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**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Applicant Hikma Pharmaceuticals  
(US Agent: West-Ward Pharmaceuticals)

Formulation(s) 0.6 mg capsules  
Dosing Regimen 0.6 mg QD or BID  
Indication(s) Prophylaxis of gout flares  
Intended Population(s) Adult patients with chronic  
gout

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

This marketing application is for approval of colchicine 0.6 mg capsules for the prophylaxis of gout flares in adults, under the proposed trade name, Mitigare. 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 Col-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 four open-label studies from the literature conducted in adults. 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 (PK) studies and data obtained from the published literature. Overall there was substantial evidence of sufficient quality to adequately assess the safety and efficacy of colchicine for use in patients with chronic gout.

This clinical reviewer recommends approval of colchicine 0.6 mg capsules for the prophylaxis of gout flares in adult patients.

### **1.2 Risk Benefit Assessment**

The administration of colchicine to prevent gout flares in patients with chronic gout is well documented in the published literature and provides a clinically meaningful benefit to this patient population. Additionally, colchicine is the only member of its pharmacologic class and has been used clinically as a single entity in the US for over 70 years; consequently, its safety profile has been well-documented over this period of time and it 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. Gastrointestinal toxicity, including abdominal pain, diarrhea and vomiting, is the major adverse event associated with colchicine when taken in therapeutic doses and can be reduced by lowering the dose of colchicine. Overall, the safety data provided by the Applicant in the current submission are consistent with what has been reported in postmarketing databases and in the published literature. Lastly, case reports from the published literature clearly demonstrate that the concomitant use of colchicine with the certain known CYP3A4 and P-gp inhibitors is hazardous and has been associated with patient fatality. Drugs with

known or potential drug interactions with colchicine should be avoided if possible; and used concomitantly with caution and dose reduction as clinically indicated.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

Given the long history of clinical use of colchicine, the well documented and well known adverse event (AE) profile associated with the drug, and the lack of identification of additional safety signals in this review, no additional postmarketing risk evaluation and mitigation strategies (REMS) are warranted for the gout prophylaxis indication.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

Given the long history of clinical use of colchicine, the well documented and well known AE profile associated with the drug, and the lack of identification of additional safety signals in this review, no additional postmarketing requirements or commitments are warranted for the gout prophylaxis indication.

## 2 Introduction and Regulatory Background

Gout is an inflammatory disease characterized by recurrent attacks of acute inflammatory arthritis, chronic arthropathy, soft tissue deposits of urate crystals (tophi), and uric acid nephrolithiasis. The disease results from the deposition of uric acid crystal deposition in tissues and fluids within the body. While all patients with gout have hyperuricemia at some point in the disease, many individuals with hyperuricemia never develop the disease; however, the likelihood of developing gout is strongly correlated with increasing serum uric acid levels above 6 mg/dL. Most patients' first manifestation of gout begins with an acute, painful attack of monoarthritis, classically involving the first metatarsophalangeal joint. The large majority of patients progress to develop chronic gout that manifests as recurrent episodes of acute gout and tophi.

The first goal for treatment of chronic gout is reducing the serum uric acid level to less than 6 mg/dL to reduce the risk of gout flares and to resolve tophi. Initial management begins with diet modification, weight loss, limitation of alcohol consumption, and management of concomitant medications that are known to increase serum uric acid, e.g., HCTZ. If these lifestyle modifications fail, then patients begin pharmacologic treatment with a urate-lowering drug, e.g., probenecid or allopurinol. Ironically, the initiation of urate-lowering therapy frequently precipitates gout flares as a result of mobilization of uric acid stores in the body. To prevent flares, clinicians typically initiate prophylactic treatment with NSAIDs, corticosteroids, or colchicine until the risk of flare diminishes.

### 2.1 Product Information

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 already 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 US to treat disease since the early 19<sup>th</sup> century. Colchicine is currently available as a 0.6 mg single-ingredient tablet marketed under the trade name, Colcrys, by Takeda Pharmaceuticals, which has been approved for the treatment of FMF, and acute and chronic gout since 2009. Colchicine is also available as a combination product with probenecid (Colchicine-Probenecid), which was initially approved in 1961 and is marketed by generic manufacturers for the treatment of chronic gout.

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. 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-1 $\beta$  activation.

The Applicant is proposing to license colchicine 0.6 mg capsules, under the trade name Mitigare, for the prophylaxis of gout flares in adults. The proposed dosage is the oral administration of colchicine 0.6 mg QD or BID.

## **2.2 Tables of Currently Available Treatments for Proposed Indications**

The treatment of patients with chronic gout start with non-pharmacologic measures aimed to reduce hyperuricemia including weight reduction, a low purine diet, limiting alcohol intake, and effectively managing concomitant drugs known to increase serum uric acid, e.g., HCTZ. Unfortunately, in clinical practice these life-style interventions only minimally lower patients serum uric acid and do little to reduce the frequency of gout flares. Pharmacologic intervention is indicated when patients with gout develop frequent and disabling attacks of gouty arthritis, radiographic evidence of chronic joint erosions, tophaceous deposits in soft tissue and chondral bone, gout flares in the setting of renal insufficiency, and recurrent nephrolithiasis.

The vast majority of patients with chronic gout have hyperuricemia defined as serum uric acid concentrations greater than 6.5 mg/dL. Pharmacologic management begins with using urate-lowering drugs with the goal of lowering patients' serum uric acid levels below 6 mg/dL. Urate-lowering drugs can be divided in to three classes the uricosuric drugs, xanthine oxidase inhibitors, and the biologic uricase agents.

Patients with relative renal underexcretion of uric acid are candidates for the FDA approved drug, probenecid. However, probenecid is rarely used in the US due to the small proportion of hyperuricemic patients who are candidates for uricosuric therapy, and because of poor patient compliance related to multiple daily dosing. As a result, most patients are treated with one of the two FDA approved xanthine oxidase inhibitors, allopurinol or Febuxostat. In patients who can not tolerate, or are refractory to, either probenecid or xanthine oxidase inhibitors may be eligible candidates for treatment with the biologic uricase drugs which enzymatically catalyzes the oxidation of uric acid to the more water soluble purine metabolite allantoin. Two uricase drugs are marketed in the US, pegloticase and rasburicase, of which only the former is approved for use in patients with chronic gout in adult patients refractory to conventional therapy.

As mentioned above, the initiation of urate-lowering therapy frequently precipitates gout flares as a result of mobilization of uric acid stores in the body. Consequently, prophylactic treatment with an NSAID, corticosteroid, or colchicine is recommended when initiating urate-lowering therapy. None of the NSAID medications are specifically approved for the prevention of gout flares but are commonly used off label. Colchicine

prophylaxis has been used for this purpose for decades with unapproved, single-ingredient colchicine products.

Currently, three products are approved for the prophylaxis of gout flares and include the colchicine-probenecid combination products Col-Probenecid (Watson Laboratories) and Probenecid/Colchicine (Ivax Pharmaceuticals) and the single ingredient colchicine product Colcrys (Takeda Pharmaceuticals America, Inc).

### **2.3 Availability of Proposed Active Ingredient in the United States**

Currently, three colchicine containing products are approved in the US and include the colchicine-probenecid combination products Col-Probenecid (Watson Laboratories) and Probenecid/Colchicine (Mirror Pharmaceuticals) and the single ingredient colchicine product Colcrys (Takeda Pharmaceuticals America, Inc).

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Colchicine is the only member of its pharmacologic class and has been used clinically as a single entity in the US 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 rather severe and consequently dose-limiting.

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

The Division held meetings with the Applicant in July and November 2011 to discuss their proposal to submit a 505(b)(2) application to market 0.6 mg colchicine capsules for the prophylaxis of gout flares. The Applicant stated their intention to base the application solely on the clinical literature and without reliance on FDA's finding of safety and effectiveness for the currently marketed single ingredient product, Colcrys (colchicine) tablets. Four principle topics were discussed as follows:

- Drug-Drug Interaction Studies

To address the potential for drug-drug interactions, the Applicant discussed conducting four drug-drug interaction studies using four different potentially interacting drugs including a strong CYP3A4 inhibitor, moderate CYP3A4 inhibitor, weak CYP3A4 inhibitor, and a P-gp inhibitor. These studies were performed and submitted in the current application.

- Acute Flare Dosing  
To address the dosing of their product during an acute flare the Applicant recommended patients consider alternative therapies. The Applicant also considered how to convey to patients that their product not be used for acute gout flares.
- Dosing Recommendations in Renal and Hepatic Impairment  
The Applicant proposed dose modification recommendations in renal and hepatic impairment estimated from information available in the published literature. Based on the literature, for mild to moderate renal impairment, dose adjustment is not required, but patients should be closely monitored. For severe renal impairment, the dose should be reduced to 0.6 mg every 2 to 3 days, with close monitoring and further dose adjustment as clinically indicated. Similarly, for mild to moderate hepatic impairment, no dose modification is needed, and for severe hepatic impairment, dose reduction should be considered but a specific reduction has not been quantified.
- Food Effect Study  
The Applicant was allowed to use the results of its previous tablet formulation food effect study to the capsule formulation provided that the formulation comparison between capsules and tablets, as well as the dissolution profiles, were similar. The Applicant performed relevant comparison studies and the results are submitted in the current application.

On October 5, 2012 the Applicant filed the present 505(b)(2) application for 0.6 mg colchicine capsules with the proposed indication of prophylaxis of gout flares in adults. The current application relies on FDA's finding of safety and effectiveness for the colchicine containing combination product, Col-Probenecid (colchicine/probenecid) 0.5 mg/500 mg tablets and published literature.

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

The submission was appropriately organized and enabled the extraction of necessary information. Though there are inherent limitations associated with a literature-based 505(b)(2) submission the overall quality of this application is acceptable. The Applicant uses sufficient resources to establish the safety and efficacy of colchicine for prevention of gout flares.

#### **3.2 Compliance with Good Clinical Practices**

Compliance with good clinical practices was followed for the Applicant-initiated PK studies. The remainder of the submission was derived from published literature and not subject to the review of good clinical practice.

#### **3.3 Financial Disclosures**

All studies were either directly performed by the Applicant or derived from a published literature. Submitted financial disclosures were adequate.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

This portion of the application was reviewed by Craig M Bertha, PhD who recommended approval of the application from the perspective of Chemistry, Manufacturing, and Controls (CMC).

