between study procedures including the length of treatment and collection of data regarding gout flares, the compiled data was deemed not adequately quantified and the assessment of the efficacy of colchicine could not be meaningfully assessed. Consequently, data from this last study was not included for the review.

To support the safety of colchicine for the prophylaxis of gout flares indication, Romeg has submitted an analysis of safety data obtained from the published literature and the results of their pharmacokinetic studies, which will be reviewed in the safety analysis discussion of this review. In addition, this reviewer has supplemented the submitted safety review to include further evaluation of the scientific literature for oral colchicine, regardless of indication, FDA and WHO postmarketing safety databases, and labeling from the U.S. and foreign colchicine products.

There may be limitations to the use of literature reviews for the analysis of clinical trials to serve as the primary source of data to support a marketing application. For example, the design of the studies may have limitations, such as enrolled patients may not represent the target patient population, the primary source data and case report forms are not available for scrutiny, the inability to account for patient dropouts if not mentioned by the study authors, and inability to confirm statistical analyses or perform additional analyses if necessary. Overall, the two randomized and controlled trials by Borstad and Paulus that are used for the primary evidence of efficacy of colchicine were adequately designed and conducted to allow for meaningful interpretation of the results as they relate to the proposed indication of prophylaxis of gout flares. These trials are further supported by the additional open-label and retrospective studies listed above.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Randomized Controlled Studies

Study 1: Borstad GC, Bryant LR, Abel MP, et al. Colchicine for the prevention of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol 2004; 31(12): 2429-2432.

Study Design:
This was a randomized, placebo-controlled trial of 43 subjects with crystal-proven gouty arthritis who met criteria for initiating urate-lowering therapy with allopurinol to assess the ability of colchicine to prevent acute gout flares during initiation of urate lowering therapy. Major inclusion criteria included the presence of tophi, uric acid overproduction, ≥3 gout attacks/yr, elevated serum urate concentrations in the setting of chronic renal insufficiency, and nephrolithiasis. Subjects were excluded from the study if they were under 19 years of age, had received colchicine with the previous 3 months, had a history of allergic reaction to allopurinol or colchicine, had a creatinine clearance <20 mL/min, were female with childbearing potential, or had evidence of active hepatitis. Although the study was double-blinded, the colchicine and placebo tablets were not identical. Subjects initiated allopurinol therapy at a dose of 100 mg daily and increased allopurinol dosing by 100 mg/d increments until serum uric acid was less than 6.5 mg/dL. Subjects received given blinded study drug (placebo or colchicine 0.6 mg BID) for 3 months beyond attaining a serum urate level of <6.5 mg/dL. Subjects were evaluated at 3 and 6 months for gout flares and adverse events, both of which were retrospectively recorded by subjects. The primary analysis population was all subjects who received at least one dose of study medication.

Demographics:
As seen in Table 9, baseline demographics and clinical characteristics were typical of the gout population and were balanced between treatment arms with the exception of diuretic use, which was more common in the colchicine treatment arm (57%) compared to the placebo treatment arm (27%), and alcohol use, 33% vs. 18%, respectively. Since diuretics and alcohol intake are known to increase serum concentrations of uric acid, an increased use of diuretics and alcohol would make subjects more prone to gout flares, so this imbalance would not tend to bias in favor of observing a drug effect.

Table 9: Baseline Demographics and Clinical Characteristics of Enrolled Subjects

Demographic/Characteristic	**Colchicine** (n=21)	**Placebo** (n=22)
Mean Age, years	64	63
Gender, % male subjects	81	91
Race, % Caucasian subjects	67	73
Chronic Renal Insufficiency, % subjects	14	9
Hypertension, % subjects	90	77
Hypothyroidism, % subjects	<1	<1
Coronary Artery Disease, % subjects	29	27
Tophi, % subjects	62	64
Alcohol use, % subjects	33	18
Drugs affecting serum Urate Levels, % subjects	38	55
Diuretic use, % subjects	57	27
Mean Number of Gout Flares during previous year	2.5	2.1

*Table adapted from manuscript

Subject Disposition:

A total of 51 subjects were initially enrolled with 8 subjects discontinuing prior to receiving study drug. The remaining 43 subjects were randomized to receive oral colchicine 0.6 mg BID (n=21) or placebo (n=22). Overall, 36 of 43 (84%) subjects completed the study. Of the 7 subjects withdrawing, 3 (14%) were from the colchicine treatment arm and 4 (18%) subjects were from the placebo treatment arm. The 3 colchicine-treated subjects discontinued the study due to one case each of stroke at 3 months (not considered to be related to colchicine), subjective muscle weakness at 2.5 months without physical or laboratory evidence of muscle damage, and one subject was lost to follow-up after 3 months. Of the four placebo-treated patients who withdrew, two were due to gout flares, one was due to discontinuation of study medication, and one was due to inadequate follow-up. In addition, there was no indication of excess toxicity or irregularities in study management that would have accounted for subjects not completing the study.

Efficacy Analysis:

The intent-to-treat subject population was used for the primary analysis and included all subjects who received ≥1 dose of study drug. Efficacy endpoints at the 3- and 6-month time points included the mean number of gout flares (assessed by T-test), the number of subjects with ≥1 gout flare and the number of subjects with >1 gout flare (both assessed using the chi-square test), the mean pain score per flare by visual analog scale (VAS) and the average length of flare duration (both assessed by using the Mann-Whitney test for nonparametric data).

As demonstrated in Figure 6, subjects treated with colchicine experienced fewer gout flares in the 0-3 month and 3-6 month time periods as compared to placebo-treated subjects. These

differences were clinically and statistically significant. Overall, colchicine-treated subjects had fewer total gout flares compared placebo-treated subjects, 12 vs. 65 flares, respectively. Furthermore, a smaller proportion of patients in the colchicine treatment arm experienced flares or multiple flares compared to the placebo group, 33% and 14% vs. 77% and 63%, respectively.

Figure 6. Mean number of acute gout flares at the 0-3 and 3-6 month time periods and overall*

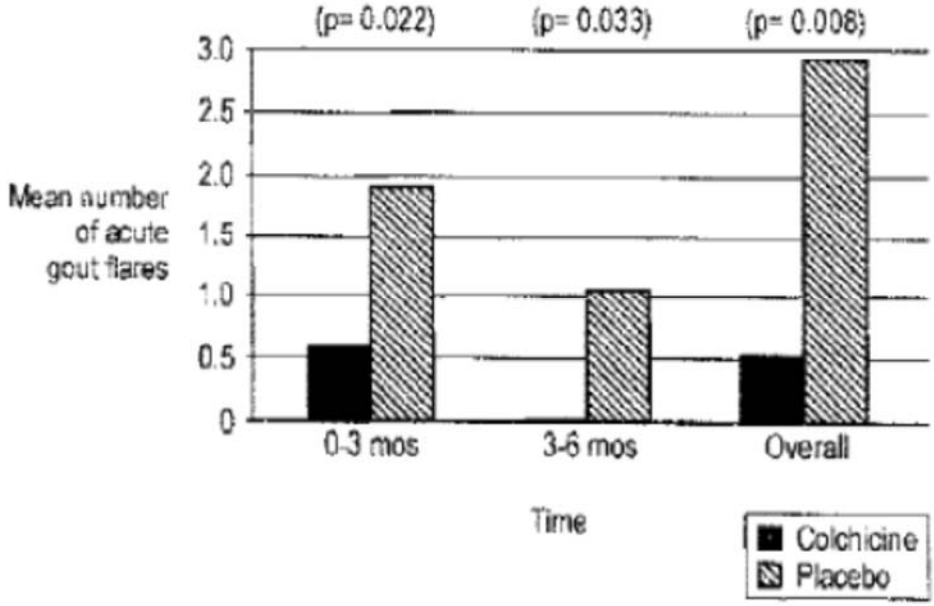

*Figure reproduced from manuscript.

