CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-353

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA/Supplement #	22-353/000
Applicant Name	Mutual Pharmaceutical Company
Date of Submission	November 25, 2008
PDUFA Goal Date	September 25, 2009
Proprietary Name / Established (USAN) Name	Colcrys / Colchicine
Dosage Forms / Strength	Tablet/ 0.6 mg
Proposed Indication(s)	Prevention of gout flares
Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Jane Gilbert, M.D. / Jeffrey Siegel, M.D.
Statistical Review	Dave Petullo, Ph.D. / Dionne Price, Ph.D.
Pharmacology Toxicology Review	Steve Leshin, D.V.M., Ph.D. / Adam Wasserman Ph.D.
CMC Review	Craig Bertha Ph.D. / Ali Al-Hakim, Ph.D.
Clinical Pharmacology Review	Srikanth Nallani, Ph.D. / Suresh Doddapaneni, Ph.D.
DDMAC	Matilda Fienkeng / Twyla Thompson / Mike Sauers
OSE/DMEPA	Lori Cantin, R.Ph. / Loretta Holmes, B.S.N., Pharm.D./ Kristina Arwine, Pharm.D. / Denise Toyer, Pharm.D. / Carol Holquist, R.Ph.

CDTL = Cross-Discipline Team Leader
CMC = Chemistry, Manufacturing, and Controls
DDMAC = Division of Drug Marketing, Advertising and Communication
DMEPA = Division of Medication Error Prevention and Analysis
OND = Office of New Drugs
OSE = Office of Surveillance and Epidemiology

1. Introduction

Colchicine is an alkaloid derived from the plant *Colchicum autumnale*, also known as the autumn crocus. It has had a role in medicinal applications dating back to the times of ancient Greece, initially as a purgative agent and later as a treatment for gout. In the United States it has been used as a purified, single active ingredient since the early part of the nineteenth century, yet it has only been formally approved by the Food and Drug Administration as part of a combination product with probenecid. The combination product, known as ColBenemid, consists of colchicine, 0.5 mg, and probenecid, 500 mg, and was initially approved in 1961. This approval predated the requirement for the demonstration of efficacy, therefore the combination underwent review by the National Academy of Sciences under the Drug Efficacy Study Implementation (DESI) process. The combination was deemed to be effective for the treatment of "chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout" in 1972. As a single-entity product, colchicine, was a marketed unapproved product until July 2009, at which time it was approved for the treatment of familial Mediterranean fever (FMF) and for the treatment of acute gout flares.

The applicant has submitted an application for the use of colchicine in the prevention of acute gout flares in adults. The proposed dosing regimen is 0.6 mg, once or twice daily.

This review will provide an overview of the regulatory and scientific facts of this supplemental application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling modifications requested by the Applicant.

2. Background

As noted in Dr. Siegel's review, gout is a rheumatologic condition known for its chronic manifestations as well as its acute flares. The underlying predisposing factor is elevated levels of uric acid, and although not everyone with hyperuricemia develops gout, the risk of the clinical development of gout increases as the circulating levels of uric acid go above 6 mg/dL. The clinical presentation is usually an acute, painful attack of monoarthritis, typically involving the great toe, also known as podagra. Some patients experience only a single episode of acute gout; however, some go on to develop chronic gout, manifested as recurrent episodes of acute gout as well as deposition of uric acid crystals in tissues, termed tophi.

Acute attacks of gout have been treated with anti-inflammatories, including non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids and ACTH. Chronic gout is treated with therapies intended to reduce uric acid levels to below 6 mg/dL, a level which is associated with a reduced the risk of gout flares and the resolution of tophi.

Colchicine has been used to treat gout since before the Middle Ages, and has established itself as the standard of care for patients with this disorder, despite the limited controlled trial data. The usual treatment regimen has been guided by the patient's ability to tolerate the treatment regimen, with instructions being to treat the acute flare with periodic doses of colchicine until

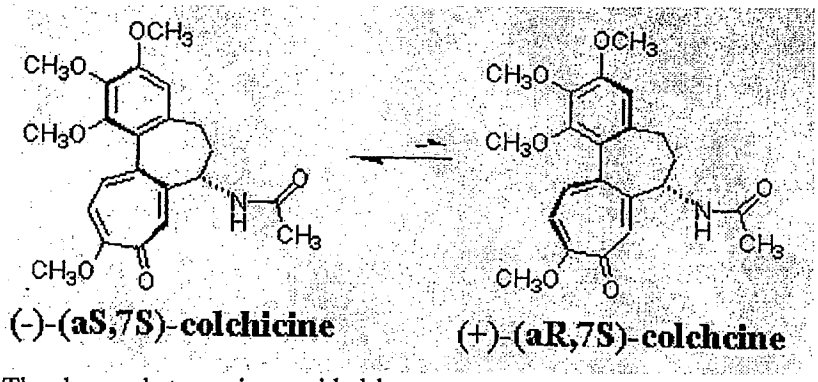
NDA 22-351 Colcrys (colchicine) the pain resolves, or dose-limiting toxicity develops. The dosage range identified in clinical texts is from 4 mg to 8 mg for an acute episode.

