

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-351**

**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**

<b>Date</b>	(electronic stamp)
<b>From</b>	Rigoberto Roca, M.D.
<b>Subject</b>	Deputy Director Summary Review
<b>NDA/Supplement No.</b>	22-351/000
<b>Applicant Name</b>	Mutual Pharmaceutical Co.
<b>Date of Submission</b>	September 30, 2008
<b>PDUFA Goal Date</b>	July 30, 2009
<b>Proprietary Name / Established (USAN) Name</b>	Colcrys / colchicine
<b>Dosage Forms / Strength</b>	0.6 mg tablets
<b>Proposed Indication(s)</b>	Treatment of gout flares
<b>Action</b>	Approval

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	Rosemarie Neuner, M.D.
Statistical Review	David 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	Andrew Haffer / Mathilda Fienkeng Pharm.D.
CDTL Review	Jeff Siegel, M.D.
OSE/DMEPA	Lori Cantin, R.Ph. / Kristina Arnwine, Pharm.D. / Denise Toyer, Pharm.D. / Carol Holquist, R.Ph.
OSE/DRISK	LaShawn Griffiths, M.S.H.S.-PH, B.S.N., R.N. / Jodi Duckhorn, M.A. / Claudia Karwoski, Pharm.D.
DSI	Susan Leibenhaut, M.D. / Constance Lewin, M.D.,M.P.H.

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

DRISK = Division of Risk Management  
 DSI = Division of Scientific Investigations  
 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, although marketed, remains an unapproved product.

The applicant has submitted an application for the use of colchicine in the treatment of acute gout flares in adults. The proposed dosing regimen is 1.2 mg followed by an additional dose of 0.6 mg in one hour, for a total dose of 1.8 mg in a 24-hour period.

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 develop 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

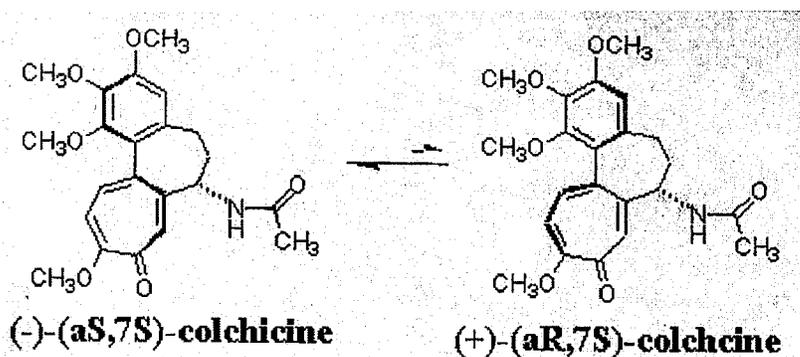
the pain resolves, or dose-limiting toxicity develops. The dosage range identified in clinical texts is from 4 mg to 8 mg for an acute episode.

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. CMC/Device

#### General Product Considerations

The chemical name of Colchicine is N-[5,6,7,9-tetrahydro-1,2,3,10-tetrahydroxy 9-oxobenzo[a]heptalen-7-yl], (S)-acetamide. The molecular formula is  $C_{22}H_{25}NO_6$  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.



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 originally scheduled inspection visits to \_\_\_\_\_ by the Office of Compliance were cancelled due to the \_\_\_\_\_. In the absence of the inspection, the Division was not able to take an action by the PDUFA date of December 20, 2008 for NDA 22-352. The inspections were postponed until January of this year, have been conducted, and the sites have been found to be acceptable. **b(4)**

A domestic site responsible for packaging the drug product in \_\_\_\_\_ for distribution of \_\_\_\_\_, and was also an alternate site used for stability testing for the drug product was inspected and found to be unacceptable by the Office of Compliance. The site, \_\_\_\_\_ was removed from the application by the Applicant, and they noted in an amendment on May 5, 2009, that they did not intend to distribute any \_\_\_\_\_ until they obtain FDA approval of the site. **b(4)**

With the withdrawal of the \_\_\_\_\_ site by the Applicant, the inspection request was removed from the Establishment Evaluation System and the Office of Compliance was requested to re-evaluate their overall recommendation. On May 7, 2009, the Office of Compliance made an Acceptable recommendation for the NDAs. **b(4)**

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. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months for the product. 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 flares of gout, 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 22-351.