Study 2. Paulus HE, Schlosstein LH, Godfrey RG, et al. Prophylactic colchicine therapy of intercritical gout. A placebo-controlled study of probenecid-treated patients. Arthritis Rheumatol 1974; 17: 609-614.

Study Design:
This was a 6-month, randomized, placebo-controlled, double-blind study of colchicine for the prevention of gout flares in patients with gout starting urate-lowering therapy with probenecid. The study enrolled male subjects with serum urate concentrations >7.5 mg/dL and a history of typical gouty arthritis flares that had responded previously to colchicine therapy. A total of 52 subjects were randomized in a 1:1 ratio to receive oral colchicine 0.5 mg/probenecid or placebo/probenecid three times daily. The study was conducted at two sites, Los Angeles and Kansas City, with minor differences in study conduct. In the Los Angeles site, urate lowering agents were withdrawn two weeks prior to beginning treatment, while in Kansas City, subjects received probenecid for the two weeks prior to receiving treatment. The difference in study design is not expected to affect the interpretation of the results of the trial. Subject reports of gout flares were recorded on a monthly basis. Gout flares that were moderate or severe were included in the analysis with "moderate" or "severe" defined as definitive pain in the joint accompanied by swelling and tenderness. Prior to unblinding of the data, the investigators examined the serum urate concentrations to determine whether probenecid therapy was successful and only those subjects who successfully lowered their serum urate concentrations were included in the analysis. The primary endpoint of the study was the number of gout flares per month of therapy for each subject.

Demographics:
As seen in Table 10, baseline demographics and clinical characteristics were typical of the gout population and were balanced between treatment arms.

Table 10: Baseline Demographics and Clinical Characteristics of Enrolled Subjects

Demographic/Characteristic	**Colchicine + Probenecid** (n=29)	**Placebo + Probenecid** (n=23)
Age (years); mean (range)	53 (34-77)	52 (43-73)
Subjects with tophi	3	4
Duration of gout (years); mean ± SE	11 ± 2	11 ± 2
Gout attacks past 12 months; mean ± SE	4 ±1	3 ± 0.5
Subjects treated with urate lower therapy past 12 months	12	12
Months of therapy	108	94
Serum urate concentration prior to study; (mg/dL)	8.4	9.2

*Table adapted from manuscript

Subject Disposition:

As shown in Table 11, a total of 28 subjects were enrolled at the Los Angeles site with 12 subjects randomized to receive placebo and 16 subjects to receive colchicine. Only 11 of the 12 subjects who were randomized to placebo were analyzed, and of these, only 8 subjects completed the entire 6-month study with the three remaining subjects being lost to follow-up after 1, 2, and 4 months. Similarly, 15 of the 16 subjects who were randomized to receive colchicine were analyzed, but only 12 of the subjects completed the entire 6-month study, with the three remaining subjects being lost to follow-up before 4-months. The Kansas City site enrolled a total of 24 subjects with 11 subjects randomized to receive placebo and 13 subjects to receive colchicine but only 12 subjects were included in the analysis (5 placebo-treated subjects and 7 colchicine-treated subjects) due to non-compliance of the drug regimen as per the author. Additionally, one colchicine-treated subject was not included due to the discontinuation due to an adverse event (alopecia). In total, 38 of 52 (73%) subjects were analyzed between the two study sites with 18 subjects treated with placebo and 20 subjects treated with colchicine.

Table 11: Subject Disposition

	Placebo + Probenecid	**Colchicine + Probenecid**	**Total**
Los Angeles Site			
Subjects Enrolled (n)	12	16	28
Subjects analyzed	11	15	26
Kansas City Site			
Subjects Enrolled (n)	11	13	24
Subjects analyzed	4	7	12

*Table adapted from manuscript

Efficacy Analysis:

As discussed above, 38 subjects were included in the analysis of the primary endpoint which was defined as the number of gout flares per month of therapy for each subject. As shown in Table 12, colchicine/probenecid-treated subjects had a lower rate of gout flares per month compared to placebo/probenecid-treated subjects, 0.19 vs. 0.48, respectively. It is also important to note that probenecid lowered serum urate concentrations similarly between treatment arms suggesting that the difference in gout flare rates was due to concomitant colchicine therapy and not due to lowering of serum urate concentrations by probenecid.

Table 12: Effects of Therapy

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

*$P < 0.05$
†$P < 0.01$
‡$0.1 > P > 0.05$ (chi square analysis)
*Table reproduced from manuscript.

Supportive Studies

Five published open-labeled studies further support the efficacy of colchicine in the prevention of gout flares.

Study 1: Becker MA, Schumacher HR, Wortman RL, et al. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase. A twenty-day, multicenter, Phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. Arthritis Rheum 2005; 52:916-923.

This study was a randomized, double-blind, placebo-controlled trial of 153 subjects with gout and hyperuricemia. Subjects were randomized 1:1:1:1 to receive placebo or one of three doses of febuxostat (40 mg, 80 mg, or 120 mg), a xanthine oxidase inhibitor intended to lower serum urate concentrations. Subjects received study drug for 28 days and colchicine 0.6 mg BID for gout flare prophylaxis for the 14 days prior to and 14 days after initiation of study drug. The primary endpoint was the proportion of subjects with serum urate concentrations below 6 mg/dL on Day 28. As seen in Table 13, gout flares occurred with a similarly low frequency (8-13%) in the placebo and febuxostat treatment arms when subjects received concomitant colchicine; however, during the period of the study when subjects were not treated with colchicine, gout flares markedly increased greater than 5-fold. The results of this study provide strong supportive evidence demonstrating the efficacy of colchicine in preventing gout flares in this patient population.

Table 13: Incidence of Gout Flares

		Febuxostat		
Study Period	**Placebo (n=38)**	**40 mg/d (n=37)**	**80 mg/d (n=40)**	**120 mg/d (n=38)**

Entire Study Period, %	37	35	43	55
Colchicine/Study Drug, %	11	8	8	13
Study Drug Only, %	34	30	40	42

* Table adapted from manuscript.

Study 2: Yu, TF. The efficacy of colchicine prophylaxis in articular gout- a reappraisal after 20 years. Seminar Arthritis Rheum 1982; 12:256-264

This open-label, retrospective study evaluated the experience of 540 subjects (518 males and 22 females) who were treated with colchicine for up to 20 years. Eighty-one percent of subjects had 3 or more gout flares per year and 53% of the subjects had a serum urate concentration greater than 10 mg/dL with 69% reporting tophi and 30% having a history of renal calculi. Overall, 75% of subjects reported comorbidities typically seen in the hyperuricemic/gout population including 48% subjects with hypertension, coronary artery disease or cerebrovascular disease. The majority of subjects had received colchicine 0.5 mg to 1 mg daily for prophylaxis of gout flares. Although the study is limited by the fact that it was not randomized and is based on retrospective data, the results shown in Table 14 demonstrate a strong association between colchicine prophylaxis and the reduction of gout flares.