### **4.3 Preclinical Pharmacology/Toxicology**

The nonclinical portion of this application was reviewed by Lawrence S Leshin, PhD who recommended approval of the application from the perspective of Preclinical Pharmacology/Toxicology.

### **4.4 Clinical Pharmacology**

The clinical pharmacology portion of this application was reviewed by Sheetal Agarwal, PhD who recommended approval of the application from the perspective of Clinical Pharmacology. The reader is referred to Dr. Agarwal's review for details of the PK and drug-drug interaction studies.

#### **4.4.1 Mechanism of Action**

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. 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-1 $\beta$  activation.

#### **4.4.2 Pharmacodynamics**

The reader is referred to Dr. Agarwal's review for further details regarding the pharmacodynamics of the Applicant's colchicine product.

#### **4.4.3 Pharmacokinetics**

The reader is referred to Dr. Agarwal's review for further details regarding the PK of the Applicant's colchicine product.

## 5 Sources of Clinical Data

The Applicant submitted the current NDA under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and relied on published literature as the primary source of data necessary to demonstrate the clinical safety and efficacy of colchicine for the prevention of gout flares in adult patients. Consequently, the majority of data presented in this application is derived from the published literature.

### 5.1 Tables of Studies/Clinical Trials

The studies used to assess efficacy are shown in Table 1.

**Table 1. Sources used to support the efficacy of colchicine.**

<b>Randomized, Controlled Trials</b>				
<b>Reference</b>	<b>N</b>	<b>Study Design</b>	<b>Treatment Dose and Duration</b>	<b>Primary Outcome</b>
Paulus et al. <sup>1</sup> , 1974	52	R, DB, PC	Colchicine 0.5 mg or PBO TID	Number of Gout Flares
Borstad et al. <sup>2</sup> , 2004	43	R, DB, PC	Colchicine 0.6 mg or PBO BID	Number of Gout Flares
<b>Non-Randomized, Open-Label Trials</b>				
<b>Reference</b>	<b>N</b>	<b>Study Design</b>	<b>Treatment Dose and Duration</b>	<b>Primary or Secondary Outcome</b>
Yu TF <sup>3</sup> , 1982		RA	Colchicine Dosing Varied	Number of Gout Flares
Becker et al. <sup>4</sup> , 2005a		NR, OL	Colchicine 0.6 mg x 2 wks	Number of Gout Flares
Becker et al. <sup>5</sup> , 2005b		NR, OL	Colchicine 0.6 mg x 8 wks	Number of Gout Flares
Karimzadeh et al. <sup>6</sup> , 2006		NR, OL	Colchicine 1 mg QD X 26, 39, or 52 weeks	Gout Flare Probability
R: Randomized; DB: Double-blind; PC: Placebo-controlled; NR: Non-randomized; OL: Open-label; RA: Retrospective analysis; PBO: Placebo				

### 5.2 Review Strategy

The data used to support the clinical efficacy of colchicine for preventing gout flares in adult patients with chronic gout is derived entirely from the published literature. Two randomized, placebo-controlled studies comprise the primary efficacy data for this application and are further supported by four open-labeled studies (Table 1). Safety analyses were based on data obtained from over 2000 publications identified during a search of the scientific literature for colchicine, although a lesser number of representative citations were submitted for analysis. Additionally, six Applicant-initiated, Phase 1 PK studies were included in the safety review.

<sup>1</sup> Paulus HE et al. Arthritis Rheum 1974; 17(5):609-14.

<sup>2</sup> Borstad GC et al. J Rheumatol 2004; 31(12):2429-32.

<sup>3</sup> Yu TF Seminar Arthritis Rheum 1982; 12:256-64.

<sup>4</sup> Becker MA et al. Arthritis Rheuma 2005; 52:916-23.

<sup>5</sup> Becker MA et al. N Engl J Med 2005; 353:2450-61.

<sup>6</sup> Karimzadeh H et al. J Res Med Sci 2006; 11:104-7.

Literature reviews can be problematic regarding the analysis of clinic trials when they serve as the primary source of data to support a marketing application. For example, the design of the studies may not be ideal, enrolled patients may not represent the targeted patient population, the primary source data and case report forms are not available for scrutiny, inability to account for patient dropouts if not mentioned by the study authors, and inability to confirm statistical analyses or perform different analyses if necessary.

Studies from the published literature used to support approval of a new product should contain several key factors to justify their use:

- Multiple studies conducted by different investigators where each of the studies clearly had an adequate design and consistent results across studies
- A high level of detail in the published reports regarding statistical plans, analytic methods, study endpoints, and patient disposition
- Appropriate clinical endpoints that can be objectively assessed and are less subject to patient or investigator bias
- Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require post hoc analyses
- Studies conducted by groups with properly documented operating procedures and a history of implementing such procedures effectively

Indeed, the quality of data from the primary studies used to support the efficacy of colchicine was less than ideal. The first controlled study used to support the efficacy of colchicine in this application was published by Paulus et al. in 1974 and had several shortcomings including:

- Differences between study sites regarding the administration of urate-lowering drugs. Specifically, the Los Angeles site discontinued patients from urate-lowering drugs prior to initiating the study while the Kansas City site stabilized patients on probenecid prior to beginning colchicine. Since the original data is not available, it is not possible to further assess what effect this difference may have had on the results.
- The authors did not use the intent-to-treat population in their analysis as they excluded patients who did not demonstrate a reduction in serum uric acid levels, and thus, introduced the potential for bias.

- There is insufficient information from the publication accounting for patients who discontinued from the study and whether their data was included in the final analysis.
- Differences between patient-reported flares and investigator-reported flares may have existed and what impact the potential differences could have on the results cannot be determined.

The second study by Borstad et al. also presented several concerns including:

- The trial was not truly blinded as the colchicine tablets and placebo tablets differed in appearance.
- Uncertainty regarding how the analyses accounted for patients who had multiple flares and for patients who discontinued from the study.

Despite these concerns, the two controlled studies generally provide sufficient data to assess the clinical efficacy of colchicine for preventing gout flares in adult patients with gout and were conducted by respected investigators in their field of study published in respected medical journals. Both studies were adequately designed and demonstrated similar degrees of robust therapeutic effect using clinically meaningful endpoints (i.e., frequency of attacks). It should be noted that although the identification of gout flares was retrospective in both studies and without verification by investigators, patients with gout are generally able to identify a gout flare and it is unlikely that collection of the data in this manner would have affected the outcome of the study. As mentioned above, one concern from the Paulus et al. study was the exclusion from the final analyses of patients who did not achieve a decrease in serum uric acid, and thus did not use the intent-to-treat population. This point was addressed by the author who stated that “the serum urate-lowering effect of probenecid was used to monitor compliance in a placebo-controlled study of prophylactic colchicine therapy for intercritical gout”, suggesting that this may have been a pre-specified design feature to measure patient compliance.

Both studies provided clear descriptions of statistical plans, analytic methods, and study endpoints; however, given the nature of publications, it is not possible to determine whether these were pre-specified in a protocol or performed after the studies were completed. Lastly, the results of the efficacy data from the two controlled studies are further supported by four open-label studies that demonstrate similar degrees of efficacy for colchicine in a similar patient population.

In summary, the combination of published literature and Applicant-initiated PK studies submitted by the Applicant are sufficient to assess the safety and efficacy of colchicine to prevent gout flares in adult patients.

### 5.3 Discussion of Individual Studies/Clinical Trials

The randomized, placebo-controlled studies by Paulus et al. and Borstad et al. are discussed in Section 5.3.1 and provide the primary sources of data for demonstrating the efficacy of colchicine for this application. The four open-label studies are discussed in Section 5.3.2 and provide supportive evidence to the primary data. Due to the manner in which studies are published in the literature, discussion of study design, study conduct, statistical methods, and results will be discussed here as well as summarized in Section 6.

#### 5.3.1 Randomized, Placebo-Controlled Studies

5.3.1.1 Study 1: “Colchicine for the prevention of gout flares when initiating probenecid”. Paulus HE et al. *Arthritis Rheum* 1974; 17(5): 609-14.

Paulus et al. conducted a six-month, randomized, double-blind, placebo controlled study for the prevention of gout flares in patients with gout starting on urate-lowering therapy with the uricosuric drug, probenecid. A total of 52 male patients with a confirmed diagnosis of gout and serum uric acid level greater than 7.5 mg/dL were randomized to receive probenecid 500 mg + placebo or probenecid 500 mg + colchicine 0.5 mg three times daily. Differences in the administration of probenecid occurred at the two different study sites. Patients at the Los Angeles site had their probenecid discontinued two weeks prior to therapy while patients at the Kansas City site were continued on a stable dose of probenecid two weeks before beginning colchicine therapy. Patients reported gout flares on a monthly basis and were recorded as mild, moderate, or severe by the investigator based on the degree of pain and accompanied swelling and tenderness described by the patient. Only moderate and severe flares were included in the analysis. Prior to the unblinding of data, the investigators reviewed the serum urate levels to determine whether the urate-lowering therapy was successful. Only those patients who successfully lowered their levels of serum uric acid were included in the analysis. Baseline demographics and disease characteristics of the two groups reflected a typical gout population and no significant differences between treatment arms were observed (Table 2).

**Table 2. Patient demographics and baseline disease characteristics**

	Colchicine- Probenecid	Placebo- Probenecid
Number enrolled	29	23
Number analyzed	20	18
Age (years) mean*	53	52
range	34-77	43-73
Number with Tophi*	3	4
Number with crystals in synovial fluid*	6	7
Duration of gout (years) (mean ± SE)*	10.5 ± 2.3	10.5 ± 1.8
Attacks of acute gout during 12 months prior to study (by history) mean ± SE*	4.2 ± 1.1†	3.2 ± 0.4
Number treated with uric acid lowering drug for at least 12 months prior to study*	12	12
Months of therapy*	109	94
Serum urate (mg/100 ml ± SE) before study*	8.4 ± 0.4‡	9.2 ± 0.6

\*Data for patients included in the analysis

†P > 0.2 (no significant difference)

\*Source: Table 1 from Paulus et al., 1974

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

The number of acute gout flares per month was used as the primary endpoint to assess the efficacy of colchicine to prevent gout flares. As shown in Table 3, colchicine-treated patients reported a clinically meaningful reduction in the number of acute gout flares compared with patients treated with placebo (0.19 attacks/month vs. 0.48 attacks/month, respectively).