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 human, 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 and Reproductive Toxicology

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  $\beta$ - and  $\gamma$ -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  $\mu\text{g/day}$  total daily intake (TDI). Dr. Bertha has noted that the proposed packaging of the drug product in HDPE bottles or \_\_\_\_\_ packages (the latter form for \_\_\_\_\_ ) 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  $\beta$ - and  $\gamma$ -lumicolchicine to a limit of not more than 1.5  $\mu\text{g}$  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- demethylcolchicine). 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, 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 1.1 to 4.4 ng/mL) 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  $C_{max}$  after multiple dosing was 3.1 to 3.6 ng/mL. Absolute bioavailability was reported to be approximately 45%.

*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  $39 \pm 5\%$ , and binds primarily to albumin; it crosses the placenta and distributes into breast milk.

*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 colchicine). 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  $C_{max}$  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 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**

The Division had indicated to the Applicant that, in principle, the application for the treatment of gout flares could potentially rely on one adequate and well-controlled study, supplemented by publicly available information, specifically, published articles in the scientific and medical literature. Subsequently, the Applicant has submitted the results of a study they conducted, Study MCP-004-06-001, and the published results of the study by Ahern, et. al., (Aust NZ J Med 17:301-304, 1987).

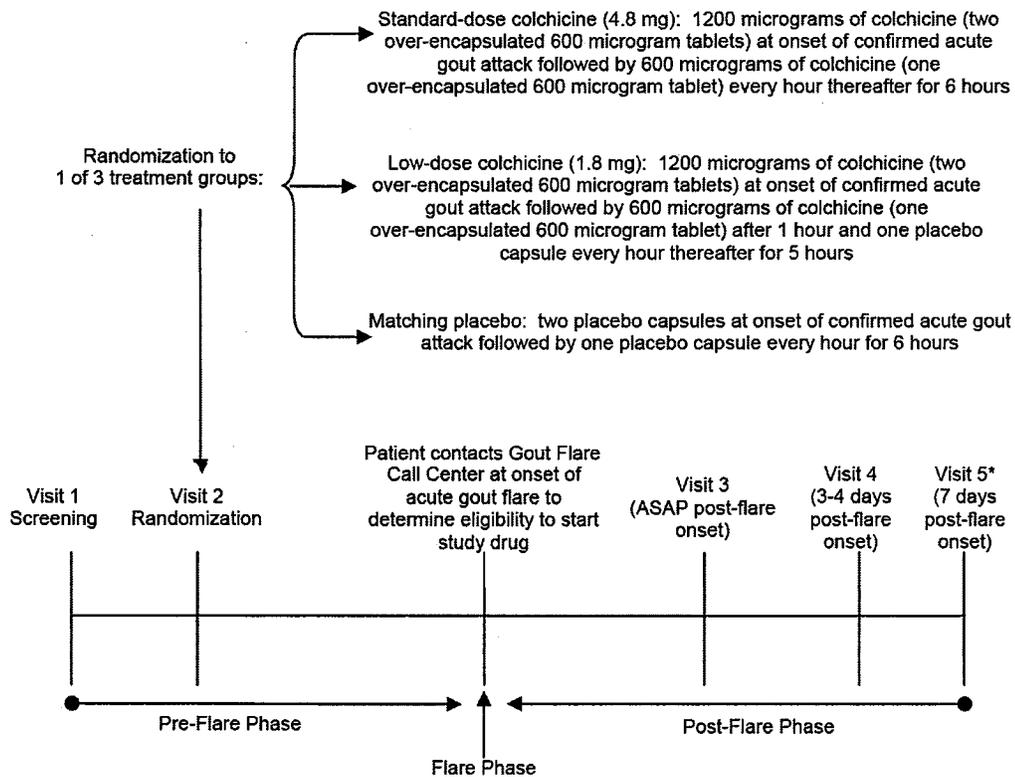
#### Study MCP-004-06-00:

*"A multicenter, randomized, double-blind, placebo-controlled, parallel group, 1-week, dose-comparison study to evaluate the efficacy, safety, and tolerability of colchicine in subjects with an acute gout flare."*

This study evaluated the efficacy of colchicine by comparing higher-dose to a lower-dose regimen, in patients with a confirmed diagnosis of crystal-proven gout per the diagnostic criteria set forth by the American College of Rheumatology (ACR). As noted in Dr. Neuner's review, these included presence of characteristic urate crystals in the joint fluid, and/or tophus proven to contain urate crystals by chemical or polarized light microscopic means, and/or the presence of at least 6 of the following clinical, laboratory, and x-ray phenomena:

- more than one prior attack of acute arthritis;
- maximum inflammation developed within 24 hours;
- monoarthritis attack;
- redness observed over joints;
- first metatarsophalangeal (MTP) joint painful or swollen;
- unilateral first MTP joint attack;
- unilateral tarsal joint attack;
- proven or suspected tophus;
- hyperuricemia;
- asymmetric swelling within a joint on x-ray;
- subcortical cysts without erosions on x-ray;
- monosodium urate monohydrate microcrystals in joint fluid during attack
- joint fluid culture negative for organisms during attack

Patients were excluded if they had acute polyarticular gout involving 4 or more joints, if they had arthritis due to any other cause, or chronic renal or hepatic toxicity. The details of the study design are described in Drs. Neuner’s and Siegel’s review, and graphically depicted in the diagram below, reproduced from the Applicant’s submission.



\*Visit 5 will take place 7 days after the onset of the acute gout flare in patients who took at least one dose of study drug whose acute gout flare was still ongoing at Visit 4.

The trial evaluated two doses of colchicine: a low dose consisting of 1.2 mg followed by 0.6 mg one hour later, for a total dose of 1.8 mg, and a high dose, consisting of 1.2 mg followed by 6 additional doses of 0.6 mg at hourly intervals, for a total dose of 4.8 mg. The higher-dose regimen is consistent with regimens of colchicine for the treatment of a gout flare identified in medical texts and can, therefore, be considered a “standard regimen.”

The primary endpoint for the clinical trial was the response to treatment regimen in the target joint based on patient self-assessment at 24 hours. The analysis was based on the intent-to-treat population and the response was defined as a 50% or greater reduction in pain scores in patients who did not use rescue medication. Patients who discontinued prior to the 24 hour assessment were deemed non-responders.

A total of 72 clinical sites in the United States enrolled 575 subjects. The final dispositions of the patients enrolled in the study are summarized in the table below, adapted from Dr. Neuner’s review.

	Colchicine		Placebo N=189 n (%)	Total N=575 n (%)
	4.8 mg Dose N=193 n (%)	1.8 mg Dose N=193 n (%)		
Number of Subjects Randomized	193	193	189	575
Number of Subjects with Qualifying Flare	52 (27%)	75 <sup>†</sup> (39%)	58 (31%)	185 (32%)
Number of Subjects with No or Non-Qualifying Flare	141	118	131 <sup>‡</sup>	390 <sup>‡</sup>
Number of Subjects in the ITT population	52	74	58 <sup>‡</sup>	184 <sup>‡</sup>
Number of Subjects who completed the study	45 (87%)	71 (96%)	55 (95%)	171 (92%)
Number of Subjects who Withdrew from the Study:	7 (13%)	3 (4%)	4 (7%)	14 (8%)
Lack of Efficacy	0 (0%)	1 (1%)	1 (2%)	2 (1%)
Withdrew Consent	1 (2%)	0 (0%)	1 (2%)	2 (1%)
Lost to Follow-Up	1 (2%)	1 (1%)	1 (2%)	3 (2%)
Other	5 (10%)	1 (1%)	1 (2%)	7 (4%)

<sup>†</sup> Subject 1010-1011 had a qualifying flare but was directed not to take study medication because of a burst capsule. Therefore he is counted in the qualifying flare group but not included in any study population.