Table 14: Recurrent Acute Attacks Before and After Colchicine Prophylaxis

Attacks/Year During Colchicine Prophylaxis	Attacks/Year Before Colchicine Prophylaxis									
	1–2		3–4		5–9		10–12		Total	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Hardly Any Attacks	89	(88)	143	(76)	57	(54)	74	(50)	363	(67)
Gradually Decreased to 0–1	6	(6)	20	(11)	25	(24)	32	(22)	83	(15)
1–2	1	(1)	19	(10)	16	(15)	29	(20)	65	(12)
Milder, Not Less	5	(5)	5	(3)	6	(6)	9	(6)	25	(5)
Unchanged	0	(0)	0	(0)	1	(1)	3	(2)	4	(1)
Total No. (%)	101	(19)	187	(35)	105	(19)	147	(27)	540	

*Table reproduced from manuscript.

Study 3: Karimzadeh H, Nazari J, Mottaghi P, et al. Different duration of colchicine for preventing recurrence of gouty arthritis. J Res Med Sci 2006; 11:104-107.

This study enrolled 229 subjects with gout and hyperuricemia and was designed to evaluate the optimal duration of prophylactic colchicine for prevention of gout arthritis in patients being treated with a urate-lowering agent. Entry criteria stipulated that subjects had to have a diagnosis of ≥1 year and had at least one indication of long-term treatment with urate-lowering therapy. All subjects received allopurinol and were randomly divided into three groups receiving oral colchicine 1 mg/d for 3-6 months (Group 1), 7-9 months (Group 2), and 10-12 months (Group 3). Colchicine was subsequently discontinued at the end of the prescribed timeline per treatment arm and subjects were followed for one year for evidence of gout flares.

One-hundred-ninety of 229 (83%) subjects completed follow-up and were included in the final analysis of the study. At the end of six-months, the probability of a gout flare was 46%, 11%, and 6%, respectively, and at the end of one year, the probability of a gout flare was 54%, 28%, and 23%, respectively. The proportion of subjects who experienced recurrence of gout symptoms and mean time to recurrence was similar in the groups that received colchicine prophylaxis for 6-9 months and for 10-12 months. These data demonstrate that colchicine prophylaxis for more than 6 months was associated with a lower rate of recurrence of gout. Overall, these data support the efficacy of colchicine to prevent gout flares in this patient population.

Study 4: Schumacher HR, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008; 59:1540-1548.

This was a randomized, double-blind, allopurinol- and placebo-controlled, parallel-group, multicenter trial designed to compare the urate-lowering efficacy and safety of febuxostat, allopurinol, and placebo in subjects with hyperuricemia (≥8 mg/dL) and gout. Eligible subjects were randomized in a 2:2:1:2:1 ratio to once daily febuxostat 80 mg, febuxostat 120 mg, febuxostat 240 mg, allopurinol, or placebo. Those subjects who had been taking a urate-lowering agent were required to undergo a two-week washout period prior to being randomized. Subjects were prescribed either naproxen 250 mg BID or colchicine 0.6 mg/d for gout flare prophylaxis during the washout period and first eight weeks of the study. The primary endpoint of the study was the proportion of subjects with serum urate concentrations below 6 mg/dL in the last three monthly measurements. A major clinical secondary endpoint was the proportion of subjects requiring treatment for acute gout flares between weeks 8 and 28. Between weeks 8 and 28, after gout flare prophylaxis was discontinued, there were no statistically significant differences in the proportion of subjects requiring treatment for gout flares observed between the treatment arms. Furthermore, the proportion of subjects requiring treatment for gout flares tended to diminish with continued urate-lowering therapy. Conversely, during the first eight weeks of the study when gout flare prophylaxis was administered, a larger proportion of subjects receiving febuxostat 120 mg and 240 mg required treatment for acute gout flares compared to the febuxostat 80 mg, febuxostat 120 mg, allopurinol, and placebo treatment arms. However, since the data presented in the publication does not specify the rates of gout flares for subjects receiving colchicine compared to a control arm, it is difficult to assess whether colchicine was efficacious in decreasing the number of gout flares or if the result was due to naproxen or febuxostat-induced lowering of serum uric acid concentrations. In total, this publication does not lend supportive evidence of the efficacy of colchicine for the prophylaxis of gout flares during urate-lowering therapy.

Study 5: Becker MA, Schumacher HR, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005; 353:2450-2461.

This study was a randomized, double-blind, 52-week, multicenter trial, comparing the efficacy of febuxostat with allopurinol in subjects with gout and hyperuricemia greater than 8 mg/dL. Subjects who were previously receiving urate-lowering therapy underwent a two-week washout period prior to randomization. On Day 1 of the trial, subjects were randomized 1:1:1 to receive febuxostat 80 mg/d, febuxostat 120 mg/d, or allopurinol 300 mg/d. Due to the known increase in gout flares associated with the initiation of urate-lowering therapy, subjects received prophylaxis with either naproxen 250 mg BID or colchicine 0.6 mg/d during the washout period and for the first eight weeks of the study. The primary endpoint of the study was the proportion of subjects with serum urate concentrations below 6 mg/dL in the last three monthly measurements. A major clinical secondary endpoint was the proportion of subjects requiring treatment for acute gout flares from weeks 9 through 52. During weeks 9 through 52, similar proportions of subjects in each treatment arm required treatment for ≥1 gout flare. In contrast, during the 8-week prophylaxis period, a significantly lower amount of subjects required treatment for gout flares. Withdrawal of prophylaxis of naproxen or colchicine at Week 9 was accompanied by a clearly increased incidence of gout flares in all treatment arms. As discussed above, since the data presented in the publication does not specify the rates of gout flares for subjects receiving colchicine compared to a control arm, it is difficult to assess whether colchicine was efficacious in decreasing the number of gout flares or if the result was due to naproxen or febuxostat-induced lowering of serum uric acid concentrations. In total, this publication does not lend supportive evidence of the efficacy of colchicine for the prophylaxis of gout flares during urate-lowering therapy.

DESI REVIEW

The DESI review of Col-Benemid, a probenecid/colchicine combination product, included the review of two publications in support of the clinical efficacy of colchicine in preventing gout flares:

- Gutman AB. Treatment of primary gout: the present status. Arthritis Rheum 1965; 8:911-920.
- Yu TF, Gutman AB. Efficacy of colchicine prophylaxis in gout. Prevention of recurrent gouty arthritis over a mean period of five years in 208 gouty subjects. Ann Intern Med 1961; 55:179-192.

Gutman summarized his clinical experience of treating patients with gouts as follows:

> "The ideal double-blind, long-term, large-scale study of the efficacy of prophylaxis has yet to be reported. Nevertheless, there is now a considerable experience with colchicine prophylaxis by a number of observers, and when the frequency and severity of acute attacks with colchicine prophylaxis are compared to the course anticipated without such treatment, in the gouty population at risk and in the individual patient, there can be little question as to the value of the preventive program."

Table 15 shows Gutman's summary of his clinical experience that included 260 patients, who he deemed reliable in giving their history prior to initiating colchicine prophylaxis, with severe (≥4 gout flares/year) or moderately severe (repeated interruption of work by one or two fulminating and protracted seizures *[sic]* and/or multiple minor attacks/year).

Table 15: Effect of colchicine prophylaxis, with or without concomitant uricosuric therapy, on the course of recurrent acute arthritis in subjects followed ≥2 years

	Before		After	
	No.	%	No.	%
Severe	101	39	6	2
Moderately severe	159	61	32	12
Mild			82	32
Virtually no attacks			138	53

*Table reproduced from manuscript

In the study published by Yu and Gutman, the authors describe their study of 208 subjects who had an established pattern of recurrent gouty arthritis. Seventy-six of these subjects were identified as severe cases and unable to work regularly due to ≥4 or more gout flares/year. The remaining 132 subjects had moderately severe disease with several attacks/year that were also associated with interruption of work. Oral colchicine prophylaxis was initiated at 1 to 1.2 mg daily and maintained in 66% of subjects for ≥2 years. Subjects who could not tolerate this dose of colchicine decreased the dose to 0.5 mg/d. Eighty-nine of 208 (43%) subjects received a concomitant uricosuric agent in addition to colchicine. Table 16 shows that in general, colchicine-treated subjects had a reduction in the number of gout flares regardless of whether or not a uricosuric agent was added to their regimen, and further supports that the reduction in recurrent gout flares is due to colchicine and not urate-lowering therapy.