When the Applicant met with the Division in 2006 to discuss the clinical development for this indication, they were advised that a 505(b)(2) route was appropriate, but that they would need to conduct at least one adequate and well-controlled clinical trial to support the efficacy of their proposed regimen. They were also advised that they could supplement their application with data from published studies.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

The chemical name of Colchicine is N-[5,6,7,9-tetrahydro-1,2,3,10-tetratmethoxy 9-oxobenzo[a]heptalen-7-yl], (S)-acetamide. The molecular formula is C22H25NO6 and the molecular weight is 399.44 g/mole. In nature, colchicine exists in two forms, (-)-(aS,7S)-colchicine and (+)-(aR,7S)-colchicine. The two conformers interconvert relatively quickly when the compound is in solution and at ambient temperatures. The ratio of the two conformers is 99:1. b(4)



The drug substance is provided by ——— The Drug Master File (DMF ——— for the drug substance was initially found to be deficient and comments were sent to the applicant in a Discipline Review letter for NDA 22-352. The applicant responded to Dr. Bertha's concerns and the DMF has now been found to be adequate for approval. b(4)

The drug product is formulated as a tablet with the following excipients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and a proprietary coating from ——— The drug product will be packaged in HDPE bottles with internal desiccants, in the following tablet counts: 30, 60, 100, 250, 500, and 1000. The applicant also intends to ——— The expiration period proposed by the applicant for the bottled product is 24 months, and is supported by data in the application. b(4)

Facilities Review/Inspections

The Office of Compliance has completed the manufacturing site inspections and found them acceptable.

Outstanding or Unresolved Issues
I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Stability testing supports an expiry of 24 months at 20°C to 25°C (68°F to 77°F). There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The Applicant had previously submitted an application for the treatment of familial Mediterranean fever (NDA 22-352), which contained non-clinical data supporting the use of colchicine in humans. The Applicant did not submit any additional non-clinical data for this application for the treatment of acute gout flares, intending to support NDA 22-351 with the data submitted in NDA 22-352.

The observations below, which were made by Drs. Leshin and Wasserman with respect to NDA-22-352 and which appear in the Division Summary Review for Regulatory Action for that NDA, also apply to NDA 22-353.

General Considerations
The applicant has relied almost entirely on the published literature to support the nonclinical aspects of the application. As such, the pharmacology/toxicology review team has noted several important aspects of the application:

- The nonclinical studies submitted in support of the application are almost exclusively old, pre-dating the Good Laboratory Practices (GLP; in most cases they do not use current and preferred evaluation methodologies).
- The dose levels used in the nonclinical studies were intended to determine the effects, rather than the safety, of colchicine.
- The nonclinical studies available are almost exclusively of short duration (i.e., $\leq$ 5 weeks) and, therefore, do not support chronic dosing.
- The colchicine product used in the published studies is frequently of unknown quality and comparability when compared with the Applicant's drug product.
- The nonclinical data in the submission do not address all the nonclinical sections of the label (e.g. carcinogenicity).
- Genetic toxicology studies and the mechanism of action indicate colchicine may reasonably be expected to promote or induce neoplasia.
- Reproductive toxicology studies conducted in nonclinical models indicate a significant risk for embryofetal harm and reduced parental fertility.
- There is a potential drug product photo-degradant impurity which possesses a structural alert for mutagenicity and is not adequately controlled by specifications, or qualified through nonclinical studies.

Nevertheless, while cognizant of the limitations identified above, Dr. Wasserman has noted that "...the mechanism of action of colchicine (as a microtubule inhibitor/mitotic spindle poison) is certainly operative in all eukaryotic organisms. This is the reason that the manifestations of toxicity are so similar across species, including humans, as mentioned by Dr. Leshin. This, when combined with the well-understood clinical toxicity of long-term colchicine administration, precludes the need to provide modern, GLP-compliant chronic

toxicology studies in animals for support of the application." Drs. Wasserman and Leshin proceed to note that given the extensive clinical experience with colchicine, there is sufficient information available to support labeling of the product.

Genotoxicity

Colchicine is not directly genotoxic, but as a mitotic spindle poison, promotes the development of aneuploidy (a deviation from the normal complement of chromosomes) in the affected cells. The severity of the developmental outcome is dependent on when, and to which cells, the aneuploidy occurs. Dr. Wasserman noted that embryonic or germ line aneuploidy causes developmental abnormalities in many species, and that colchicine administration in reproductively aged animals induces significant reductions in fertility through direct effects on germ cells as well as hormonal alterations supporting the embryonic environment. Teratogenic effects have been noted in multiple species after maternal exposure to colchicine. The degree and nature of the defects are dependent on the developmental stage of embryo exposure.

Carcinogenicity

Colchicine has not been studied in the standard rodent carcinogenicity bioassays; however, aneuploidy, which is in itself a risk for tumorigenesis, has been known to occur in eukaryotes that have been exposed to colchicine. Drs. Wasserman and Leshin have noted that there is sufficient information to label the product; however, they note that the literature raises the question whether colchicine, at clinically therapeutic doses, may promote de novo tumorigenesis via aneuploidy, may inhibit progression of malignancy by impairing the ability of mutant and transformed cells to divide, or both (in an exposure-dependent fashion). Their recommendation is that colchicine should be evaluated in a standard 2-year rat bioassay, as well as in a 6-month transgenic mouse study, but, that in view of the existing clinical experience, they do not need to be conducted prior to approval.