**Table 3. Analysis of efficacy endpoints**

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)

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

The authors conclude that treatment with colchicine 0.5 mg TID decreases the frequency of gout flares in patients whose hyperuricemia has been satisfactorily controlled with probenecid. Safety data from this study is included in the safety analysis section below (Section 7). It is interesting to note that the authors stated that based on the common occurrence of side effect attributable to colchicine and its failure to prevent all attacks of gout, physicians should exercise clinical judgment in deciding when to treat and what dose of colchicine to use.

5.3.1.2 Study 2: “Colchicine for prevention of gout flares when initiating allopurinol”.  
 Borstad GC et al. J Rheumatol 2004; 31(12):2429-32.

Borstad et al. reported the results from a randomized, placebo-controlled study that enrolled patients with confirmed gouty arthritis and who met criteria for initiating allopurinol. A total of 43 patients were randomized to receive colchicine 0.6 mg twice daily or placebo. Patients with renal insufficiency received colchicine 0.6 mg once daily. Baseline demographics and disease characteristics of the two groups reflected a typical gout population and were generally similar between treatment arms; however a greater percentage of patients in the colchicine-treatment arm used diuretics compared to the placebo treatment arm, 57% versus 27%, respectively (Table 4). This discrepancy should not affect the final results since diuretics are known to elevate serum uric acid levels and make a patient more susceptible to gout flares. Thus, this imbalance would not tend to bias in favor of seeing drug effect.

**Table 4. Patient demographics and baseline disease characteristics**

Demographic/Characteristic	Colchicine	Placebo	p
Mean age, yrs	63.5	62.5	0.798
Male, %	81	91	0.412
Caucasian race, %	67	73	0.665
Chronic renal insufficiency, %	14	9	0.664
Hypertension, %	90	77	0.412
Hypothyroidism, %	0.05	0.05	1.000
Coronary artery disease, %	29	27	1.000
Tophi, %	62	64	0.907
Alcohol use, %	33	18	0.255
Drugs affecting serum urate levels, %	38	55	0.364
Diuretic use at baseline, %	57	27	0.047
Flares during prior year (mean number)	2.48	2.09	0.343

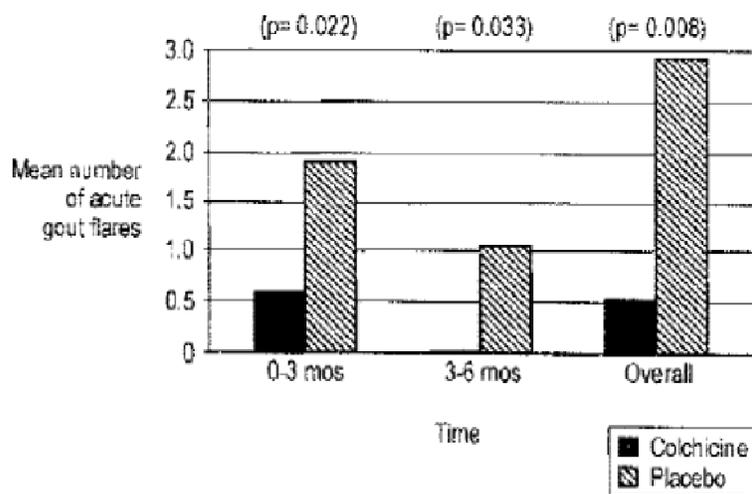
\*Source: Table 1 from Borstad et al., 2004

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

who had received at least one dose of study medication. The primary efficacy endpoint was the mean number of flares at three and six months. Statistical analysis of the primary endpoint assessed the differences between means using Students t-test. The number of patients with at least one flare, and the number of patients with more than one flare, was tested using the chi-square test. The mean pain score per flare by visual analog scale (VAS) and the average length of flares were analyzed by the Mann-Whitney test for nonparametric data because of the non-normal distribution the data.

Colchicine-treated patients reported fewer acute gout flares in the 0-3 month and 3-6 month time periods compared to placebo-treated patients (Figure 1). A total of 33% of colchicine-treated patients reported gout flares compared with 77% of placebo-treated patients as well as fewer multiple flares, 14% vs. 63%, respectively.

**Figure 1. Analysis of efficacy endpoints**



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

The authors concluded that colchicine therapy reduces the mean number of gout flares, decreases the probability of experiencing one or multiple gout flares, and decreases the severity of gout flares when given concomitantly with allopurinol. Safety data from this study is included in the safety analysis section below (Section 7).

### 5.3.2 Non-randomized, Open-Label Studies

5.3.2.1 “The efficacy of colchicine prophylaxis in articular gout—a reappraisal after 20 years”. Yu TF Seminar Arthritis Rheum 1982; 12:256-64.

The publication by Yu reviewed the experience of 540 colchicine-treated patients with chronic gout over a twenty-year period. The patient population was representative of patients with chronic gout including 53% of patients with a serum uric acid level greater than 10 mg/dL, 69% of patients had at least one tophi, and 30% of patients had a history of nephrolithiasis. A proportion of patients had been treated with urate-lowering drugs. Analysis of the results showed that approximately 82% of colchicine-treated patients reported an “excellent” result as evidenced by a reduction of gout flares over the reviewed period of time. While the data does demonstrate a correlation between colchicine prophylaxis and a reduced frequency of acute gout attacks, the study is limited by the fact that it was retrospective in nature and not randomized and well controlled. However, the results lend support that colchicine treatment effectively prevents gout flares in patients with chronic gout.

5.3.2.2 “Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase. A twenty-eight day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout”. Becker MA et al. Arthritis Rheum 2005; 52:916-23.

Becker et al. conducted a Phase 2, 4-week, randomized, placebo-controlled trial in 153 patients with gout to assess the urate-lowering effect of febuxostat compared to allopurinol. Eligible patients were randomized to receive one of three doses of febuxostat or standard-dose allopurinol. To prevent gout flares, patients were administered colchicine 0.6 mg twice daily for the first two weeks of the study after which point it was withdrawn. The proportion of colchicine-treated patients who reported gout flares was 11%, 8%, 8%, and 13% in the three febuxostat treatment arms and the allopurinol treatment arm, respectively. Following discontinuation of colchicine, the rate of gout flares increased to 34%, 30%, 40%, and 42%, respectively. This increased rate of gout flares following discontinuation of colchicine suggests that colchicine was directly preventing gout flares during the period when it was administered.

5.3.2.3 “Febuxostat compared with allopurinol in patients with hyperuricemia and gout”. Becker MA et al. N Engl J Med 2005;353:2450-61.

In a second study, Becker et al. reported the results of a Phase 3, 52-week, controlled trial that randomized 762 patients with gout to receive either one of two doses of febuxostat or allopurinol. To prevent gout flares, patients were administered colchicine 0.6 mg twice daily for the first eight weeks of the study after which point it was

withdrawn. As shown in Table 5, during the first eight-weeks of the study 22%, 36%, and 21% of the colchicine-treated patients reported a gout flare in the two febuxostat-treatment arms and the allopurinol-treatment arm, respectively; however, following discontinuation of colchicine, 64%, 70%, and 64%, of patients reported a gout flare over the next 44-weeks in their respective treatment arms.

**Table 5. Number of gout flares**

End Point	Febuxostat, 80 mg/day	Febuxostat, 120 mg/day	Allopurinol, 300 mg/day
Incidence of gout flares			
Day 1–wk 8 (prophylaxis)			
No./total no. (%)	55/255 (22)	90/250 (36)	52/251 (21)
P value	<0.001	<0.001¶	
Wk 9–52			
No./total no. (%)	147/228 (64)	150/215 (70)	150/234 (64)
Wk 49–52			
No./total no. (%)	13/167 (8)	9/153 (6)	20/185 (11)

Source: Table 3 from Becker et al., 2005

These data lend further support to the evidence that colchicine prophylaxis during the initiation of urate-lowering therapy reduces the incidence of gout flares.

5.3.2.4 “Different duration of colchicine for preventing recurrence of gouty arthritis”.  
 Karimzadeh H et al. J Res Med Sci 2006;11:104-7.

In 2006, Karimzadeh et al. published the results of an open-labeled study designed to assess the optimal treatment duration of prophylactic colchicine in patients with chronic gout. A total of 229 patients with chronic gout were enrolled and initiated on urate-lowering therapy with allopurinol and randomized to one of three colchicine treatment arms: 1 mg/day for 3-6 months (Group 1); 1 mg/day for 7-9 months (Group 2); 1 mg/day 10-12 months (Group 3). Patients were assessed at regular intervals and colchicine was discontinued at the prespecified time points and clinically followed for a period of one year. At the end of six months, the probability of a gout flare was 46%, 11%, and 6% in Groups 1, 2, and 3, respectively. At the end of 12 months, the likelihood of an attack was 54%, 28%, and 23%, respectively. A log-rank test showed significant differences between Group 1 and the other two treatment arms but no difference between Group 2 and 3. The mean time of recurrence was approximately eight months. These data provide supportive evidence that colchicine prophylaxis effectively reduces the number of gout flares in patients with chronic gout.

## 6 Review of Efficacy

### **Efficacy Summary**

The primary data supporting the efficacy of colchicine for preventing gout flares is provided by two randomized placebo-controlled studies from the published literature.

The first study, published by Paulus et al., randomized 52 male patients with a confirmed diagnosis of gout to receive probenecid 500 mg + placebo or probenecid 500 mg + colchicine 0.5 mg three times daily. The authors used the number of acute gout flares/patient/month as the primary endpoint and reported a clinically meaningful reduction in the number of acute gout flares in patients treated with probenecid + colchicine compared with patients treated with probenecid + placebo (0.19 attacks/month vs. 0.48 attacks/month, respectively).

Borstad et al. reported the results from a trial designed to assess the ability of colchicine to prevent acute gout flares during initiation of allopurinol therapy for chronic gouty arthritis. A total of 43 patients with confirmed gouty arthritis who met criteria for initiating allopurinol were randomized to receive colchicine 0.6 mg twice daily or placebo. Patients with renal insufficiency received colchicine 0.6 mg once daily. Subjects began allopurinol therapy with increased dosing until serum uric acid levels were less than 6.5 mg/dL at which time patients were given blinded study drug. The primary endpoint was the number of flares at three and six months. A total of 33% of colchicine-treated patients reported gout flares compared with 77% of placebo-treated patients.