Table 16: Colchicine prophylaxis and recurrent gout flares

	A. Colchicine Alone			B. Colchicine and Uricosuric Agents		
Response	Severe Cases	Moderately Severe Cases	All Cases	Severe Cases	Moderately Severe Cases	All Cases
Excellent	29(66%)	60(80%)	89(75%)	23(72%)	41(72%)	64(72%)
Satisfactory	10(23%)	12(16%)	22(18%)	7(22%)	13(23%)	20(22%)
Unsatisfactory	5(11%)	3(4%)	8(7%)	2(6%)	3(5%)	5(6%)

*Table reproduced from manuscript.

Although the two studies are retrospective and uncontrolled, these studies provide support for the efficacy of colchicine when used to prevent recurrent gouty flares.

8.2. Review of Safety

Given the nature of this primarily literature-based 505(b)(2) application, there are a number of limitations in the safety data in this submission:

- The safety data provided by the Applicant are not reported using a standardized coding dictionary such as COSTART or MedDRA. Additionally, since the safety data were not collected from Applicant-initiated clinical trials, the data are not presented in a manner that directly compares the types or incidences of adverse events between an active treatment arm and a placebo treatment arm from a randomized trial.
- One limitation of using the publicly available data is that only the more serious and life-threatening AEs or those resulting in death are likely to be reported to the FDA and WHO databases or published in the literature. Thus, this safety review is likely to be skewed toward the more serious AEs and less so toward common and less severe AEs.

However, on balance, this review has included numerous sources of reliable safety data and categorized these data in a manner that facilitated adequate assessment of the safety of orally administered colchicine. These data are consistent in supporting the conclusion that orally administered colchicine is generally well-tolerated when used in therapeutic doses and adjusted for patients with renal and/or hepatic insufficiency. Gastrointestinal AEs are typically the most common toxicity and when severe can be viewed as the harbinger of more serious colchicine toxicity and allows for discontinuation/dose adjustment to prevent serious toxicity from occurring. Even with long-term treatment, AEs other than gastrointestinal toxicities are uncommon (<15%). The majority of significant AEs that do occur are most often related to inappropriate dosing in patients with renal or hepatic insufficiency, concomitant drug-interactions, or intentional/unintentional overdosing. Serious and life-threatening AEs associated with colchicine include myelosuppression, leukopenia, pancytopenia, agranulocytosis, thromboocytopenia, neuromuscular toxicity, and rhabdomyolysis.

8.2.1. Clinical Studies Used to Evaluate Safety

Colchicine has been used clinically as a single drug entity for over 70 years and its safety profile has been well-documented over this period of time and did receive approval as part of the DESI reviews in 1972 as the combination product Col-Benemid (colchicine 0.5 mg and probenecid 500 mg) for use in patients with chronic gouty arthritis. The data submitted for safety analysis in this review are compiled from a thorough review of the scientific literature for oral colchicine, regardless of indication, FDA and WHO postmarketing safety databases, labeling from US and foreign colchicine products, and three Applicant-initiated, Phase 1 PK studies

(Table 17). This review focuses solely on the safety for the oral administration of colchicine since the Applicant is seeking an indication to use oral colchicine for prophylaxis of gout flares.

Table 17: Sources of Safety Data

Source	Population	N	Data Source / Study Design
Applicant's Pharmacokinetic Studies	Healthy Adults	84	Single- and multiple-dose pharmacokinetic and drug-drug interaction studies (83 subjects single dose/1-day regimen and 43 subjects 10- to 14-day steady state regimen)
Medical Literature			
Efficacy studies in FMF	Adults and children	3545	3 randomized and 21 non-randomized studies contributing efficacy data
Meta-analyses of studies in other indications (Cochrane Reviews)	Randomized. controlled trials	443	11 studies in patients with alcoholic and non-alcoholic cirrhosis (Rambaldi et al., 2005)
		228	11 studies in patients with primary biliary cirrhosis (Gong et al., 2004)
Case reports	--	--	Additional case reports of adverse effects
Postmarketing Safety Data			
U.S. Food and Drug Administration	Primarily U.S. but includes foreign reports	--	751 adverse event reports from 1969 through 30 June 2007
World Health Organization	79 countries including the U.S.	--	1380 adverse event reports from 1968 – March 2006
Labeling			
Col-Probenecid (Watson—US; ANDA 84-279)	--	--	FDA-approved probenecid and colchicine combination product (500 mg-0.5 mg), providing for a maximum daily colchicine dose of 2 mg
Other Countries	--	--	Labeling from oral colchicine obtained from Argentina, Australia, Britain, Germany, Mexico, France, Singapore, and Uganda

*adapted from Applicant's submission and reviewer's analysis of scientific literature

Applicant-Initiated Studies

The safety data from the three Applicant-initiated PK studies enrolling a total of 84 subjects will be discussed in this section of the review. The three PK studies are briefly outlined below and

the reader is directed to the Clinical Pharmacology section of this review for a detailed description of the study designs and efficacy results.

Study RMG-COL-PK001 was designed as a randomized, open-label, single-dose, 3-way, relative bioavailability study of colchicine oral solution 0.6 mg under fed and fasted conditions compared with probenecid/colchicine (500 mg/0.5 mg) tablets USP under fed and fasted conditions in healthy adult volunteers. A total of 36 subjects were randomized and 34 (83%) completed the study. Of the two subjects who did not complete the study, one was withdrawn at the subject's request and one was noncompliant with the protocol. There were no deaths, SAEs, or AEs of moderate or severe intensity during the course of the study. The types and frequency of AEs were similar across treatment groups and were consistent with the known safety profile of colchicine including headache and nausea. No new safety signals were identified.

Study RMG-COL-PK002 was designed as an open-label, two-period, sequential study to assess the effects of multiple oral doses of carvedilol phosphate extended-release capsules on the PK of a single dose of colchicine oral solution in healthy adult volunteers. A total of 24 subjects were randomized and 21 (88%) completed the study. Of the three subjects who did not complete the study, one was withdrawn at the subject's request, one was noncompliant with the protocol, and the third subject tested positive for drug screen at Period 2 of the admission. There were no deaths, SAEs, or AEs of moderate or severe intensity during the course of the study. There was only one (4%) subject reporting an AE in the colchicine treatment arm (viral infection) compared to two (10%) subjects in the carvedilol 20 mg arm and three (14%) subjects in the carvedilol 40 mg treatment arm. A total of four (19%) subjects reported an AE in the combination arm of colchicine 0.6 mg and carvedilol 40 mg treatment arm. In general, the types and frequency of AEs were similar across treatment groups and were consistent with the known safety profile of colchicine and/or carvedilol. No new safety signals were identified.

Study RMG-COL-PK003 was designed as a three-cohort, open-label, two-period, sequential study to assess the effects of multiple oral doses of posaconazole delayed release tablets, ciprofloxacin tablets, and amlodipine tablets on the PK of a single dose of colchicine oral solution in healthy adult subjects. A total of 24 subjects were randomized and 22 (92%) completed the study. Of the two subjects who did not complete the study, one was withdrawn at the subject's request and one was noncompliant with the protocol. There were no deaths, SAEs, or AEs of moderate or severe intensity during the course of the study. The types and frequency of potential colchicine-related AEs were similar across treatment groups and were consistent with the known safety profile of colchicine including headache and nausea. No new safety signals were identified.