Outstanding or Unresolved Issues

There is the potential for the presence of photo-degradants which contain a structural alert for mutagenicity (identified as β- and γ-lumicolchicine), which has not been adequately addressed in the submission. The Applicant has indicated that they have not observed these degradants in the drug product; however, they have not developed detection methods which are sensitive enough to preclude such impurities being above the current standard of 1.5 μg/day total daily intake (TDI). Dr. Bertha has noted that the proposed packaging of the drug product in HDPE bottles ——————————————— should protect the product sufficiently from light such that significant photo-degradant development should not occur. The final recommendation from Dr. Wasserman is that the Applicant must improve their detection assays to allow reduction of the specifications for the photo-degradant impurities β- and γ-lumicolchicine to a limit of not more than 1.5 μg TDI for the combined degradants. Alternatively, the applicant may conduct genetic toxicology studies, which, if negative, would support the current proposed specifications.

b(4)

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology information submitted by the applicant includes the studies submitted to support NDA 22-352, for the treatment of familial Mediterranean fever, and additional drug interaction studies submitted with this NDA. The table below summarizes the six studies reviewed for NDA 22-352:

MPC-004-07-1001	A single-dose crossover study in 28 healthy subjects to assess the bioavailability of colchicine 0.6 mg tablets compared to Col-Probenecid, administered under standard fasting conditions.
MPC-004-07-1002	A single-dose, double-blind, double-dummy study in 18 healthy subjects to evaluate the pharmacokinetic profile of colchicine and its metabolites (2-, 3-, and 10- demethylocolchicine). In addition to the pharmacokinetic evaluation, the effect of these doses on subjects' electrocardiograms (ECGs) was assessed.
MPC-004-07-1003	A single-dose (1.2 mg), open-label study in 13 healthy subjects to further assess the pharmacokinetic profile of colchicine and its metabolites.
MPC-004-07-1004	A single- and multiple-dose open-label study in 13 healthy subjects to determine the single- and multiple-dose pharmacokinetics of colchicine.
MPC-004-07-1005	A multiple-dose, randomized, double-blind, two-sequence study in 30 healthy subjects to determine whether the steady-state dosing of colchicine influences the steady-state pharmacokinetic profile of ethinyl estradiol or norethindrone
MPC-004-07-1006	A single-dose, open-label study in 24 healthy subjects to confirm the extent to which multiple oral doses of clarithromycin influence the single-dose pharmacokinetic profile of colchicine and its metabolites.

In addition, the Applicant has submitted the results from eight new pharmacokinetic drug interaction studies, summarized in the table below:

MPC-004-08-1010	A one-directional, open-label drug interaction study to investigate the effects of multiple-dose colchicine on single-dose pharmacokinetics of theophylline in healthy volunteers.
MPC-004-08-1011	A one-direction, open-label drug interaction study to investigate the effects of multiple-dose azithromycin on the single-dose pharmacokinetics of colchicine in healthy volunteers.
MPC-004-08-1012	A one-direction, open-label drug interaction study to investigate the effects of multiple-dose ketoconazole on the single-dose pharmacokinetics of colchicine in healthy volunteers.
MPC-004-08-1013	A one-direction, open-label drug interaction study to investigate the effects of multiple-dose ritonavir on the single-dose pharmacokinetics of colchicine in healthy volunteers.
MPC-004-08-1014	A one-direction, open-label drug interaction study to investigate the effects of multiple-dose verapamil HCl on the single-dose pharmacokinetics of colchicine in healthy volunteers.
MPC-004-08-1015	A one-direction, open-label drug interaction study to investigate the effects of multiple-dose extended-release diltiazem on the single-dose pharmacokinetics of colchicine in healthy volunteers.
MPC-004-08-1016	A one-direction, open-label drug interaction study to investigate the effects of single-dose cyclosporine on the single-dose pharmacokinetics of colchicine in healthy volunteers.
MPC-004-08-1017	A one-direction, open-label drug-food interaction study to investigate the

effects of multiple-daily consumptions of grapefruit juice on the single-dose pharmacokinetics of colchicine in healthy volunteers.

General Considerations

Colchicine is predominantly eliminated by biliary excretion and through the stool; gastrointestinal tract lining cell turnover has a variable role in colchicine elimination. As noted in Dr. Okada's review of NDA 22-352, colchicine is extruded from cells, including the enteric lining cells, into the gastrointestinal tract, mediated by the multidrug resistance transporter molecule ABCB1 (full name: ATP-binding cassette subfamily B member 1, MDR1, PGY1; also known as P-glycoprotein [P-gp] or CD243). Normally, a lesser but significant role in colchicine metabolism (~5 to 20%) is played by enteric and hepatic cytochrome P450 3E4 (CYP3A4), which catalyzes demethylation of colchicine to inactive metabolites. Hepatic demethylation of colchicine dependent on CYP3A4 occurs before hepatobiliary excretion of colchicine. Renal elimination has been estimated to be responsible for 10 to 20% of drug disposition in normal subjects. CYP3A4 and renal disposition of colchicine become more critical with certain drug–drug interactions that affect ABCB1, with hepatobiliary dysfunction and with aging.