<sup>‡</sup> Subject 1057-1012 had a flare but never called the Flare Call Center and started study treatment without authorization. This subject is counted in the no flare or non-qualifying flare group and is included in the safety population (but not the intent to treat population).

The table below, adapted from Dr. Neuner’s review, summarizes the demographics of the ITT population in the study. The typical patient was male, white/Caucasian and over 50 years old.

Demographic variable	Colchicine Dose		Placebo N=59	Total N=185
	4.8 mg N=52	1.8 mg N = 74		
Age:				
Mean (SD)	52 (10)	51 (12)	51 (11)	52 (11)
Median (Min, Max)	52 (33, 75)	50 (31, 76)	51 (24, 78)	51 (24, 78)

Demographic variable	Colchicine Dose		Placebo	Total
	4.8 mg N=52	1.8 mg N = 74	N=59	N=185
Age Group:				
<45 years	14 (27%)	26 (35%)	12 (20%)	52 (28%)
45-65 years	32 (62%)	35 (47%)	41 (70%)	108 (58%)
>65 years	6 (12%)	13 (18%)	6 (10%)	25 (14%)
Gender:				
Male	49 (94%)	72 (97%)	55 (93%)	176 (95%)
Female	3 (6%)	2 (3%)	4 (7%)	9 (5%)
Race:				
American Indian/Alaska Native	0	1 (1%)	0	1 (1%)
Asian	0	1 (1%)	1 (2%)	2 (1%)
Black/African American	10 (19%)	4 (5%)	11 (19%)	25 (14%)
Native Hawaiian/Pacific Island	0	0	0	0
White/Caucasian	40 (77%)	66 (89%)	47 (80%)	153 (83%)
Other	2 (4%)	2 (3%)	0	4 (2%)
Ethnicity:				
Hispanic/Latino	6 (12%)	6 (8%)	1 (2%)	13 (7%)
Not Hispanic/Latino	46 (89%)	68 (92%)	58 (98%)	172 (93%)
Weight (lb):				
Mean (SD)	228 (38)	228 (42)	228 (42)	228 (41)
Median (Min, Max)	222 (149, 322)	226 (153, 361)	219 (166, 339)	221 (149, 361)
Body Mass Index (lb/in2):				
Mean (SD)	33 (4.6)	33 (6.3)	33 (5.8)	33 (5.7)
Median (Min, Max)	32 (21, 46)	32 (23, 50)	31 (23, 49)	32 (21, 50)
Estimated Creatinine Clearance (based on actual body weight) <sup>*†</sup> :				
< 80 mL/min	5 (10%)	8 (11%)	7 (12%)	20 (11%)
≥ 80 mL/min	47 (90%)	66 (89%)	52 (88%)	165 (89%)
Estimated Creatinine Clearance (ideal body weight for BMI >30) <sup>‡</sup> :				
< 60 mL/min	5 (10%)	11 (15%)	8 (14%)	24 (13%)
60 – 80 mL/min	18 (35%)	22 (30%)	11 (19%)	51 (28%)
≥ 80 mL/min	29 (56%)	41 (55%)	40 (68%)	110 (59%)

\* Baseline is the measure taken closest in time to first dose date except in the case of Subject 1069-1015 where an earlier measure of body weight (274 lb) was substituted for the closer in time measure of 177 lb; this latter value was judged to be in error because all other body weights were in the 270 lb range.

† Actual body weight was used for all patients.

‡ Actual body weight was used for patients with a BMI ≤ 30 and ideal body weight was used for patients with a BMI > 30.

### Efficacy Results

A greater proportion of patients receiving standard-dose colchicine experienced a response compared to placebo. Similarly, a greater proportion of patients receiving low-dose colchicine achieved a response compared to placebo. The point estimate of the response rate for the 1.8 mg treatment group was higher than in the 4.8 mg treatment group (38% vs. 33%).