Published Scientific Literature

Comprehensive database searches were performed to identify publications relating to the clinical safety of colchicine. Search terms included colchicine and terms related to adverse event (e.g., safety, adverse effect, adverse reaction, toxic, drug reaction) as well as specific organ system classes (e.g., kidney, renal, bladder, urinary, urethra). For all searches, all titles and abstracts were reviewed for safety information and references or the retrieved publications were examined for information and selected primary sources were obtained as needed.

Postmarketing Safety Data

A summary of the marketing experience with colchicine was conducted using the Spontaneous Reporting System (ADR Database; 1969 to 1997) and the FDA's Adverse Event Reporting System (AERS Database; 1977 to 2008). Approximately 751 MedWatch reports were obtained in which colchicine was a primary or secondary suspected drug. Additionally, review of the literature obtained reports of AEs for colchicine that were submitted to the WHO, which include both regulatory as well as voluntary reports. A total of 1380 reports were obtained from 79 countries between 1968 and 2006.

Labeling

A review of safety information from the US package insert for the generic combination product, colchicine-probenecid was reviewed. Additional safety information is provided from 6 foreign labels involving colchicine: Argentina (Xuric), Australia (Colgout; Lengout), France (Colchimax, Colchicine-Opocalcium), Germany (Colchysat), Mexico (Cochiquim), Signapore (Colchicine tablets), Uganda (Goutnil), and the UK (Colchicine tablets).

8.2.2. Adequacy of Data

The bulk of the safety data in this submission are derived from the published literature and therefore have inherent limitations as discussed above in the safety summary. However, the literature is a rich source of safety data with regard to colchicine's toxicities and these toxicities have been well described in the long history of its clinical use. Thus controlled data are not necessary to explore for potential safety signals, as would be important for a new molecular entity, and sufficient information exists to adequately inform the colchicine label. In this submission, the Applicant has provided a comprehensive and well-organized safety section that facilitates the assessment of safety.

8.2.3. Pooling Data Across Studies to Estimate and Compare Incidence

The data presented for the analysis of safety was acquired largely from publications, product labels, and postmarketing safety reports and is not amenable to pooling.

Major Safety Results

Orally administered colchicine is generally well-tolerated when used in therapeutic doses and adjusted for patients with renal and/or hepatic insufficiency. Therapeutic concentrations of colchicine range from 0.015 to 0.03 mg/kg. Toxicity is noted when given in concentrations greater than 0.1 mg/kg and lethal at doses exceeding 0.8 mg/kg. Gastrointestinal AEs are typically the most common toxicity and when severe can be viewed as a harbinger of more serious colchicine toxicity. Even with long-term treatment, AEs other than gastrointestinal toxicities are uncommon. The majority of significant AEs that do occur are most often related to inappropriate dosing in patients with renal or hepatic insufficiency, concomitant drug-interactions, or intentional/unintentional overdosing.

8.2.4. Deaths

There were 234 deaths reported from the estimated 751 total reports obtained from the ADR and AERS databases for colchicine. A total of 169 of the 234 (72%) deaths were associated with oral colchicine with the remaining deaths due to either an unspecified (19%) or intravenous (9%) route administration. The disproportionate number of reported deaths with oral colchicine likely reflects the far greater use of oral colchicine compared to intravenous route of administration. Of the 169 reports of death associated with oral administration, 96 (57%) reported actual dosages of colchicine but overall 117 (69%) of the reports were not reported as overdoses and the majority reported colchicine doses were in the therapeutic range of ≤2 mg/day. No information was obtained regarding patients' renal or hepatic function which may increase colchicine toxicity.

Deaths reported in the published literature were generally associated with acute or chronic overdoses of colchicine or drug interactions with concomitant potent P-gp inhibitors. No deaths were reported in the Applicant-initiated PK studies.

8.2.5. Nonfatal Serious Adverse Events

For purposes of this review, serious adverse events and significant adverse events will be discussed together. Given the different sources used to analyze safety data, discussion of colchicine's adverse events will be organized based on the originating source of data as follows: Applicant-initiated PK studies, published scientific literature, postmarketing safety data, and labeling.

Adverse Events from Applicant-Initiated PK Studies

There were no SAEs or AEs of severe intensity reported in any of the three Applicant-initiated PK studies. The types and frequency of potential colchicine-related AEs were similar across treatment groups and were consistent with the known safety profile of colchicine including headache, nausea, flatulence and abdominal pain. No new safety signals were identified and none of the AEs required discontinuation from the study

Adverse Events from Published Scientific Literature

This section will review the AEs by organ system from the published scientific literature obtained through the Applicant's and reviewer's database searches. Many of these reports are the serious toxic manifestations associated with colchicine, e.g., bone marrow suppression, disseminated intravascular coagulation, and cellular injury. Many of these effects have occurred after attempted suicide with very large amounts of colchicine.

Cardiovascular System

No cardiovascular AEs with therapeutic doses of colchicine were identified in the literature search; however, AEs were identified with colchicine overdosing.

Gastrointestinal System

Gastrointestinal effects are the most common side effect in patients receiving colchicine and include abdominal pain, cramping, diarrhea, and vomiting. Generally, these symptoms are mild, transient, and reversible upon discontinuation of the drug or reduction of the dose; however, if the symptoms are severe they may be an indication of more significant toxicity. Table 18 shows the incidence of AEs from two randomized, placebo-controlled, double-blinded studies in patients treated for prevention of acute gout. The incidence of the AEs is similar to that reported in various review articles.

Table 18. Adverse Events in Two Randomized, Placebo-Controlled Trials for Acute Gout

	Colchicine	Placebo
Borstad et al., 2004	0.6 mg once or twice daily × 3 months	
N	21	22
Any AE	9 (43%)	8 (36%)
Diarrhea	8 (36%)	1 (5%)
Paulus et al., 1974	0.5 mg TID × 6 months	
N	20	18
Any AE	15 (75%)	8 (44%)
Gastrointestinal AEs	15 (75%)	8 (44%)
Diarrhea	9 (45%)	6 (33%)
Nausea, vomiting, or anorexia	11 (55%)	5 (28%)
Steadily increasing SGOT / SGPT	1 (5%)	0

Hepatotoxicity

No serious hepatotoxic AEs with therapeutic doses of colchicine were identified in the literature search. Even with severe colchicine toxicity, hepatotoxicity is an uncommon manifestation and may present as hepatomegaly with liver tenderness and increased transaminases. One review from the literature search reported elevations in serum transaminases are frequently seen in FMF patients treated with colchicine. It was unclear whether the elevation was caused by liver or muscle toxicity.

Hematologic and Lymphatic System

Myelosuppression is a known dose-related AE associated with colchicine. Life-threatening granulocytopenia and/or thrombocytopenia may occur 24 to 48 hours after an acute overdose. Several published reports of leukopenia and granulocytopenia were identified from the literature search as well as one report each of thrombocytopenia, pancytopenia, and aplastic anemia with colchicine use in typical doses, although the doses were not adjusted appropriately for the patient's renal and/or liver function.

One publication studied the epidemiology of aplastic anemia in France based on a national registry over an approximate 10-year period in 83 medical centers. Associations between medical conditions, drug use, and aplastic anemia were approximated by using a case-control series for a 3-year period. A significant association was found with any use of colchicine. There was an odds ratio of 13 (95% CI: 1.5-115) compared to controls when the association was limited to use within the year prior to onset of aplastic anemia.