Absorption:

In healthy adults, colchicine appears to be readily absorbed when orally administered, reaching a mean C_{max} of 2.5 ng/mL (range ——————— in 1 to 2 hours (range 0.5 to 3 hours) after a single 0.6-mg dose administered under fasting conditions. Following repeated dosing, colchicine appears to achieve steady state concentrations within 14 days. The mean Cmax after multiple dosing was 3.1 to 3.6 ng/mL. Absolute bioavailability was reported to be approximately 45%. b(4)

Distribution:

Colchicine is lipid-soluble and has a mean apparent volume of distribution in healthy young volunteers of approximately 5 to 8 L/kg. Colchicine binding to serum protein is ———and binds primarily to albumin; it crosses the placenta and distributes into breast milk. b(4)

Metabolism:

There are two primary metabolites, 2-O-demethylcolchicine and 3-O-demethylcolchicine (known as 2- and 3-DMC, respectively), and one minor metabolite, 10-O-demethylcolchicine (also known as 10-DMC or colchiceine). Human liver microsomes studies have shown that CYP3A4 is involved in the metabolism of colchicine to 2- and 3-DMC. In vivo, exposure to 2-DMC and 3-DMC metabolites is less than 5% of parent drug.

Elimination/Excretion:

A major route of elimination is thought to be enterohepatic recirculation and biliary excretion, mediated by P-gp. The mean elimination half-life in young healthy volunteers after multiple oral doses (0.6 mg twice daily) was 26.6 to 31.2 hours. Colchicine is excreted in the urine by both glomerular filtration and tubular secretion, reportedly as glucuronides. Renal clearance has been reported to account for about 10-20% of total body clearance; colchicine is not removed by hemodialysis.

Critical Intrinsic Factors
The Applicant did not conduct any studies to evaluate the effects of age, race, body weight, organ dysfunction, or pregnancy on the pharmacokinetics of colchicine. The submission addressed the following intrinsic factors.

Age:
Pharmacokinetics of colchicine was not evaluated in elderly; however, since decreases in renal and hepatic function are common in the elderly, caution is warranted when using colchicine in this population. There is no information on the pharmacokinetics of colchicine in pediatric patients in the published literature; however, there is a fairly extensive literature on the use of colchicine in pediatric patients.

Renal impairment:
Renal elimination accounts for approximately 10-20% of colchicine clearance. Although a dose adjustment is not required for patients with mild to moderate renal impairment being treated with the dose recommended for the treatment of gout flares, Drs. Nallani and Doddapaneni recommended that dose reduction be considered in patients with severe renal impairment.

Hepatic impairment:
Published studies with intravenous and oral colchicine in patients with severe hepatic impairment suggest that colchicine clearance is decreased in these patients, with reports ranging from 2.5-fold lower clearance up to 10-fold lower clearance reported in cirrhotic patients, when compared to healthy subjects. Drs. Nallani and Doddapaneni recommended caution when colchicine is considered for patients with mild hepatic impairment and consideration should be given to the reduction of the dosage in patients with moderate and severe hepatic impairment.

Thorough QT Study
Study MPC-004-07-1002 included an informal assessment of QT prolongation. Subjects were randomized to receive colchicine (n=15) or moxifloxacin (n=3); however, as noted by Drs. Nallani and Doddapaneni, this study was insufficiently powered to detect a difference between colchicine and moxifloxacin, which was intended to serve as a positive control. Moxifloxacin response was lower than expected and the time course was not consistent with the typical findings; however the QTcB and QTcF values in colchicine-treated subjects were lower at all time points compared to moxifloxacin-treated subjects. There was little change in QT interval regardless of correction methodology [Fridericia (QTcF) or Bazett's (QTcB)]. Overall, in this study and in the other pharmacokinetic studies conducted by the Applicant, no effect on QTc or any other ECG parameter was noted with therapeutic doses of colchicine.

Drug-drug Interactions
The macrolide antibiotics erythromycin and clarithromycin, and the statins, e.g., lovastatin, simvastatin, atorvastatin, have the potential to increase colchicine toxicity via dual modulation of ABCB1 and CYP3A4. There are case reports suggesting that use of these agents, particularly clarithromycin, may result in fatal colchicine toxicity, even when the concomitant doses of colchicine are in the therapeutic range. Case studies have reported acute myopathy after concurrent use of colchicine with a statin, which could be attributed to either drug.

The Applicant conducted Study MPC-004-07-1006 to evaluate the potential interaction between colchicine and clarithromycin, since in vitro studies had demonstrated colchicine to be a substrate of CYP3A4 and P-gp and clarithromycin, a strong inhibitor of P-gp and CYP3A4. A three-fold increase in colchicine's C_{max} and AUC was noted when colchicine was coadministered with clarithromycin and, based on the current information, this drug interaction appears mainly due to P-gp inhibition rather than CYP3A4 inhibition.