Together, these two studies provide sufficient evidence to demonstrate a clinically meaningful effect of colchicine to prevent gout flares in patients with chronic gout. As further supportive evidence, the Applicant also included a number of open-label studies from the literature, of which four were deemed to be of adequate design to provide supportive evidence of the efficacy of colchicine.

Yu et al. reviewed the experience of 540 colchicine-treated patients with chronic gout over a twenty-year period. While a significant proportion of patients were receiving concomitant urate-lowering therapy, approximately 50% of patients were reported to still have a serum uric acid level greater than 10 mg/dL. Analysis of the results showed that approximately 82% of colchicine-treated patients had an “excellent” result as evidenced by a reduction of gout flares over the reviewed period of time. This retrospective study is limited and the quality of the data is less than ideal; however, the results lend support that colchicine treatment effectively prevents gout flares in patients with chronic gout.

Becker et al. conducted a Phase 2, 4-week, randomized, placebo-controlled trial in 153 patients with gout to assess the urate-lowering effect of febuxostat compared to allopurinol. Eligible patients were randomized to receive one of three doses of febuxostat or standard-dose allopurinol. To prevent gout flares, patients were also

treated with colchicine 0.6 mg twice daily for the first two weeks of the study after which point it was withdrawn. The proportion of colchicine-treated patients who reported gout flares was 11%, 8%, 8%, and 13% in the three febuxostat treatment arms and the allopurinol treatment arm, respectively. Following discontinuation of colchicine, the rate of gout flares increased to 34%, 30%, 40%, and 42%, respectively. This increased rate of gout flares following discontinuation of colchicine suggests that colchicine was directly preventing gout flares during the period when it was administered.

Becker et al. published a second study designed as a Phase 3, 52-week, controlled trial that randomized 762 patients with gout to receive either one of two doses of febuxostat or allopurinol. To prevent gout flares, patients were administered colchicine 0.6 mg twice daily for the first eight weeks of the study after which point it was withdrawn. During the first eight-weeks of the study 22%, 36%, and 21% of the colchicine-treated patients reported a gout flare in the two febuxostat-treatment arms and the allopurinol-treatment arm, respectively. Following discontinuation of colchicine, 64%, 70%, and 64%, of patients reported a gout flare over the next 44-weeks in their respective treatment arms. These data lend further support to the evidence that colchicine prophylaxis during the initiation of urate-lowering therapy reduces the incidence of gout flares.

In 2006, Karimzadeh et al. published the results of an open-labeled study designed to assess the optimal treatment duration of prophylactic colchicine in patients with chronic gout. A total of 229 patients with chronic gout were enrolled and initiated on urate-lowering therapy with allopurinol and randomized to one of three colchicine treatment arms: 1 mg/day for 3-6 months (Group 1); 1 mg/day for 7-9 months (Group 2); 1 mg/day 10-12 months (Group 3). Patients were assessed at regular intervals and colchicine was discontinued at the prespecified time points and clinically followed for a period of one year. At the end of six months, the probability of a gout flare was 46%, 11%, and 6% in Groups 1, 2, and 3, respectively. At the end of 12 months, the likelihood of an attack was 54%, 28%, and 23%, respectively. A log-rank test showed significant differences between Group 1 and the other two treatment arms but no difference between Group 2 and 3. The mean time of recurrence was approximately eight months. These data provide supportive evidence that colchicine prophylaxis effectively reduces the number of gout flares in patients with chronic gout.

In summary, when taken as a whole, the large treatment effect size and consistency between the two randomized controlled studies, combined with the supportive evidence from the four open-labeled studies, supports the conclusion that colchicine is efficacious in preventing gout flares in patients with chronic gout.

## 6.1 Indication

The Applicant is seeking the following indication for their colchicine 0.6 mg capsule:

*“Colchicine Capsules are indicated for prophylaxis of gout flares in adults”*

### 6.1.1 Methods

The current submission is a 505(b)(2) application that relies primarily on data from the published literature. The primary efficacy data is derived from two published randomized, controlled trials. The reader is referred to Section 5 of this document for further discussion of individual study design and overall review strategy.

### 6.1.2 Demographics

As detailed in Section 5.3, the demographic composition of patients who participated in the two randomized controlled studies, as well as the four open-labeled studies, were representative of the targeted patient population of adults with chronic gout and who could be expected to use colchicine. In general, baseline demographics and disease characteristics were well balanced between treatment arms in both studies.

### 6.1.3 Subject Disposition

Patient disposition in the two randomized controlled trials was adequately reported for the two randomized controlled studies and there did not appear to be a disproportionate amount of patient discontinuations in colchicine-treated patients compared to placebo-treated patients. The reader is referred to Section 5.3 for greater detail.

### 6.1.4 Analysis of Primary Endpoint(s)

Overall, the data presented in the publications by Paulus et al. and Borstad et al. provide convincing evidence that colchicine is effective in reducing the frequency of gout flares in adults with chronic gout. As discussed in Section 5.3, Paulus et al. demonstrated that colchicine-treated patients reported a clinically meaningful reduction in the number of acute gout flares compared with patients treated with placebo (0.19 attacks/month vs. 0.48 attacks/month, respectively). Similarly, Borstad et al. reported fewer acute gout flares patients treated with colchicine during the 0-3 month and 3-6 month time periods compared to placebo-treated patients. The same study reported that 33% of colchicine-treated patients reported gout flares compared with 77% of placebo-treated patients as well as fewer multiple flares over the same time period, 14% vs. 63%, respectively.

### 6.1.5 Analysis of Secondary Endpoints(s)

Borstad et al. was the only publication that reported additional endpoints. The authors attempted to analyze the “time to benefit” as a secondary endpoint by dividing the number of flares in to two time periods, 0-3 months and 3-6 months. These data demonstrated that the number of flares decreased to nearly zero during the 3-6 month period. This timeline is consistent with what was reported in the open-label trial by Karimzadeh et al. While suggestive that colchicine treatment of at least six months may be appropriate, no definitive recommendations can be made on the basis of these data.

### 6.1.6 Other Endpoints

Additional endpoints explored by Borstad et al included the severity of gout flares as measured using a VAS, length of flares, and the proportion of patients experiencing multiple gout flares. The authors reported that the average severity score (VAS) for colchicine-treated patients averaged 3.64 compared to 5.08 in the placebo-treated patients. Additionally, fewer patients in the colchicine treatment arm experienced multiple gout attacks compared to placebo-treated patients, 14% vs. 63%, respectively. There was no meaningful difference between treatment arms regarding the average length of gout flares, which was reported to be approximately 6 days for both groups.

### 6.1.7 Subpopulations

Neither analyzed efficacy data based on patient subpopulations; however, both group of investigators excluded patients with renal insufficiency.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No formal dose-ranging studies have been done with colchicine for the prophylaxis of gout flares. .

In regards to safety, the two trials studied colchicine doses ranging from 0.6 mg/d to 1.5 mg/d. In the study by Borstad et al., patients were treated blindly with colchicine 0.6 mg twice daily with the option of reducing the dose 0.6 mg once daily if they could not tolerate the dose or experienced adverse effects. While only 43% of patients reported having an adverse effect with colchicine 0.6 mg twice daily, a total of 62% of colchicine-treated patients reduced their dose 0.6 mg once daily. These data suggest that higher doses of colchicine may not be well tolerated.

In the Paulus study, patients received up to 1.5 mg of colchicine daily. Although the authors do not report the number of patients who may have reduced their dose, there were a large number of patients who are not analyzed due to the fact that serum uric acid was not adequately reduced. Paulus reported that three of the nine subjects were assigned to the colchicine-probenecid group, and who were not analyzed, decreased

their dosage of colchicine due to diarrhea, a common symptom associated with colchicine.

When taken together, the data suggest that a recommended dose of colchicine 0.6 mg to 1.2 mg daily, with reduction as needed for gastrointestinal side effects, appears to be supported by these studies.

## 7 Review of Safety

### **Safety Summary**

The current submission is a 505(b)(2) application that relies primarily on data from the published literature. Consequently, there are a number of limitations in regards to analysis of the safety data including:

- Lack of a standardized coding dictionary such as COSTART or MedDRA. Since the safety data was not collected from Applicant-initiated clinical trials, the data is 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.
- Only the more serious and life-threatening AEs, or those resulting in death, are likely to be reported in the published literature. Thus, this safety review is likely to be skewed toward the more serious AEs and less so toward more common and less severe AEs.

However, on the whole, the Applicant has included sufficient safety data to allow for an adequate assessment of the safety of orally administered colchicine for the intended indication. The data submitted for safety analysis in this review is based on a thorough review of the scientific literature for colchicine, regardless of indication, and six Applicant-initiated, Phase 1 PK studies. It is helpful that the majority of the literature reports regarding the safety of colchicine are related to its use in the treatment of gout.

Overall, these data are consistent in supporting the conclusion that orally administered colchicine is generally well-tolerated when used in therapeutic doses. Gastrointestinal AEs are typically the most common and earliest toxicity to present in patients and can occur even at therapeutic doses. Consequently, gastrointestinal symptoms can be viewed as a harbinger of more serious colchicine toxicity and provides a warning to the healthcare provider to discontinue or adjust the dose of colchicine to limit more serious toxicities 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, thrombocytopenia, neuromuscular toxicity, and rhabdomyolysis.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials 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. Colchicine initially received FDA 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 gout. For this review, a total of over 2000 publications were identified during a review of the scientific literature for colchicine, although a lesser number of representative citations were submitted for analysis. Additionally, six Applicant-initiated, Phase 1 PK studies were included in the safety review.

Colchicine has been, and is, most commonly prescribed for the treatment of gout, consequently, the majority of the safety data reviewed here was obtained from patients with gout, the intended indication. The majority of literature reports concerning colchicine toxicity are related to intravenously administered colchicine, intentional/unintentional overdoses, and high serum colchicine concentrations due to concomitant administration with a drug known to interfere with the metabolism of colchicine. While these toxicities are discussed, this review attempts to focus primarily on the safety of orally administered colchicine since the Applicant is seeking an indication to use oral colchicine for the treatment of patients with chronic gout and (b) (4). It is important to note again that common and less severe AEs are less likely to be reported to the FDA or in the published literature, rather AEs that are serious and life-threatening, or those resulting in death, are most likely to be reported. Thus, this safety review is likely to be skewed toward the more serious AEs and less so toward common and less severe AEs.