The results are summarized in the table below, adapted from Dr. Petullo's review.

	Placebo	Colchicine	
	N = 58	1.8 mg dose N = 74	4.8 mg dose N = 52
Number of responders, n (%)	9 (16)	28 (38)	17 (33)
p-value		0.005	0.03

The 95% confidence interval around the difference between the proportions of responders in the two colchicine treatment groups compared to placebo is summarized in the table below.

	Placebo	Colchicine	
	N = 58	1.8 mg dose N = 74	4.8 mg dose N = 52
Number of responders, n (%)	9 (16)	28 (38)	17 (33)
95 % Confidence interval around the difference in proportion, compared to placebo		22 (8,37)	17 (1,33)

Results for the secondary outcome measures also showed better outcomes with the colchicine groups than the placebo group, including the magnitude of pain relief, time to response, time to complete (90%) pain relief, time to use of rescue medications, signs and symptoms of inflammation per investigator assessment and investigator global response.

#### Supportive studies

The Applicant submitted the result from the published literature on a randomized, double-blind, placebo-controlled study in patients with crystal proven gout (Ahern MJ, Reid C, Gordon TP et al. *Does Colchicine Work? The Results of the First Controlled Study in Acute Gout*. Aust NZ J Med, 1987). In this study, patients who met the diagnostic criteria of an acute flare were hospitalized and randomized to either colchicine or placebo. The colchicine regimen consisted of 1 mg, followed by 0.5 mg every 2 hours until the patient experienced either a complete response or toxicity (nausea, vomiting, or diarrhea). The protocol-specified response was a decrease of 50% or greater from baseline in the patient-assessed pain, based on a visual analog scale. Investigator assessments, made by blinded assessors, generated a compound clinical score based on pain, swelling and redness, and tenderness on palpation.

The following table, adapted from Drs. Siegel's and Neuner's reviews, summarizes the demographics of the patients enrolled in the study.

Demographic and Disease Characteristic	Colchicine (N=22)	Placebo (N=21)
Number of Joints Involved	22	22
Size *		
Large	8	6
Small	14	16
Age (years):	69 ± 8	70 ± 8
Mean (SD)	55 – 85	56 – 91
Range		
Duration of Symptoms (hours)	38 ± 51	38 ± 29
Weight (kg)	71 ± 9	74 ± 11
Serum Uric Acid (normal range:0.12-0.45 mmol/l)	0.55 ± 0.16	0.50 ± 0.15
Serum Creatinine (normal range: 0.06-0.13 mmol/l)	0.14 ± 0.08	0.12 ± 0.03
Clinical Score	9.5 ± 2.8	10.3 ± 2.4
Pain Score	56 ± 21	68 ± 21

\* Large = knee, ankle, wrist

Small = metatarsophalangeal, metacarpophalangeal, interphalangeal

The study protocol specified that pain and clinical assessments were to continue until 48 hours had elapsed from study drug initiation, even if the study treatment had been discontinued secondary to the development of toxicity. As noted in Dr. Neuner's review, nine patients reportedly had 50% improvement in their pain scores before colchicine toxicity occurred, one patient was symptomatically toxic concurrently with a 50% improvement in pain score, and 12 patients had 50% improvements in their pain scores post-toxicity. In regard to the clinical scores, two patients achieved 50% improvement prior to developing colchicine toxicity, while twenty patients reached this level of improvement post-toxicity.

The table below, adapted from Dr. Siegel's review, summarizes the proportion of patients with a 50% or greater reduction in pain scores or clinical scores. More patients had a response in the colchicine arm than in the placebo arm, with a difference apparent as early as 12 hours post-treatment, becoming more pronounced over time.