The additional studies conducted by the Applicant have provided data that permits dosage recommendations based on the degree of CYP3A4 inhibition exhibited by the concomitant medication. The available data suggest a dosage adjustment is necessary with strong CYP3A4 and P-gp inhibitors. Drs. Nallani and Doddapaneni recommended that the colchicine dose for the treatment of gout flares should be reduced by 50% when patients are treated concomitantly with strong CYP3A4 inhibitors such as macrolides (e.g., clarithromycin), azole antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir, atazanavir, saquinavir), and the serotonin/norepinephrine reuptake inhibitor nefazodone. Specifically, the colchicine dosage regimen should consist of an initial dose of 0.6 mg, followed by an additional dose of 0.3 mg an hour later if the first dose is well-tolerated.

If the patient is being treated concomitantly with moderate CYP3A4 inhibitors the colchicine dosage regimen should be reduced by 33% of the regular dose; specifically, an initial dose of 0.6 mg followed by an additional dose of 0.6 mg one hour later if the first dose is well-tolerated.

If the patient is being treated concomitantly with weak CYP3A4 inhibitors, the colchicine dosage regimen does not need to be adjusted, and can remain at an initial dose of 1.2 mg, followed by 0.6 mg an hour later.

If the patient is being treated concomitantly with a strong P-gp inhibitor, the dosage regimen should be reduced by 66%; an initial dose of 0.6 mg, with no additional doses for the next 72 hours.

The applicant also conducted a drug-drug interaction study to assess the effects of colchicine on oral contraceptives (Study MPC-004-07-1005). This study demonstrated that multiple dose administration of colchicine does not affect plasma levels of ethinyl estradiol and norethindrone.

Outstanding or Unresolved Issues

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Colchicine is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical-Efficacy

On July 31, 2006, the Applicant met with the Division to discuss what would be the data requirements to support applications for the three indications of interest: treatment of familial Mediterranean fever, treatment of acute gout flares, and prevention of gout flares. For the third indication, the Applicant was told that a review and analysis of the available clinical literature, including the published results of the two randomized controlled trials that were known to exist, would be sufficient to support the filing of a 505(b)(2) application.

Summary of Efficacy Findings

The Applicant submitted the results of the two randomized studies available in the literature, as well as the results of several open-label studies. Although the results of open-label studies are often supportive, the results from randomized, controlled trials are generally more useful in assessing the Applicant's claim.

As was noted in the review team's reviews, the two randomized studies did provide supportive evidence for colchicine's efficacy in the prevention of gout flares, each study had significant deficiencies. The two studies are well-described in Dr. Siegel's review; below is a brief synopsis of the pertinent findings.

"Prophylactic Colchicine Therapy of Intercritical Gout: A Placebo-Controlled Study in Probenecid-Treated Patients" by Paulus, et al. (Arthritis & Rheumatism, 17:5, 609, 1974)

As noted by Dr. Siegel, this was a 6-month, randomized, double-blind, placebo-controlled study of colchicine for the prevention of gout flares in patients started on urate-lowering therapy with probenecid. The study enrolled male patients with a serum uric acid level greater than 7.5 mg/dL and a history of typical acute arthritis that responded promptly to treatment with colchicine.

The study was conducted at two clinical sites, one in Los Angeles and one in Kansas City. Differences were noted between the two sites with respect to the study conduct; specifically patients at the Los Angeles site had all urate lowering therapies discontinued 2 weeks before initiation of study therapy, while patients at the Kansas City site were to be on a stable dose of probenecid 2 weeks before beginning study therapy. Patient reports on gout flares were recorded on a monthly basis. Moderate or severe gout flares were included in the analysis, with "moderate" or "severe" defined as definite pain accompanied by swelling and tenderness, and based on the patient's description of the attack.

Prior to the unblinding of the data, the investigators examined the serum urate levels to "... determine the number of moderate or severe attacks of gout and to compile the evidence for drug-related toxicity as judged by laboratory parameters and clinical judgment." Only patients who "...clearly showed and maintained reduction in serum uric acid..." were included in the analysis, and reported in the results.

Dr. Siegel summarized the patient population studied, and their disposition, as follows:

> A total of 52 patients were randomized 1:1 to colchicine 0.5 mg/probenecid or placebo/probenecid 3 times daily. Baseline characteristics of the two groups reflected a typical gout population and there were no significant imbalances between study arms. For the Los Angeles site, 28 patients were enrolled. One patient in each arm

was excluded from the analysis. In the placebo group 8 of 11 completed all 6 months; the remaining 3 dropped out after 1, 2 and 4 months, respectively. In the colchicine group 12 of 15 patients completed all 6 months; the remaining 3 dropped out after 3, 4 and 4 months, respectively. In the Kansas City site, 24 patients were studied but only 12 were included in the analysis. Seven in the colchicine group and 4 in the placebo group were excluded from analysis because of apparent non-compliance. An additional patient in the colchicine group was excluded from the analysis because they developed toxicity at month 2, consisting of an adverse reaction of alopecia.