#### 7.1.1.1 Applicant-Initiated Studies

A total of 112 healthy volunteers were exposed to at least one dose of 0.6 mg colchicine in the Applicant-initiated PK studies. Thirty-six patients received two successive days of 0.6 mg colchicine doses and again 21 days later for a total of 2.4 mg colchicine exposure. The remainders of the patients were exposed to two 0.6 mg doses eight day apart. Laboratory evaluations were obtained at screening, study check-in, and at discharge. Vital sign measurements were performed at screening, prior to dosing, and at multiple post-dose intervals. Adverse events were monitored throughout all six studies.

### 7.1.1.2 Published Scientific Literature

A database search was performed to identify publications relating to the clinical safety of colchicine. Search terms included colchicine and terms related to adverse events (e.g., safety, toxicity, adverse effect), specific organ system classes (e.g., kidney, muscle, lung), or specific adverse events of interest (e.g., agranulocytosis, pancreatitis). The titles and abstracts for the results for all searches were reviewed for safety information, and where appropriate, publications were obtained and reviewed in greater detail. The Applicant included 102 publications to support the safety of colchicine for the proposed indication and doses.

## 7.2 Adequacy of Safety Assessments

The bulk of the safety data in this submission were 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.

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As noted above, the majority of safety data comes from the use of colchicine in patients with gout, a patient population that tends to have a high incidence of co-morbidities. Consequently, adverse event reporting in this patient population may overestimate the risk of colchicine and thus provides a more conservative analysis.

A total of 112 healthy volunteers were exposed to at least one dose of 0.6 mg colchicine in the Applicant-initiated PK studies. Thirty-six patients received two successive days of 0.6 mg colchicine doses and again 21 days later for a total of 2.4 mg colchicine exposure. The remainders of the patients were exposed to two 0.6 mg doses eight day apart. Subjects ranged in age between 18 and 56 years, Subjects ranged in age between 18 and 56 years, were largely Caucasian (77%), and mostly male (70%). The majority of the data from the published literature comes from the use of colchicine in the treatment of gout but also other less common inflammatory diseases (e.g., FMF, Behçet's disease) and for the treatment of cirrhosis. The literature

encompasses both sexes of all ages (under 1 year to elderly) and a variety of ethnicities.

Taken together, the sources of data submitted by the Applicant are adequate for the assessment of safety of colchicine in terms of exposure, range of doses, and patient population.

#### 7.2.2 Explorations for Dose Response

Not applicable to this application.

#### 7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this application.

#### 7.2.4 Routine Clinical Testing

Not applicable to this application.

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4, Clinical Pharmacology

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable as colchicine is the only member of its drug class.

### 7.3 Major Safety Results

Orally administered colchicine is generally well tolerated when used in therapeutic doses. Gastrointestinal AEs are typically the most common toxicity and when severe can be viewed as a harbinger of more serious colchicine toxicity should dosing continue. Even with long-term treatment, AEs other than gastrointestinal toxicities are uncommon. The majority of significant colchicine-related AEs reported in the literature are related to inappropriate dosing, intentional/unintentional overdosing, and drug-drug-interactions.

#### 7.3.1 Deaths

Oral colchicine-related deaths reported in the published literature were more commonly described in patients who had a combination of impaired organ function, complicating diseases, high doses of colchicine, and/or co-administration of a strong CYP3A4 and P-gp inhibitor. In fact, a large proportion of the deaths were reported in patients who were receiving therapeutic doses of colchicine with concomitant clarithromycin, which is

believed to dramatically increase serum concentrations of colchicine<sup>7, 8</sup>. No deaths were reported in the Applicant-initiated PK studies. Overdoses are discussed further in Section 7.6.4.

### 7.3.2 Nonfatal Serious Adverse Events

For purposes of this review, serious adverse events and significant adverse events will be discussed together.

#### 7.3.2.1 Adverse Events from Applicant-Initiated PK Studies

A total of 107 AEs were reported in 56 patients from the Applicant-initiated PK studies. No deaths or serious adverse events were reported. The most commonly reported AEs among the 112 healthy volunteers exposed to at least one oral dose of colchicine 0.6 mg were headache (10%) and nausea (10%). All of the AEs were of mild to moderate severity and none of the AEs required discontinuation from the study. Other AEs reported in less than 2 subjects included fatigue, pollakuria, numbness, psoriasis flare, sore throat, somnolence, dyspepsia, constipation, decreased appetite, blurry vision, venous puncture site pain, dizziness, sinus congestion, red eye, abdominal pain, loose stool, metallic or bitter taste, dry mouth, venous puncture site hematoma, insomnia, hand pain, muscle cramping, and increased thirst.

In general, the AEs reported during the Applicant's PK studies serve limited utility in the overall safety assessment of colchicine since the subjects were healthy volunteers and only received two doses of colchicine. Furthermore, approximately half of the patients received a concomitant drug per protocol that may also have been responsible for the AE. Overall, no new safety signals were identified during the review of the safety data from the Applicant's PK studies.

#### 7.3.2.2 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 database searches. Many of these reports describe 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 doses of colchicine. Overdosing of colchicine is discussed separately in Section 7.6.4.

##### 7.3.2.2.1 Cardiovascular System

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<sup>7</sup> Cheng VC et al. South Med J 2005; 98:811-13

<sup>8</sup> Dogukan A et al. Clin Nephrol 2001; 55:181-82.

Review of the literature did not identify any cardiovascular AEs at therapeutic doses of colchicine; however, AEs were identified with colchicine overdosing (Section 7.6.4).

#### 7.3.2.2.2 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. Typically, discontinuation or reduction of the dose leads to resolution of symptoms. Table 6. GI adverse events from the Paulus and Borstad studies shows the frequency of gastrointestinal adverse events in the Paulus and Borstad studies.

**Table 6. GI adverse events from the Paulus and Borstad studies**

	Colchicine	Placebo
<b>Borstad et al., 2004</b>	0.6 mg once or twice daily × 3 months	
N	21	22
Any AE	9 (43%)	8 (36%)
Diarrhea	8 (36%)	1 (5%)
<b>Paulus et al., 1974</b>	0.5 mg t.i.d. × 6 months 3	
N	20	18
Any AE	15 (75%)	8 (44%)
Gastrointestinal AEs	15 (75%)	8 (44%)
Diarrhea	9 (45%) <sup>4</sup>	6 (33%)
Nausea, vomiting, or anorexia	11 (55%)	5 (28%)
Steadily increasing SGOT/SGPT	1 (5%)	0

Severe gastrointestinal AEs associated with overdosing of colchicine are described in Section 7.6.4.

#### 7.3.2.2.2.1 Hepatotoxicity

Although patients with hepatic insufficiency are at a higher risk of developing colchicine toxicity as a result of decreased metabolism, no directly related colchicine-induced hepatotoxic AEs were identified in the literature with therapeutic doses of colchicine. However, hepatotoxicity has been reported in patients exposed to overdoses of colchicine and is further discussed in Section 7.6.4.

#### 7.3.2.2.2 Pancreatitis

Review of the literature found a single reported case of acute pancreatitis occurring in an elderly male patient with pre-existing renal impairment treated with therapeutic doses of colchicine.

#### 7.3.2.2.3 Blood Dyscrasias

Suppression of bone marrow function is a well-known dose-related AE associated with colchicine and cases of pancytopenia, agranulocytosis, leukopenia, and thrombocytopenia have been reported in the literature. The vast majority of these reports were related to overdoses of colchicine, or cases where therapeutic doses were administered to patients with hepatic and/or renal insufficiency or who were receiving concomitant drugs known to interfere with the metabolism of colchicine. However, review of the literature did describe several cases of colchicine-related leukopenia given at therapeutic doses:

- A young female patient with FMF demonstrated a temporal relationship between repeated doses of colchicine and decreases in her leukocyte and platelet counts. Although the patient was later found to have had a concomitant cytomegalovirus infection, the authors contributed the leukopenia to colchicine<sup>9</sup>.
- A 68-year-old male developed neutropenia following several days of treatment with therapeutic doses of colchicine<sup>10</sup>. The neutropenia resolved following discontinuation of colchicine and initiation of filgrastim.
- An 85-year-old male was reported to develop a colchicine-related leukopenia following long-term colchicine therapy<sup>11</sup>. Review of the case report revealed that the patient had several potential contributing factors including chronic lymphocytic leukemia and potentially reduced renal function.

#### 7.3.2.2.4 Metabolic and Nutritional Disorders

No metabolic or nutritional disorder AEs with therapeutic doses of colchicine were identified in the literature search.

#### 7.3.2.2.5 Musculoskeletal System

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<sup>9</sup> Ben-Chetrit E and Navon P Clin Exp Rheumatol 2003; 21:S38-40.

<sup>10</sup> Dixon AJ and Wall GC Ann Pharmacother 2001; 35:192-195.

<sup>11</sup> Beggs AE et al. Am J Health Syst Pharm 2012; 69:2147-48

#### 7.3.2.2.5.1 Neuromuscular Toxicity

Colchicine-related neuromuscular toxicity has been well described in the medical literature and was extensively reviewed by Kuncl et al. in 1987<sup>12</sup>. Two subsequent articles were also published that essentially agreed with the conclusions drawn by Kuncl et al.<sup>13,14</sup> Patients with colchicine-induced neuromuscular toxicity typically present with proximal muscle weakness and elevated creatine kinase levels, which may be mistakenly diagnosed as an inflammatory myopathy. Patients with renal impairment and elderly patients, even with normal renal and hepatic function, are at increased risk to develop colchicine-induced neuromuscular toxicity. Additionally, review of the literature demonstrated that use of statins, fenofibrate, or cyclosporine may also potentiate the development of colchicine-induced myopathy.

#### 7.3.2.2.6 Rhabdomyolysis

Over 30 publications in the literature have reported colchicine-associated rhabdomyolysis with a significant proportion of the cases occurring in patients receiving therapeutic concentrations of colchicine in conjunction with concomitant drugs or who have renal/hepatic insufficiency.

#### 7.3.2.2.7 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; however, symptoms typically improve following discontinuation of colchicine.