Leukopenia

Three cases of leukopenia were identified and brief narratives appear below. The first case occurred in an otherwise healthy young female being treated with colchicine 1.5 mg/day for two years for FMF with a positive dechallenge and rechallenge. The other two cases involved doses of colchicine that were likely inappropriate given their medical status.

- A 19-year-old female patient with FMF was being treated with colchicine 1.5 gm/day over a two year period when a routine blood count demonstrated a WBC of 2650/mm^3. The patient discontinued colchicine and had an increase in her WBC; however, after restarting colchicine, her WBC decreased. Further diagnostic evaluation suggested a recent CMV infection and following a recovery period she was rechallenged with colchicine and did not experience any further episodes of leukopenia despite treatment with colchicine.
- A 76-year-old female with primary biliary cirrhosis and "adult polycystic liver disease" developed granulocytopenia while being treated with colchicine 1.2

mg/day for 2 months. The patient was also receiving concomitant hydrochlorothiazide/amiloride. During an evaluation she was found to be leukopenic with a WBC of 1500/mm^3 and both medications were discontinued. Four days later her WBC had risen to 5100/mm^3 and her hydrochlorothiazide/amiloride was restarted without a recurrence of the granulocytopenia.

- A 68-year-old male treated with colchicine 0.6 mg BID for 3 years was hospitalized for an attack of acute gout. Upon admission his dose of colchicine was increased to 0.6 mg every four hours and subsequently decreased to 0.6 mg TID on hospital day 2 and further reduced to 0.6 mg QD on hospital day 4 due to diarrhea. Colchicine was discontinued on hospital day 9. The patient also had a medical history significant for diabetes mellitus, COPD, SVT, and cardiomyopathy (EF 38%). Concomitant medications included metformin, glyburide, verapamil (a moderate P-gp inhibitor), warfarin, theophylline, KCl, lisinopril, digoxin (P-gp substrate/inhibitor), metolazone, ASA, lansoprazole (P-gp inhibitor), various inhalers and a nasal spray. During the four day period his WBC decreased from 11.2 x 10^3/mm^3 to 2 x 10^3/mm^3. He was administered G-CSF on hospital days 9 and 12 with a resulting increase in his WBC to 18 x 10^3/mm^3.

Agranulocytosis

A single report was identified of an 86-year-old female with end-stage renal disease who was started on colchicine 0.5 mg/day for gouty arthritis and subsequently developed agranulocytosis. Seven days after starting colchicine the drug was discontinued due to diarrhea. At the start of therapy her WBC was 8700 cells/mm^3 (67% neutrophils) but decreased to 3500 cells/mm^3 by day 7. On day 9 her neutrophil count was <500 cells/mm^3. A serum colchicine level was found to be 6 µl/L, which is two-times the upper limit of normal. The patient's neutrophil count subsequently returned to normal.

Thrombocytopenia and Leukopenia

A 69-year-old male on no medications was administered intravenous colchicine 4 mg/day for 2 days to treat an attack of acute gout, followed by oral colchicine 2 mg/d for 3 months. After 2 months of therapy the patient was found to have an elevated GGT level and thrombocytopenia (<10 x 10^3/mm^3). Colchicine was discontinued and his platelet count increased to 70 x 10^3/mm^3 over the following 2 months. One month later he developed thrombocytopenia again as well as leukopenia. He was treated with corticosteroids and improved; however, a bone marrow biopsy revealed a hypocellular marrow. The patient remained in stable condition.

Pancytopenia

A single report was identified of pancytopenia in a young female patient receiving no other medications but with hepatic and renal insufficiency. The patient was a 46-year-old female treated with colchicine 0.5 mg TID for polyarticular gouty arthritis. Three days after starting colchicine she presented with common signs of colchicine toxicity (abdominal pain, jaundice, moderate sensorimotor polyneuropathy, and alopecia) and was found to have developed pancytopenia with a nadir WBC of 0.24 x 10^9/L, Hgb of 8.4 g/dL, and platelet count of 54 x 10^3/mm^3. Bone marrow aspirate was consistent with drug-induced marrow suppression. Colchicine was discontinued and the patient received G-CSF and made a full recovery after 7 months.

Metabolic and Nutritional Disorders

No metabolic or nutritional disorder AEs with therapeutic doses of colchicine was identified in the literature search; however, AEs were identified with colchicine overdosing.

Musculoskeletal System

Neuromuscular Toxicity

Colchicine-induced neuromuscular toxicity is a rare adverse event associated with short- and long-term use. Patients have generally received standard oral doses of colchicine but frequently have renal impairment or are elderly and may have received excessive exposures. The typical presentation is that of proximal muscle weakness and pain that may also include mild sensory polyneuropathies. The effects are typically reversible within weeks to months following the discontinuation of colchicine.

Patients with renal impairment and elderly patients, even with normal renal and hepatic function, are at increased risk to develop colchicine-induced neuromuscular toxicity. Concomitant use of statins, fenofibrate, or cyclosporine may potentiate the development of myopathy.

Two reviews were identified that described case series of colchicine-related myopathies.

- Wilbur et al (2004) reviewed 75 published cases of colchicine-induced myopathy (mean age 58 years) and found the mean daily dose of colchicine was 1.4 mg with the duration of therapy ranging from 4 days to 11 years (mean 40 months). The majority of patients with myopathy also had either renal failure or had undergone renal transplant and had been taking standard doses of colchicine. In numerous cases, colchicine toxicity presented after short-term use of increased doses or after a recent change in the underlying disease state (e.g., organ transplant, decreased renal function).
- Wallace et al (1991) reported 17 consecutive patients with gout who had neuromyotoxicity. The patients averaged 66-years of age and all had at least a moderate degree of renal impairment. Serum creatinine was significantly

higher in these 17 patients compared to 15 matched colchicine-treated patients from the same practice without myotoxicity.

The database search also identified two novel manifestations of colchicine-induced neuromuscular toxicity which included a case of severe bilateral optic neuromyopathy and one case of involvement of respiratory muscles. Both patients recovered following discontinuation of colchicine.

Rhabdomyolysis

The literature search identified several cases of colchicine-associated rhabdomyolysis. One publication reported on 475 patients hospitalized for rhabdomyolysis. Of these, 8 cases were attributed to colchicine therapy, although details of the cases were not reported.

A second publication was a case report describing rhabdomyolysis is a 24-year-old female with FMF and severe renal impairment due to secondary amyloidosis. She had been taking colchicine 1 mg QD for 1 year and prior to her hospital admission had developed gastrointestinal symptoms and proximal muscle weakness in both legs. She was found to have an elevated CK and marked myoglobulinuria as well as renal failure. Following supportive treatment and reduction of the colchicine dose to 0.5 mg QD she recovered to her baseline health status.

Nervous System

A proportion of patients who develop colchicine-induced myopathy also experience a mild sensory polyneuropathy with distal areflexia and a minor distal sensory loss. The neuropathy typically improves following discontinuation of colchicine.

Respiratory System

No respiratory AEs with therapeutic doses of colchicine were identified in the literature search; however, AEs were identified with colchicine overdosing.

Skin and Appendages

The literature search identified several reports of rash associated with colchicine. These included a maculopapular rash occurring on the lower extremities, a single reported case of colchicine-induced toxic-epidermal-necrosis-like syndrome complicated by concomitant administration of allopurinol, and a single case of vascular purpura in a 33-year-old male.

Alopecia is clearly associated with colchicine overdose but has also been described with chronic colchicine use in children with FMF. Two publications reported a total of 3 children with FMF who developed alopecia.