The effectiveness of colchicine for preventing gout flares was analyzed by comparing the number of gout flares per month. Major findings of the study are shown in Table 1, adapted from the published article. Patients in the colchicine-probenecid group had a lower rate of gout flares per month than patients receiving placebo (0.19 vs. 0.48, p-value for the comparison < 0.05); probenecid lowered serum urate in both groups to a similar extent, and more patients in the colchicine arm experienced adverse events.

Table 1: Effects of Therapy (Paulus, 1974)

Treatment Group	Serum Urate (mg/100ml) ± 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)

Dave Petullo, the statistical reviewer, noted the following deficiencies regarding the study:

1. He had concerns regarding the manner of use of the urate-lowering agent in Kansas City versus Los Angeles. At sites in Los Angeles, all urate-lowering drugs were removed prior to starting the study, while at sites in Kansas City the patients were stabilized on probenecid prior to colchicine administration. Since there were no data provided, he was not able to examine the possible effect of this variation.
2. He noted that the authors selected only patients that showed and maintained a reduction in serum urate levels, but they did not specify the criteria used to classify a reduction in serum urate levels. Since there were no data provided on the excluded patients, it is not clear how the results would have been impacted by an intent-to-treat analysis.
3. He considered a Student's t-test an appropriate method to compare means. He assumed that the overall mean was calculated from the mean number of flares per patient, with the basis for his assumption the authors' statement that results were calculated from the number of attacks of gout per month of therapy for each patient. However without data, he could not verify the accuracy of that assumption. In addition, it was not clear if the authors' analysis accounted for patients that did not complete the study nor was the cause of withdrawal explained for every patient that withdrew.
4. He noted that there could have been discrepancies in patient reported flares versus investigator observed flares since patient described flares and investigator observed

flares were evaluated differently. He was not able to assess the impact of this potential discrepancy on the analyses.

"Colchicine for Prophylaxis of Acute Flares when Initiating Allopurinol for Chronic Gouty Arthritis" by Borstad, Bryant, et al. (J Rheum. 31:12, 2429, 2004)

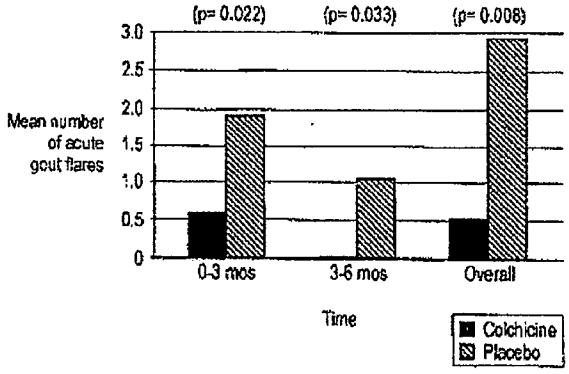
As noted by Dr. Siegel, this was a randomized, placebo-controlled trial of 43 patients with crystal-proven gouty arthritis who were initiating allopurinol due to tophi, uric acid overproduction, at least 3 attacks of gout per year, elevated serum urate with chronic renal failure and nephrolithiasis. Patients were randomized to receive colchicine 0.6 mg twice daily or placebo; once daily if they had renal insufficiency. Although the study was considered to be double-blinded, the colchicine and placebo tablets were not identical.

Subjects initiated allopurinol therapy at a dose of 100 mg daily, which was increased in 100 mg/d increments every 2 to 3 weeks until the serum uric acid was less than 6.5 mg/dL; at that point, subjects were given blinded study drug for 3 months. Patients were evaluated at the 3- and 6-month timepoint for gout flares and for adverse events. The primary analysis population was all subjects who received at least one dose of study medication. Efficacy endpoints at the 3- and 6-month time points were the mean number of flares (assessed by T-test), the number of patients with at least one flare (assessed by chi-square test), and the number of patients with more than one flare (assessed by chi-square test).

A total of 51 patients were enrolled but 8 discontinued before beginning blinded study medication. A total of 21 patients received colchicine and 22 received placebo. Baseline demographics were typical of the gout population and were balanced between study arms, with the exception of diuretic use, which was more common in the colchicine group (57%) than placebo (27%). An increased use of diuretics would make patients more prone to gout flares so this imbalance would not tend to bias in favor of seeing a drug effect.

As shown in the figure below, reproduced from the published article, patients treated with colchicine experienced fewer acute gout flares in the 0-3 month time period and in the 3-6 month time period as compared to placebo-treated patients. The p-values were less than 0.05 for both comparisons. Overall, fewer gout flares were observed in the colchicine group than in the placebo group: 12 flares vs. 65.

Figure 1: Mean number of acute gout flares in 0-3 and 3-6 month time periods, and overall



In addition, a lower proportion of patients in the colchicine arm experienced flares (33%) than in the placebo group (77%) and more patients had multiple flares in the placebo group (63%) than in the colchicine group (14%).