#### 7.3.2.2.8 Respiratory System

Review of the literature did not identify any respiratory AEs at therapeutic doses of colchicine; however, AEs were identified with colchicine overdosing (Section 7.6.4).

#### 7.3.2.2.9 Skin and Integument

Dermatologic reactions to colchicine are rare at therapeutic doses. Review of the literature identified a single case of toxic-epidermal-necrosis-like syndrome that may have been associated with colchicine; however, the case is complicated by concomitant administration of allopurinol, which is known to cause toxic epidermal necrosis syndrome. Rare cases of alopecia have been described in patients with FMF.

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<sup>12</sup> Kuncl RW et al, N Engl J Med 1987; 316:1562-68.

<sup>13</sup> Wibur K and Makowsky M, Pharmacotherapy 2004; 24(12):1784-92.

<sup>14</sup> Wallace SL et al, J Rheumatol 1991; 18(2):264-9.

#### 7.3.2.2.10 Urologic System

Review of the literature did not identify any urologic-related AEs at therapeutic doses of colchicine; however, AEs were identified with colchicine overdosing (Section 7.6.4).

#### 7.3.3 Dropouts and/or Discontinuations

Three healthy volunteers treated with propafenone were discontinued from the Applicant's PK studies due to single cases of hypotension, hypertension, and tachycardia. Two patients were removed from the studies due to alcohol or illicit drug use. Study discontinuation in the two randomized controlled studies used to support the efficacy of colchicine in the application is discussed in Section 5.

#### 7.3.4 Significant Adverse Events

Refer to Section 7.3.2

### 7.4 Supportive Safety Results

#### 7.4.1 Common Adverse Events

Refer to Section 7.3.2

#### 7.4.2 Laboratory Findings

Changes in laboratory finding are based on the limited data provided by the Applicant's PK studies and changes described in the published literature.

##### 7.4.2.1 Laboratory Findings from Applicant-Initiated PK Studies

Laboratory results were obtained at baseline and following colchicine dosing from the healthy volunteers who participated in the Applicant-initiated PK studies. Overall, there were no clinically significant changes in blood chemistry, hematologic or urinalysis laboratory values.

##### 7.4.2.2 Published Scientific Literature

Myelosuppression is a known dose-related AE associated with colchicine and life-threatening granulocytopenia and/or thrombocytopenia generally occur 24 to 48 hours after an acute overdose. As discussed above, published reports were identified that

described cases of leukopenia, thrombocytopenia, and neutropenia. Although abnormal serum chemistry values during AEs or toxic exposures have been reported, in general clinically significant serum chemistry values have not been reported with therapeutic doses of colchicine.

#### 7.4.3 Vital Signs

There were no clinically meaningful changes in vital signs observed in the Applicant-initiated PK studies. Similarly, no publications were identified from the scientific literature search regarding colchicine-related changes to patient vital signs.

#### 7.4.4 Electrocardiograms (ECGs)

The Applicant was not required to pursue formal QT prolongation studies based on the known toxicity profile of colchicine.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

Specific analyses exploring dose dependency for adverse events were not performed for this application; however, 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. Nevertheless, 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 rather severe and consequently dose-limiting.

Specific to the current application, the two randomized controlled trials studied colchicine doses ranging from 0.6 mg/d to 1.5 mg/d. In the study by Borstad et al., patients were treated blindly with colchicine 0.6 mg twice daily with the option of reducing the dose 0.6 mg once daily if they could not tolerate the dose or experienced adverse effects. While only 43% of patients reported having an adverse effect with colchicine 0.6 mg twice daily, a total of 62% of colchicine-treated patients reduced their dose 0.6 mg once daily. These data suggest that higher doses of colchicine may not be well tolerated.

#### 7.5.2 Time Dependency for Adverse Events

Not applicable to this application.

### 7.5.3 Drug-Demographic Interactions

While definitive evidence is lacking, at least one literature publication noted that elderly individuals may be more sensitive to the toxic effects of colchicine due to age-related impairments in renal and hepatic function<sup>15</sup>.

### 7.5.4 Drug-Disease Interactions

Despite limited data regarding colchicine metabolism and PK in patients with hepatic and/or renal insufficiency, the large number of the case reports describing colchicine-related AEs in this patient population strongly suggests an increased risk of toxicity as a result of reduced colchicine metabolism and excretion. Indeed, hepatic impairment may significantly decrease the clearance of colchicine and increase its plasma half-life compared to healthy subjects. A 2005 meta-analysis evaluated the safety of colchicine in patients with liver fibrosis and cirrhosis and reported a greater frequency of serious adverse events in patients taking colchicine compared to patients not receiving colchicine (2% vs. 0, respectively)<sup>16</sup>. Similarly, in the same study, a larger proportion of patients reported a non-serious AE compared to patients in the control arm (9% vs. 1%, respectively). Similarly, renally impaired FMF patients treated with colchicine were reported to have significantly reduced clearance and prolonged plasma half-life of the drug.<sup>17</sup> These authors recommended caution in treating patients with renal insufficiency with colchicine and suggested a dose reduction based on the patients' creatinine clearance.

In summary, colchicine-related serious adverse events, including death, have been reported in the scientific literature with the use of therapeutic doses of colchicine in patients with hepatic and renal impairment. As a result, healthcare providers should use caution when prescribing colchicine in this patient population and consider lower doses than that recommended for patients with normal renal and hepatic function. However, given the lack of data correlating specific serum concentrations with increasing frequency or severity of AEs in this population, and given the potential for multiple confounding factors in individual patients (e.g., concomitant drugs), it is difficult to make specific dosing recommendations that one would be confident would improve safety. It may not be any safer to have specific dose modification recommendations than to instruct the healthcare practitioner to adjust on a case-by-case basis, based on close monitoring for clinical toxicity, e.g., gastrointestinal symptoms, and adjust, or discontinue dosing as applicable.

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<sup>15</sup> Terkeltaub RA. *N Engl J Med* 2003; 349:1647-55.

<sup>16</sup> Rambaldi A and Gluud C. *Cochrane Database Syst Rev* 2005; 18(2): CD002148.

<sup>17</sup> Ben-Chetrit E et al. *J Rheumatol* 1994; 2(4):710-13.

### 7.5.5 Drug-Drug Interactions

Colchicine metabolism includes demethylation by the CYP3A4 pathway and elimination via P-gp-mediated biliary excretion. The reader is referred to the Clinical Pharmacology review by Dr. Agarwal for a thorough analysis of the drug-drug interaction data.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

No reports of malignancies were identified in the data submitted by the Applicant.

### 7.6.2 Human Reproduction and Pregnancy Data

The Applicant is proposing colchicine be labeled as an FDA Category C based on animal reproduction studies demonstrating adverse effects on the fetus but in the absence of adequate and well-controlled studies in humans. Although not well-controlled studies, there are data suggesting that colchicine may be safe during pregnancy. One retrospective study reviewed patients of childbearing age with gout who conceived children while taking colchicine for 5 to 20 years<sup>3</sup>. Rabinovitch et al.<sup>18</sup> conducted a study in 116 women with FMF and reported there was no increase in fetal abnormalities, growth disturbances or other developmental abnormalities in 130 children of mothers treated with colchicine. Additionally, Berkenstadt et al.<sup>19</sup> reviewed the reproductive histories of 326 couples referred for prenatal diagnosis at Sheba Medical Center between 1976 and 2003 because one, or both, partners were diagnosed with FMF. Patients were asked to report on the outcome of each previous pregnancy and whether colchicine had been taken at conception and/or during pregnancy. There were a total of 901 pregnancies recorded among the couples of which 14 were reported with chromosomal abnormalities. The authors concluded that the rates and types of abnormalities observed in their patient cohort were not higher than background rates of individuals not receiving colchicine.

It cannot be assured that these data are free from bias. For example, the data are derived from patients who were able to present to medical attention while pregnant; patients who may have had early miscarriages related to fetal teratogenicity may not have been aware and would not have been accounted for. There are also limited data on pregnancy outcomes in patients with gout or FMF who did not receive colchicine and whether patients did or did not continue colchicine during pregnancy was not at random.

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<sup>18</sup> Rabinovitch O et al. *Am J Reprod Immunol* 1992; 28(3-4):245-6.

<sup>19</sup> Berkenstadt M et al. *Am J Obstet Gynecol* 2005; 193:1513-16.

For these reasons, the data in the published literature are not definitive, although the accrued clinical experience of the last 3 decades appears to support a recommendation to continue colchicine during pregnancy in order to control attacks of FMF, which appear to have a greater negative impact on pregnancy outcomes. That said, it remains an open question whether the benefits of continuing colchicine for gout in pregnant women who have gout (this is uncommon) would outweigh the risks colchicine for the fetus. There are no human data to address this question and the animal data would not be superseded in the case of gout patients. Therefore, despite several reports suggesting the safety of colchicine during pregnancy, a rating of FDA Category C is appropriate.

#### 7.6.2.1 Lactation

No publications, postmarketing reports, or data from US or foreign labels of AEs were identified regarding breast-feeding infants of mothers treated with colchicine.

#### 7.6.2.2 Fertility

No well-controlled trials have been conducted to assess the effect of colchicine on male and female fertility. There are conflicting reports in the literature regarding the effects of colchicine on male fertility in patients with FMF<sup>20,21</sup> and only very limited studies in females<sup>22</sup>. Given the lack of data, it is not possible to conclude whether colchicine affects fertility in humans.

#### 7.6.3 Pediatrics and Assessment of Effects on Growth

Except in rare circumstances, gout does not occur in the pediatric population. Most of the information on colchicine in pediatric patients comes from the use of colchicine for the treatment of FMF.

#### 7.6.4 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 rather severe and if ingestion is discontinued based on gastrointestinal symptoms, life-threatening toxicity can usually be avoided. Severe toxicities were common with intravenously administered colchicine as

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<sup>20</sup> Ehrenfeld et al. *Andrologia* 1986; 18:420-26.

<sup>21</sup> Levy M and Yaffe C *Fertil Steril* 1978; 29:667-68.

<sup>22</sup> Ben-Chetrit E and Navon P *Clin Exp Rheumatol* 2003; 21:S38-40.

therapeutic doses could be exceeded without the patient experiencing the dose-limiting GI 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 variable 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 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.

