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RESEARCH**

*APPLICATION NUMBER:*

**204820Orig1s000**

**SUMMARY REVIEW**

## SUMMARY REVIEW OF REGULATORY ACTION

Date: September 26, 2014

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

Subject: Division Director Summary Review  
NDA Number: 204820  
Applicant Name: Hikma Pharmaceuticals, West-Ward Pharmaceuticals (US Agent)  
Date of Submission: March 28, 2014 (original NDA was submitted on October 5, 2012)  
PDUFA Goal Date: September 28, 2014 (PDUFA due date for the original NDA was 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: Approval

### 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 effectiveness 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 finding of safety and effectiveness for Col-Probenecid; a food effect study; and drug-drug interaction studies to support relevant dose modification recommendations for its product 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 was not approved in the first review cycle because of an outstanding facility inspection, which is now resolved.

### 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 (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. (b) (4)

(b) (4) 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. Manufacturing and testing facilities associated with the drug substance and drug product have an acceptable GMP recommendation from Office of Compliance.

### 4. Nonclinical Pharmacology and Toxicology

No new nonclinical 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 interaction (DDI) 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 submitted DDI studies are considered to inhibit only the CYP3A4 pathway or the P-gp pathway, but not both pathways. Whereas, interaction potential cited in the literature involved 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	
	Absence	Presence	Absence	Presence	Absence	Presence	Absence	Presence
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

<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/>

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 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 the 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 findings and published reports suggest that the results are highly variable from one CYP3A4 inhibitor to another, or from one P-gp inhibitor to another. Therefore, it may not be appropriate to recommend precise dose modifications based on currently available drug-drug interaction information for colchicine.

## **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 gout 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.

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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.

c. REMS/RiskMAP

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

### **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 OPDP, 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, 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.

### **c. Carton and Immediate Container Labels**

These were reviewed by various disciplines of this Division, ONDQA, OPDP, 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. The regulatory action on this application will be Approval.

### **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 is known from the clinical literature and established clinical practice.

### **c. Post-marketing Risk Management Activities**

None.

### **d. Post-marketing Study Commitments**

None.

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BADRUL A CHOWDHURY  
09/26/2014