The following are concerns identified by Mr. Petullo regarding the Borstad study:

1. Blinding may have been compromised as colchicine tablets and placebo tablets looked different. An awareness of treatment assignment could introduce observer bias and possible result in an inflated treatment effect.
2. While the t-test is an appropriate statistical method for comparing group means, it was unclear if the analyses accounted for patients having multiple flares. In addition, the authors provided a table that specified that 14% of patients withdrew in the colchicine arm compared to 18% in the placebo arm. It was not clear if the authors' analysis accounted for patient withdrawal.

Mr. Petullo's conclusion regarding the strength of the results from the two published randomized controlled studies is reproduced below:

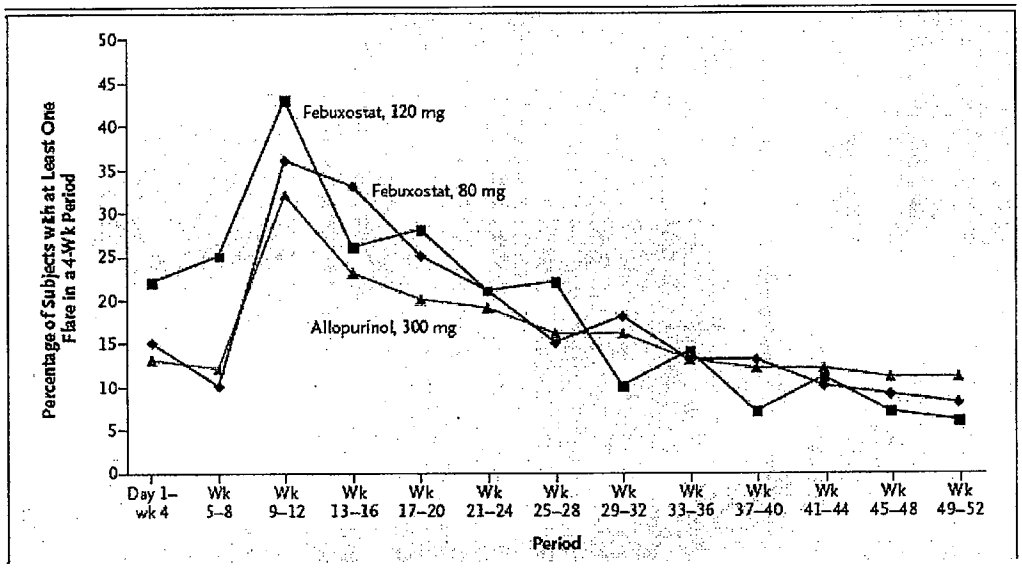
> "In conclusion, while the results from both studies seem to indicate that prophylactic use of colchicine in combination with a serum urate lowering drug reduces the occurrence of acute gout flares, I am unable to confirm the Authors' conclusions. There were shortcomings in the studies which raised concerns regarding the design, conduct, and statistical analyses of the data. Further, these studies appear to have been conducted for research purposes and were not subject to the rigor required for confirmatory studies submitted for regulatory review. With inclusion of the data and/or more details regarding the analysis, my concerns may have been alleviated. However because of the lack of needed information, I am unable to conclude that the articles have provided statistical evidence of efficacy."

Additional supportive trials:
The Applicant also submitted the results from other published trials, intended to be supportive. Dr. Siegel has commented on two trials which, while intending to evaluate the effectiveness of febuxostat, a urate-lowering agent, seem to suggest a role for colchicine in the prevention of gout flares.

The first is a study by Becker (Becker MA et al. Arthritis Rheum 2005;52:916-923), which was a 4-week randomized, placebo-controlled, Phase 2 trial of the urate-lowering agent febuxostat in 153 patients with gout randomized to one of three doses of febuxostat or allopurinol. During the first two weeks, patients took colchicine 0.6 mg twice daily, at which point it was withdrawn. During the 2 weeks when patients received colchicine the proportion of patients with gout flares was 11%, 8%, 8% and 13% in the three febuxostat arms and the allopurinol arm, respectively. When colchicine was discontinued, the proportion of patients with gout flares rose to 34%, 30%, 40% and 42%, respectively. The increase in the rate of flares is suggestive that colchicine was preventing gout flares during the period when it was being administered.

The second study, also by Becker (Becker MA et al. N Engl J Med 2005;353:2450-2461), was a 52-week, randomized, controlled, Phase 3 trial that compared two doses of febuxostat to

allopurinol. Colchicine 0.6 mg twice daily was administered for the first 8 weeks of the trial, then stopped. As shown in the figure below, reproduced from the published article, the proportion of patients experiencing gout flares increased when the colchicine was stopped.



Due to the concerns identified above, none of the studies provided from the literature could, by itself, be used to support the application; however, together, they form a supportive framework that strongly suggests the efficacy of colchicine for the prevention of gout flares.

DESI finding for ColBenemid

ColBenemid, a combination product containing colchicine in combination with probenecid had been approved by the FDA in 1961 (NDA 12-283). It subsequently underwent review under the Drug Efficacy Study Implementation (DESI) process, during which the panel concluded that 1 tablet of probenecid 0.5 gm and colchicine 0.5 mg per day for one week, followed by 1 tablet twice a day, was effective in lowering serum urate levels and in reducing the frequency of recurrent acute attacks of gout.