Urologic System

The literature search identified one publication that reported two cases of Peyronie's disease while receiving chronic colchicine therapy for FMF; however, the clinical significance of these cases are unclear.

Postmarketing Safety Data

The most common AEs associated with colchicine as reported to the FDA's ADR and AERS databases are shown in Table 19. Data from the ADR database demonstrates that diarrhea, myopathy, and pancytopenia were the most commonly reported AEs prior to 1997, and using the AERS database showed that diarrhea, drug interactions, vomiting, acute renal failure, and nausea have been the most common events since 1997. Individual cases were not reviewed further.

Table 19: Adverse Events reported from the FDA's ADR and AERS Databases

FDA ADR Database (1969-1997)	# Reports (n=241)	FDA AERS Database (1997-2007)	# Reports (n=510)
Diarrhea	29	Diarrhea	69
Myopathy	21	Drug interaction	69
Pancytopenia	19	Vomiting	65
Overdose	18	Renal failure acute	59
CK elevation	17	Nausea	54
Hypotension	17	Gout	50
Neuropathy	17	Diarrhea NOS	49
Intentional overdose	15	Blood creatinine increased	44
LFT abnormality	12	Abdominal pain	43
Acute kidney failure	11	Pyrexia	41
Asthenia	11	Rhabdomyolysis	40
Leukopenia	10	Completed suicide	35
Sepsis	10	CK elevation	34
Thrombocytopenia	10	Myopathy	32
Agranulocytosis	9	Pancytopenia	31
Shock	9	Vomiting NOS	31
Apnea	8	Dehydration	30

Dehydration	8	Asthenia	28
Kidney function abnormal	8	AST elevation	27
Marrow depression	8	Renal Failure NOS	27
Myasthenia	8		
Peripheral neuritis	8		

The most common AEs associated with colchicine treatment were obtained from the WHO database and included diarrhea, vomiting and nausea (Table 20). Individual cases were not reviewed further.

Table 20: Adverse Events Reported from the WHO database

WHO 1968 – March 2006 Adverse Event Term	No. Reports
Total	1380
Diarrhea	382
Vomiting	117
Nausea	80
Rash	78
Pruritus	62
Renal Failure Acute	56
Abdominal Pain	54
Thrombocytopenia	54
Death	48
Leukopenia	43
Creatine phosphokinase increased	41
Rash maculo-papular	41
Myopathy	39
Fever	38
Granulocytopenia	36
Rash erythematous	36
Renal function abnormal	34
Dehydration	32
Pancytopenia	31
Dyspnea	30
Rhabdomyolysis	30
SGOT increased	30
SGPT increased	30

Labeling

The FDA approved label for Col-probenecid (Watson Labs; ANDA 84-279) lists nausea, vomiting, abdominal pain, diarrhea, aplastic, anemia, agranulocytosis, peripheral neuritis, muscular weakness dermatitis, purpura, and alopecia as AEs of the product and notes that the adverse effects due to colchicine appear to be a function of the dose.

Review of the labels for colchicine from foreign countries included the following AEs: gastrointestinal disturbances (nausea, diarrhea, vomiting, abdominal pain), skin disturbances (skin irritation, morbilliform rash, purpura, alopecia, urticaria), dizziness, kidney disturbances, low blood pressure, hypersensitivity reaction, and azoospermia.

8.2.6. Overdose, Drug Abuse Potential, Withdrawal and Rebound

Colchicine is generally well-tolerated at normal therapeutic doses with the most common side effects being related to gastrointestinal symptoms, e.g., diarrhea, nausea and vomiting. Although colchicine has a narrow therapeutic index, oral administration generally limits the majority of patients from achieving toxic serum levels since the gastrointestinal adverse effects become severe. Severe toxicities were common with intravenously administered colchicine as therapeutic doses could be exceed without the patient experiencing the typical side effects seen with orally administered colchicine; however, the intravenous formulation of colchicine has been removed from the market. Currently, when toxic levels of colchicine are reached it generally occurs as a result of a drug interaction or an accidental/intentional overdosing, often with life-threatening complications.

The specific dose of colchicine that produces significant toxicity is unknown as fatalities have occurred after ingestion of a dose as small as 7 mg over a four day period while other patients have survived after ingestion of more than 60 mg. A retrospective study of 150 patients who overdosed on colchicine reported that patients who ingested <0.5 mg/kg survived and tended to have mild gastrointestinal symptoms, those patients who ingested between 0.5 to 0.8 mg/kg experience more severe AEs, and those patients ingesting >0.8 mg/kg had a one-hundred percent mortality.

Ben-Chetrit and Levy (1998) proposed dividing the manifestations of colchicine toxicity into three sequential overlapping stages as outlined in Table 21. Stage 1 starts within 24 hours of ingestion and includes gastrointestinal symptoms. Stage 2 begins 24 to 72 hours after drug ingestion and is accompanied by life-threatening complications due to multi-organ failure and death. Survival through Stage 2 is followed by recovery which is manifested by alopecia, rebound leukocytosis, and recovery from multi-organ failure.

Table 21. Clinical Stages of Colchicine Overdose

Stage 1	Stage 2	Recovery
Abdominal pain	Renal failure	Leukocytosis
Nausea	Respiratory failure	Alopecia
Vomiting	Cardiac failure	
Diarrhea	Pancytopenia	

Dehydration	Metabolic Acidosis	
	Electrolyte disturbances	
	DIC	
	Convulsions	
	Coma	

Putterman et al (1991) published a summary of the toxic effects of colchicine on the different body systems in which the authors concluded that the most common cause of death from colchicine overdose is cardiovascular collapse, which is manifested by cardiogenic shock. Respiratory involvement occurs in approximately 33% of colchicine overdoses with increasing respiratory distress leading to hypoxemic respiratory failure. Hematologic manifestations occur in all three stages of colchicine overdosing. In Stage 1, patients may have leukocytosis but during the second stage bone marrow hypoplasia and coagulation abnormalities including diffuse intravascular coagulation are evident. Marrow recovery typically begins around day 8 post-ingestion and is manifested by a rebound leukocytosis. Neurologic involvement includes mental status changes, transverse myelitis, ascending paralysis, and seizures. Renal complications associated with colchicine overdose include azotemia, proteinuria, and hematuria, all of which may progress to acute renal failure. Rhabdomyolysis may occur with colchicine overdoses and this may also contribute to renal failure. Liver damage is an uncommon manifestation of colchicine toxicity but hepatomegaly with liver tenderness and elevated transaminases may be evident. Fever has also been reported and may occur as a direct drug effect or perhaps as a sign of infection following the onset of leukopenia. Alopecia is well-documented in colchicine overdoses and most cases are reversible after drug discontinuation. Dermatological manifestations are rare but may include toxic epidermal necrosis.

Treatment of acute colchicine overdose includes aggressive bowel decontamination with gastric lavage and administration of activated charcoal as soon as possible. Hemodialysis is ineffective due to the extensive volume of distribution of colchicine.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

None

8.4. Conclusions and Recommendations

This marketing application is for approval of colchicine oral solution (0.6 mg/5 mL) for the prophylaxis of gout flares in adults, under the proposed trade name, Gloperba. The application

was filed under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and relies on published literature and FDA's finding of safety and efficacy for colchicine/probenecid. Two randomized, placebo-controlled, double-blinded studies from the published literature provided the principal evidence of the efficacy of colchicine by reproducibly demonstrating a reduction in the number of gout flares in adult patients with chronic gout compared to patients treated with placebo. The primary evidence was further supported by five open-label or retrospective studies conducted in adults from the literature. Each of the studies enrolled patients with chronic gout and represented the targeted patient population. The safety analysis was provided based on data from the Applicant's pharmacokinetic studies and data obtained from the published literature. Overall there is substantial evidence of sufficient quality to adequately assess the safety and efficacy of colchicine for use for prophylaxis of gout flares in patients with gout. The availability of a colchicine oral solution will provide an additional therapeutic option for patients. The clinical review team recommends approval of colchicine oral solution (0.6 mg/5 mL) for the prophylaxis of gout flares in adult patients.

x Keith M. Hull -S

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Keith Hull, M.D. Ph.D.
Primary Clinical Reviewer

X Rachel Glaser -S

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Rachel Glaser, M.D.
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not held to discuss this NDA as the safety and efficacy for colchicine has been established in the target indication. There were no unique findings in this program that would warrant a discussion at an Advisory Committee meeting.