The manifestations of colchicine toxicity can be divided into three sequential overlapping stages as outlined in Table 7. Clinical stages of colchicine overdose.<sup>23</sup> 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 7. Clinical stages of colchicine overdose**

<b>Stage 1</b>	<b>Stage 2</b>	<b>Recovery</b>
Abdominal pain	Renal failure	Leukocytosis
Nausea	Respiratory failure	Alopecia
Vomiting	Cardiac failure	
Diarrhea	Pancytopenia	
Dehydration	Metabolic Acidosis	
	Electrolyte disturbances	
	DIC	
	Convulsions	
	Coma	

Source: Ben-Chetrit and Levy

Putterman et al. published a summary of the toxic effects of colchicine on based on body systems and concluded that the most common cause of death from colchicine overdose is cardiovascular collapse, which is manifested by cardiogenic shock<sup>24</sup>. Respiratory involvement occurs in approximately 33% of colchicine overdoses with increasing respiratory distress leading to hypoxemic respiratory failure. Hematologic

<sup>23</sup> Ben-Chetrit E and Levy M Semin Arthritis Rheum 1998;28(1):48-59.

<sup>24</sup> Putterman C et al Semin Arthritis Rheum 1991; 21(3):143-55.

manifestations were observed in all three stages of colchicine overdosing. In Stage 1, patients may develop leukocytosis but by Stage 2 bone marrow hypoplasia and coagulation abnormalities are evident. Bone marrow recovery typically begins 8 days after post-ingestion and is manifested by a rebound leukocytosis. Neurologic involvement includes mental status changes, transverse myelitis, ascending paralysis, and seizures. Renal complications 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 with colchicine overdosing. 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 has been reported to be ineffective due to the extensive volume of distribution of colchicine.

## **8 Postmarket Experience**

Not included in Applicant's submission.

## **9 Appendices**

### **9.2 Labeling Recommendations**

Specific labeling recommendations are pending following the final review of the application.

### **9.3 Advisory Committee Meeting**

An Advisory Committee Meeting was not convened for this application.

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/s/  
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KEITH M HULL  
07/09/2013

West-Ward Pharmaceuticals (a subsidiary of Hikma Pharmaceuticals PLC) has submitted a 505(b)(2) application for the development of colchicine 0.6 mg capsules for the prophylaxis of gout flares in adults. The safety and efficacy of colchicine in the treatment of gout is well-established in the scientific literature. In support of their application, West-Ward Pharmaceuticals has provided data from the published literature to support their application. Additionally, the sponsor has submitted six applicant-initiated studies including a comparative bioavailability study, six drug interaction studies, and a food effect study.

Overall, the application appears to contain adequate references to the scientific literature and is in an acceptable format to allow for the review of the data regarding the proposed claim. After reviewing the submission, the package appears to be acceptable for filing. A comment to the sponsor will need to be conveyed regarding the necessity to correctly reference the licensed drug Col-Benemid for their application. The Office of Regulatory Policy (ORP) will draft this communication to the sponsor.



NDA 204820

Hikma (West-Ward), Colchicine for Chronic Gout

Filing Meeting  
Clinical Team  
November 15, 2012

## Summary

- 505(b)(2) application for colchicine 0.6 mg capsules
  - Colchicine 0.6 mg capsules compared to colchicine/probenecid (0.5 mg/500 mg)
  - Sponsor states there is no reference listed drug for this dosage form
- Proposed Indication
  - Prophylaxis of gout flares in adults
  - 0.6 mg capsule once or twice daily in patients  $\geq 16$  years of age
- The application is adequate to be filed from a clinical perspective

## Regulatory Background

- October 16, 2009
  - Colcrys 0.6 mg tablets approved for prophylaxis & treatment of gout flares

(b) (4)





## Current Submission



## ↑ Applicant-Initiated Studies

- Comparative Bioavailability (n=35)
  - Single-dose crossover comparing colchicine 0.6 mg vs. colchicine/prob 0.5 mg/500 mg
- Interaction study cimetidine (n=12)
  - Open-label, DI study of multiple doses of cimetidine on single-dose PK of colchicine
- Interaction study voriconazole (n=12)
  - Open-label, DI study of multiple doses of voriconazole on single-dose PK of colchicine
- Interaction study fluconazole (n=12)
  - Open-label, DI study of multiple doses of fluconazole on single-dose PK of colchicine
- Interaction study propafenone (n=9)
  - Open-label, DI study of multiple doses of propafenone on single-dose PK of colchicine
- Food effect study (n=27)
  - Open-label, R, SD, two-way, study investigating the effect of a high-fat meal on the bioavailability of colchicine 0.6 mg caps

## Clinical Data to Support Efficacy

- 2 Prospective Studies
  - Bordstad GC et al, 2004
  - Paulus HE et al, 1974
- 5 Open-labeled Studies
  - Yu TF, 1982
  - Becker MA et al, 2005<sup>F</sup>
  - Becker MA et al, 2005<sup>F</sup>
  - Karimzadeh H et al, 2006
  - Schumacher HR et al, 2008<sup>F</sup>

## Clinical Data to Support Safety

- Applicant-Initiated Studies
- Published Scientific Literature
- Additional data
  - Postmarketing safety data
- Drug-Drug Interaction Studies
  - Clinical Pharmacology

## Filing Checklist

- Overall generally acceptable
  - Is referenced drug acceptable?





## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2: Paulus HE et al, 1974 Indication: prophylaxis of gout flares				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?		X		
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?		X		

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?   YES**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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Keith M. Hull, MD, PhD  
Medical Officer

November 16, 2012  
Date

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Larissa Lapteva, MD  
Acting Clinical Team Leader

November 16, 2012  
Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KEITH M HULL  
11/16/2012

LARISSA LAPTEVA  
11/16/2012

## SUMMARY REVIEW OF REGULATORY ACTION

Date: August 5, 2013

From: Badrul A. Chowdhury, MD, PhD  
Director, Division of Pulmonary, Allergy, and Rheumatology  
Products, CDER, FDA

Subject: Division Director Summary Review

NDA Number: 20-4820

Applicant Name: Hikma Pharmaceuticals, West-Ward Pharmaceuticals (US Agent)

Date of Submission: October 5, 2012

PDUFA Goal Date: August 5, 2013

Proprietary Name: Mitigare

Established Name: Colchicine

Dosage form: Capsules

Strength: 0.6 mg in each capsule

Proposed Indications: Prophylaxis of gout flares in adults and adolescents 16 years of age and older

Action: Complete Response

### 1. Introduction

Hikma Pharmaceuticals through their US agent West-Ward Pharmaceuticals submitted this 505 (b)(2) NDA for use of Mitigare (colchicine) capsules for prophylaxis of gout flares in adults and adolescents 16 years of age and older. The proposed dose is 0.6 mg capsule once or twice daily. The applicant relies on FDA's finding of safety and efficacy for the combination product Col-Probenecid (colchicine 0.5 mg and probenecid 500 mg, ANDA 84729) and published literature to support its colchicine product. In addition, the applicant conducted clinical pharmacology studies: a relative bioavailability study to support reliance on FDA's findings of safety and effectiveness for Col-Probenecid; a food effect study; and drug-drug interaction studies to support relevant dose modification recommendations for its products when used with some other drugs. The proposed regulatory pathway and the submitted clinical pharmacology data to support this application are reasonable. This summary review provides an overview of the application with emphasis on the clinical pharmacology study findings. This application will not be approved because of manufacturing site inspection deficiency findings.

### 2. Background

Gout is an inflammatory arthritis associated with hyperuricemia and caused by the deposition of monosodium urate crystals in and around the tissues of joints. Symptomatic crystal deposition includes attacks of acute inflammatory arthritis, a chronic destructive arthropathy, and soft tissue accumulation of monosodium urate crystals (tophi). Management of gout involves two primary components: (1) Treatment and prophylaxis of acute joint and bursal inflammation. Drugs used to treat with this intent include non-steroidal anti-inflammatory agents (NSAIDs), corticosteroids, and

colchicine. (2) Lowering serum urate levels with the aim of avoiding recurrent inflammatory flares and progression of joint damage, and complications from deposition of monosodium urate crystals in various tissues and organs. Drugs used to treat with this intent include the uricosuric agent probenecid, the xanthine oxidase inhibitors allopurinol and febuxostat, and the recombinant mammalian uricase, pegloticase.

Colchicine, an alkaloid originally derived from the autumn crocus (*Colchicum autumnale*), has a long history of medicinal use, dating back to its first use as a purgative agent in ancient Egypt and Greece, more than 3000 years ago. Colchicine has been used for gout prophylaxis since the 1930s. However, colchicine was first approved by the FDA in 1961 as part of combination with probenecid for the chronic treatment of gout (Col-Benemid, containing colchicine 0.5 mg and probenecid 500 mg). Col-Benemid underwent review in the Drug Efficacy Study Implementation (DESI) process (FR Vol.37, No.146, 28 July 1972), which deemed the combination effective for “chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout,” or essentially, prophylactic treatment of gout flares. Single-ingredient colchicine tablets were available in the United States for decades as marketed but unapproved products, in 0.6 mg strength. The first FDA approved single-ingredient oral colchicine product was Mutual Pharmaceutical’s colchicine 0.6 mg tablets (Colcrys), which was approved in July 2009 for treatment of familial Mediterranean fever (FMF), and treatment of acute flares of gout; approval for the prophylactic treatment of gout was given in October 2009. Approval of Colcrys for prophylactic treatment of gout was based primarily on published literature and FDA’s finding of safety and effectiveness for the colchicine-probenecid combination product.

Colchicine has dose-related adverse reactions. The most common adverse reactions of colchicine are gastrointestinal (nausea, vomiting, abdominal pain, and diarrhea), which are reversible with discontinuation of colchicine. Overdose toxicity with colchicine can include electrolyte imbalance, bone marrow suppression, cardiovascular collapse, renal failure, rhabdomyolysis, seizures, mental status changes and death. Colchicine is estimated to be effective at doses of approximately 0.015 mg/kg, toxic in doses greater than 0.1 mg/kg, and typically lethal at doses of approximately 0.8 mg/kg. In the therapeutic range, plasma levels are approximately 0.5 to 3 ng/ml.<sup>1</sup>

Colchicine’s drug-drug interaction potential, as a P-gp<sup>2</sup> and cytochrome P450<sup>3</sup> substrate (specifically CYP3A4<sup>4</sup>), has long been reported in the literature. There are no widely-accepted specific recommendations for dose reduction in the setting of potential concomitant use of drugs with known interactions, other than avoidance when possible and caution when necessary, with vigilant monitoring for clinical signs of toxicity.