As Dr. Siegel noted in his review, given that the probenecid moiety is a uricosuric agent that does not reduce the risk of gout flares, but actually increases that risk, the finding of efficacy in prevention of gout flares for the combination reflected a finding of effectiveness for the colchicine moiety. In approving ColBenemid under the DESI process, the Agency relied on the findings of the DESI panel, which articulated that "probenecid is an effective uricosuric drug and colchicine is effective as a prophylactic agent."

The DESI panel did have concerns about the combination product, but they related to the fact that a fixed-combination product does not allow separate adjustments of the dosages of the components in the combination and, therefore, the concerns are not relevant to the issue regarding the finding of efficacy of colchicine for the prevention of gout flares.

Dr. Siegel also pointed out in his review that the situation with colchicine as a component of ColBenemid is unusual in that it should not be interpreted to indicate that the approval of a combination product generally indicates efficacy of each component. The components in the ColBenemid combination product have completely different actions in the treatment of gout. The probenecid moiety reduces the elevated uric acid levels that are responsible for the propensity to develop gout. Treatment with probenecid actually increases the risk of gout flares in the short term. In contrast, the colchicine moiety prevents gout flares but does nothing for reducing elevated levels of uric acid.

This DESI finding, in conjunction with the other pieces of supporting evidence, provides a compelling argument for the effectiveness of colchicine for the prevention of gout flares.

8. Safety

The primary safety database for this application is comprised of the safety data that were submitted in support of the applications for the treatment of FMF and treatment of acute gout flares. It consisted of a review of the published literature, including the two literature reports of the randomized trials conducted by Borstad and Paulus; data from a trial, MCP-004-06-001, conducted by the Applicant in support of the application for the treatment of acute gout flares; and a review of the post-marketing adverse event reports in the FDA and WHO databases. No new safety data were submitted in this application.

These data were previously reviewed in the review of the FMF and acute gout applications, were consistent with the well-known side effect profile of colchicine, and are summarized in my review memo of July 30, 2009. The conclusion of the review team was that colchicine is generally well tolerated when it is given in the proposed dose of 0.6 mg once or twice daily.

9. Advisory Committee Meeting

The convening of an advisory committee meeting for discussion of this application was deemed to be unnecessary. This decision was reached in view of the observation that colchicine has a long history of medicinal use, the clinical experience with colchicine and the specific indication being sought in the application (prevention of acute gout flares), and the lack of any specific issues identified in the application that would warrant discussion at an advisory committee meeting.

10. Pediatrics

The Applicant requested a waiver from the requirement to conduct studies in pediatric patients as specified by the Pediatric Research Equity Act (PREA) of 2003. Since the incidence of gout in the pediatric population is extremely low, the Applicant's request was granted. The Pediatric Review Committee (PeRC) concurred with the decision.

11. Other Relevant Regulatory Issues

Consultations were obtained from the Division of Drug Marketing and Communications (DDMAC), the Division of Risk Communication (DRISK), the Division of Medication Error

Prevention and Analysis (DMEPA). Their recommendations were reviewed and incorporated in the appropriate places in the label. The Division of Scientific Investigations inspected three clinical sites; no regulatory violations were indentified.

There are no other unresolved relevant regulatory issues.

Division of Scientific Investigations (DSI) Audits
The submission did not contain data from clinical trials, therefore there was no need to have DSI conduct site audits.

Financial Disclosure
The Applicant certified that there was no financial arrangement with the study investigators whereby the value of compensation to the investigators could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that no listed investigator was the recipient of significant payments of sorts as defined in 21 CFR 54.2 (f). The Applicant also indicated that the clinical investigators were required to disclose to the Applicant whether the investigator had a proprietary interest in the product or a significant equity in the Applicant, as defined in 21 CFR 54.2(b).

12. Labeling

The Applicant has submitted enough information to support their proposed labeling. As noted above, representatives from the Office of Surveillance and Epidemiology were consulted and their recommendations were incorporated during the discussion of the label.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Approval.

Risk:Benefit Assessment

I concur with the review team that the evidence for the effectiveness of colchicine for the prevention of gout flares in patients with chronic gout is primarily, and sufficiently, derived from the previous finding of effectiveness of ColBenemid (colchicine/probenecid combination product). Although the data from the published scientific literature is deficient in several respects, it does provide additional supportive evidence.

Colchicine's safety profile has been explored and is well-known after decades of clinical practice. There is substantial information on the proposed dose of 0.6 mg, administered once or twice a day, and the most common adverse events are easily monitored and managed by dose modification. Although serious adverse events, including death, have occurred with colchicine therapy, it is usually associated with drug-drug interactions, or in populations with underlying increased risks for colchicine toxicity. These potential complications are well-described in the literature, and in the proposed package insert.

Therefore, my overall risk:benefit assessment is in favor of approval of this application.

Recommendation for Post-marketing Risk Management Activities

None.

Recommendation for other Post-marketing Study Commitments

None.

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/s/

RIGOBERTO A ROCA
10/16/2009