10 Pediatrics

The Applicant has requested a full waiver of the requirement to submit a pediatric assessment based on the justification that necessary studies are impossible or impractical because the number of children with gout is so small and patients are geographically dispersed. The proposed pediatric plan was reviewed and agreed upon by the FDA Pediatric Review Committee (PeRC) on 08/01/2018.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The proposed proprietary name, Gloperba, was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and found to be acceptable.

The Applicant provided labeling consistent with the Pregnancy and Lactation Labeling Rule (PLLR). References to the product strength were revised from (b) (4) to 0.6 mg/5mL to align with the recommended 5 mL dose of Gloperba. Changes were also made to several sections of the label to reflect current labeling practices, and to accurately present the drug interaction data generated by the Applicant. In addition, general recommendations for drug interaction and organ dysfunction related treatment were added to the label. To ascertain accurate dosing of the solution, Section 17, Patient Counseling Information, included instructions to advise patients and caregivers to ask their pharmacist to recommend an appropriate measuring device and for instructions for measuring the correct dose. Labeling consultants, including the CMC team, DMEPA, OPDP, and DMPP, have reviewed the submitted labeling and their recommendations which pertain primarily to internal consistency, improving readability and clarity of the labeling, the patient package insert, and carton and container labels, have been considered and conveyed to the Applicant. All labeling changes were agreed upon with the Applicant.

12 Risk Evaluation and Mitigation Strategies (REMS)

No postmarketing risk evaluation and mitigation strategies are recommended.

13 Postmarketing Requirements and Commitment

There are no recommendations for postmarketing requirements and commitments based on the current submission.

14 Division Director (Clinical)

This NDA provides for a new formulation of colchicine, an oral solution (0.6 mg/5mL), for the prophylaxis of gout flares in patients with gout. This 505(b)(2) application relies on published literature and FDA's finding of safety and efficacy for Col-Probenecid (Colchicine/Probenecid 0.5 mg/500 mg Tablet, Watson Laboratories Inc.). The development program included one pivotal relative bioavailability study and two drug interaction studies. The pivotal bioavailability study demonstrated bioequivalence of the proposed colchicine oral solution to the Reference Standard (Col-Probenecid; ANDA 084279). The clinical pharmacology team recommends approval.

The clinical team reviewed the relevant published literature with respect to colchicine for the prophylaxis of gout flares. The clinical team determined that overall there is substantial evidence of sufficient quality to adequately assess the safety and efficacy of colchicine for use for prophylaxis of gout flares in patients with gout. The clinical team recommends approval.

The product quality review team recommends approval. There are no outstanding issues for this application. The availability of a colchicine oral solution will provide an additional therapeutic option for patients. The regulatory action is Approval.

X Sally M. Seymour -S

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Sally Seymour, M.D.
Division Director (Acting)

15 Appendices

15.1. Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA Guidance for Industry on Financial Disclosure by Clinical Investigators. The Applicant submitted FDA Form 3454 certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. No potentially conflicting financial interests were identified.

Covered Clinical Studies (Name and/or Number): RMG-COL-PK001, RMG-COL-PK002 and RMG-COL-PK003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the	Yes ☐	No ☐ (Request explanation

reason:		from Applicant)

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/s/

BHAWANA SALUJA
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01/29/2019 04:45:57 PM

SALLY M SEYMOUR
01/29/2019 04:47:48 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM	DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH
DATE:	21 December 2018
TO:	File for NDA 210942
THROUGH:	Bhawana Saluja, Ph.D.
FROM:	Justin Penzenstadler, Pharm.D.
SUBJECT:	**Clinical Pharmacology Primary Review**
APPLICATION/DRUG:	**NDA210942/ GLOPERBA (colchicine oral solution 0.6 mg/5 mL)**

Romeg Therapeutics submitted NDA 210942 on 30 March 2018 under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for colchicine oral solution (0.6 mg/5 mL) relying on the Agency's previous findings of clinical safety and efficacy for colchicine in a combination product (colchicine 0.5 mg/ probenecid 500 mg tablet; reference standard).

The clinical pharmacology program includes a single pivotal pharmacokinetic (PK) relative bioavailability and food-effect study (RMG-COL-PK001), and two drug interaction studies (RMG-COL-PK002 and RMG-COL-PK003) to support the application. Dosing in the fasted state met the bioequivalence (BE) criteria (i.e., 90% confidence interval (CI) of 80.00-125.00%) for both Cmax and AUC for the proposed product as compared to the reference standard. Food had no impact on the extent of exposure (AUC) for the proposed oral solution of colchicine, however the Cmax was decreased by 19% (90% CI; 9 – 27%)after administration with a high fat, high calorie meal. This effect of food on colchicine exposure is not expected to have any clinically meaningful impact on the safety and efficacy of colchicine.

A multi-disciplinary unireview has been used for this application, and the clinical pharmacology review will be archived as part of the unireview.

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/s/

JUSTIN A PENZENSTADLER
12/21/2018

BHAWANA SALUJA
12/21/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation & Research

Date: December 18, 2018

To: File for NDA 210942

Through: Rachel Glaser, MD

From: Keith M Hull, MD, PhD

Subject: Clinical Primary Review

Application: **NDA 210942 GLOPERBA (colchicine)**

Romeg Therapeutics (Applicant) has submitted the current NDA under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act relying on the Agency's previous findings of clinical safety and efficacy for colchicine in the combination product (probenecid and colchicine), as well as publicly available information as the primary source of data necessary to demonstrate the clinical safety and efficacy of colchicine for the prophylaxis of gout flares in patients with chronic gout. Consequently, the majority of data in this application is derived from the scientific literature provided by the Applicant and supplemented by additional literature researched by this reviewer. Additionally, the Applicant has submitted data from two Applicant-initiated pharmacokinetic (PK) studies.

The primary efficacy data are derived from two randomized, placebo-controlled trials using the incidence of gout flares as their primary efficacy endpoints in subjects with chronic gout who were undergoing urate-lowering therapy. Further supportive evidence comes from five additional trials.

To support the safety of colchicine for the prophylaxis of gout flares indication, the Applicant has submitted an analysis of safety data obtained from the published literature and the results of their pharmacokinetic studies. In addition, this reviewer has supplemented the submitted safety review to include further evaluation of the scientific literature for oral colchicine, regardless of indication, FDA and WHO postmarketing safety databases, and labeling from the U.S. and foreign colchicine products.
I recommend approval of Colchicine Oral Solution (GLOPERBA) for the prophylaxis of gout flares in adults, pending the completion of the clinical pharmacology review and provided agreement can be reached with the Applicant on revisions to the proposed package insert.

The clinical review has been completed. A multi-disciplinary unireview has been used for this supplement and the clinical review will be archived as part of this unireview.

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/s/

KEITH M HULL
12/19/2018

RACHEL GLASER
12/19/2018