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

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

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

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

There are some regulatory issues relevant to this application. The major issues are summarized below.

In November 2010, Mutual Pharmaceuticals filed a Citizen Petition requesting, among other things, that any single-ingredient oral colchicine product reference Colcris, and include all drug-drug interaction information in Colcris labeling, including dose adjustments.<sup>5</sup> FDA disagreed that any single-ingredient oral colchicine product submitted through the 505(b)(2) pathway necessarily cite Colcris as its listed drug. With respect to drug-drug interaction labeling, FDA stated that product labeling for any single-ingredient oral colchicine product needs to include adequate information on drug-drug interactions, including relevant dose adjustment recommendations.<sup>6</sup>

(b) (4)

In November 2011, FDA met with West-Ward to discuss their development plan. West-Ward proposed to submit a 505(b)(2) application for a capsule formulation, and agreement was reached on a development program that included 4 drug-drug interaction studies: one each with a strong, moderate, and weak CYP3A4 inhibitor, and a P-gp inhibitor.

### **3. Chemistry, Manufacturing, and Controls**

The proposed commercial drug product, Mitigare Capsules, contains 0.6 mg colchicine and standard compendial excipients. The drug product will be packaged in bottles of 100 or 1000 capsules. The manufacturing process utilizes (b) (4) of the formulation. This manufacturing process was used for producing batches used in stability study, and in the clinical pharmacology studies submitted to support this application. The same manufacturing process is proposed for commercial production. Based on the stability data, a 24-month expiration-dating period is supported. The colchicine drug substance will be manufactured by (b) (4). The finished drug product manufacturing, packaging, and testing site will be West-Ward Pharmaceuticals facility at Eatontown, New Jersey. The drug substance manufacturing site in (b) (4) has acceptable inspection status. The West-Ward facility in New Jersey has unacceptable inspection findings due to general cGMP violations, and also problems specific to colchicine drug product manufacturing.

### **4. Nonclinical Pharmacology and Toxicology**

No new non-clinical toxicology studies were required or performed for this application.

<sup>5</sup> <http://www.regulations.gov/#!documentDetail;D=FDA-2010-P-0614-0002>

<sup>6</sup> <http://www.regulations.gov/#!documentDetail;D=FDA-2010-P-0614-0072>

## 5. Clinical Pharmacology and Biopharmaceutics

The applicant conducted a relative bioavailability study, a food effect study, and four drug-drug interaction studies in support of this application. Results of these studies are briefly summarized below.

The relative bioavailability of the applicant's 0.6 mg capsule product showed slightly higher C<sub>max</sub> (~17% higher C<sub>max</sub>) and equivalent AUC compared to dose-normalized C<sub>max</sub> and AUC parameters respectively of the reference, Col-Probenecid (0.5 mg colchicine and 500 mg probenecid). The food effect study did not show much effect on colchicine PK (~11% lower C<sub>max</sub>, 12% lower AUC). The food effect study was conducted with a tablet formulation, which was found to be acceptable because the tablet and capsule have similar formulations and dissolution data showed similar dissolution profiles for the tablet and the capsule formulations.

The applicant conducted four drug-drug interactions studies - one with the weak CYP3A4 inhibitor cimetidine, one with the moderate CYP3A4 inhibitor fluconazole, one with the strong CYP3A4 inhibitor voriconazole, and one with the P-gp inhibitor propafenone. These studies did not show a significant interaction with any of the four probes, except for a 40% increase in AUC of colchicine with fluconazole (Table 1). These results were unexpected, given that colchicine's drug-drug interaction potential, as a P-gp<sup>7</sup> and cytochrome P450<sup>8</sup> substrate (specifically CYP3A4<sup>9</sup>), has long been reported in the literature. These unexpected results are likely due to the fact that the drugs used in these studies are considered to inhibit only the CYP3A4 pathway or the P-gp pathway, but not both pathways. Whereas, drugs such as clarithromycin, erythromycin, cyclosporine, and azithromycin, that could be considered to significantly interact with colchicine (as indicated by > 20% inhibition in the University of Washington drug-interaction database<sup>10</sup>) appear to have effects on both CYP3A4 and P-gp pathways.

**Table 1. Pk parameters of colchicine in the presence and absence of various inhibitors**

	Voriconazole		Fluconazole		Cimetidine		Propafenone	
	Presence	Absence	Presence	Absence	Presence	Absence	Presence	Absence
C <sub>max</sub> (pg/mL)	2663	2058	1926	2299	2997	2109	2118	2206
AUC (pg.h/mL)	19605	20731	14939	21270	20382	18082	16626	16777
T <sub>1/2el</sub> (h)	30	31	34	35	35	32	30	28

Although there are no published reports for colchicine toxicity when co-administered with the four inhibitors that the applicant used (i.e., voriconazole, fluconazole, cimetidine

<sup>7</sup> AR Safa, ND Mehta, M Agresti, "Photoaffinity labeling of P-glycoprotein in multidrug resistant cells with photoactive analogs of colchicine." *Biochem and Biophys Res Com*, 1989; 162(3):1402-1408

<sup>8</sup> AL Hunter, CD Klassen, "Biliary excretion of colchicine." *J Pharmacol Exp Ther*, 1974; 192:605-17

<sup>9</sup> T Tateiski, et al. "Colchicine biotransformation by human liver microsomes: identification of CYP3A4 as a major isoform responsible for colchicine demethylation." *Biochem Pharmacol*, 1997; 10:111-16

<sup>10</sup> <http://www.druginteractioninfo.org/>

and propafenone), 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). As such, and based on these published case reports, general cautionary language informing health care providers and patients about drug-drug interaction potential of colchicine will be included in label along with simpler recommendations for close monitoring and dose adjustment based on clinical judgment if co-administered with dual inhibitors of CYP3A4 and P-gp as well as with CYP3A4 inhibitors or P-gp inhibitors. The applicant's drug-drug interaction study results and published reports suggest that it may not be appropriate to recommend precise dose modifications based on one CYP3A4 inhibitor to another, or one P-gp inhibitor to another.

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical and Statistical – Efficacy**

### **a. Overview of the clinical program**

The applicant did not conduct any efficacy studies for colchicine and none were required. The primary evidence of the efficacy of colchicine for the prophylactic treatment of gout is derived from the published literature.<sup>11, 12</sup>

### **a. Design and conduct of studies**

Not applicable.

### **b. Efficacy findings and conclusions**

The totality of evidence that includes many published studies, DESI review, and a long history of clinical use supports the efficacy of colchicine for prophylaxis of gouty flares.

## **8. Safety**

### **a. Safety database**

The applicant did not conduct any safety studies for colchicine and none were required. The evidence of safety of colchicine is derived from the published literature and use experience.

### **b. Safety findings and conclusion**

The published literature is adequate to support the safety of colchicine for prophylaxis of gout flares.

### **c. REMS/RiskMAP**

No post-marketing risk evaluation and mitigation strategies are recommended.

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<sup>11</sup> Paulus HE et al. *Arthritis Rheum* 1974; 17(5):609-14.

<sup>12</sup> Borstad GC et al. *J Rheumatol* 2004; 31(12):2429-32.

## **9. Advisory Committee Meeting**

An advisory committee was not convened for this application because colchicine is a well-known drug and the efficacy and safety of colchicine in gout is well accepted. However, a Regulatory Briefing was held on May 31, 2013, to discuss the results of the drug-drug interaction studies and labeling of this product. The discussants agreed that the clinical pharmacology data submitted by the applicant are sufficient for approval of this application for colchicine, and a product label can be written based on case reports described in the published literature and the specific clinical pharmacology studies conducted by the applicant.

## **10. Pediatric**

The applicant submitted a request for waiver of pediatric studies because gout is an adult disease and rarely occurs in children; therefore, specific pediatric studies are not feasible. In children, gout occurs almost exclusively in the setting of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency (also known as Lesch-Nyhan syndrome and Kelley-Seegmiller syndrome), which are rare diseases. The review team and the Center's Pediatric Review Committee (PeRC) agreed that a full waiver is justified.

## **11. Other Relevant Regulatory Issues**

### **a. DSI Audits**

DSI conducted an audit of one drug-drug interaction clinical pharmacology study site and the associated analytical site. The inspection did not reveal any significant deficiencies. During review of this submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

### **b. Financial Disclosure**

The applicant submitted acceptable financial disclosure statements. No potentially conflicting financial interests were identified.

### **c. Others**

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

## **12. Labeling**

### **a. Proprietary Name**

The proposed proprietary name Mitigare was reviewed by DMEPA and found to be acceptable. The name was also found to be acceptable to OPDP from a promotional perspective.

b. Physician Labeling

The applicant submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, DRISK, DMEPA, and OPDP. Various changes to different sections of the label were made to reflect the data accurately and better communicate the findings to health care providers. Because of the uncertainty raised by the applicant's drug-drug interaction studies with respect to the generalizability and accuracy of detailed dose modification recommendations (discussed in section 5 above), a less prescriptive approach to drug interaction- and organ dysfunction- related treatment recommendations will be reflected in the label. The final labeling was not done because the product will not be approved in this review cycle.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, ONDQA, OPMP, and DMEPA, and were found to be acceptable.

d. Patient Labeling and Medication Guide

The applicant submitted a Medication Guide, which was reviewed by the Division, and by OPDP and the Division of Medical Policy Programs (DMPP). Several edits were made to the Medication Guide to simplify or clarify proposed wording, remove redundancy, and ensure consistency with the prescribing information.

### **13. Action and Risk Benefit Assessment**

a. Regulatory Action

The applicant has submitted adequate data to support approval of colchicine 0.6 mg capsules for the prophylaxis of gout flares. However, the application will not be approved in this review cycle because of unacceptable inspection findings of the West-Ward facility in New Jersey (discussed in section 3).

b. Risk Benefit Assessment

The risk and benefit assessment of colchicine at the proposed dose of 0.6 mg once or twice daily supports its approval. The efficacy and safety of colchicine for the prophylaxis of gout flares of gout is known from the clinical literature and established clinical practice. This application can be approved once the unacceptable inspection findings of the West-Ward facility in New Jersey are resolved.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

None.

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BADRUL A CHOWDHURY  
08/05/2013