	Time point after initiation of study treatment			
	12 hrs	24 hrs	36 hrs	48 hrs
<b>Clinical Score:</b>				
<b>Colchicine</b>	5%	23%	50%	64%
<b>Placebo</b>	0%	0%	5%	23%
<b>Pain Score:</b>				
<b>Colchicine</b>	23%	41%	73%	73%
<b>Placebo</b>	9%	9%	32%	36%

The Applicant also submitted the published results from four uncontrolled studies. They were not reviewed to any great detail because they were all open-label, uncontrolled studies; furthermore, the doses varied from study to study, if they were documented at all, and utilized formulations not available in the United States.

## 8. Safety

### General Considerations

In addition to the safety information obtained from the efficacy study intended to support this indication, MCP-004-06-001, the Applicant conducted and submitted the data from several pharmacokinetic studies. With the additional safety data submitted in the 120-Day Safety update, the safety dataset from 14 single- and multiple-dose pharmacokinetic and drug-drug interaction studies included 314 subjects (255 subjects single dose/1-day regimen and 59 subjects 10- to 14-day steady state regimen).

The remainder of the safety information in the application, as noted by Dr. Neuner, included the following:

1. Information from the medical literature, including 3,545 patients with FMF, both adults and children, in the 3 randomized, controlled studies and 21 uncontrolled studies. There were also meta-analyses of studies of colchicine in other indications, which included 671 patients with hepatic and biliary cirrhosis;
2. The FDA post marketing adverse event report database, which included 751 adverse event reports from 1969 through 30 June 2007;

3. The World Health Organization (WHO) post marketing adverse event report database, which included 1380 adverse event reports from 79 countries, including the United States, from 1968 through March 2006; and
4. Currently approved labeling for Col-Probenecid (US), and oral colchicine labels from Argentina, Australia, Britain, Germany, Mexico, France, Singapore, and Uganda.

*Study MPC-004-06-001*

The table below, reproduced from Dr. Neuner's review, summarizes the exposure data for patients in the study. More patients were able to complete the entire treatment regimen in the 1.8-mg treatment group than in the 4.8-mg treatment group.

Exposure	Colchicine Dose		Placebo N=59	Total N=185
	4.8 mg N=52	1.8 mg N=74		
Took All 7 doses of Study Medication	38 (73%)	68 (92%)	52 (88%)	158 (85%)
Missed at Least 1 dose of Study Medication <sup>†</sup>	14 (27%)	6 (8%)	7 (12%)	27 (15%)
Took at Least the First 2 Doses of Study Medication:	49 (94%)	71 (96%) <sup>‡</sup>	56 (95%)	176 (95%)
Did Not Complete the last 6 Doses	3 (6%)	2 (3%)	0	5 (3%)

<sup>†</sup>The subsequent rows are not mutually exclusive.

<sup>‡</sup>Total dose would be 1.8 mg.

The adverse events observed in the study were primarily mild to moderate in intensity; there were no deaths or serious adverse events (SAEs) reported in the study. Less treatment emergent adverse events were observed in the 1.2 mg treatment group compare to the 4.8 mg treatment group.

Of the adverse events classified as severe in intensity, the events were primarily gastrointestinal in origin. The table below, adapted from Dr. Neuner's review, summarizes the adverse events reported in the study by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) preferred term, as well as the breakout for the severe adverse events.

Adverse Event (by MedDRA SOC Preferred Term)	Colchicine Dose		Colchicine (both doses) N = 126 n (%)	Placebo N = 58 n (%)
	4.8 mg N = 52 n (%)	1.2 mg N = 74 n (%)		
<b>Treatment Emergent Adverse Events (TEAEs)</b>				
Mild	15 (29)	19 (26)	34 (27)	9 (15)
Moderate	15 (29)	8 (11)	23 (18)	6 (10)
Severe	10 (19)	0	10 (8)	1 (2)

Adverse Event (by MedDRA SOC Preferred Term)	Colchicine Dose		Colchicine (both doses) N = 126 n (%)	Placebo N = 58 n (%)
	4.8 mg N = 52 n (%)	1.2 mg N = 74 n (%)		
<b>Severe Adverse Events</b>				
Gastrointestinal Disorders				
Diarrhea	10 (19)	0	10 (8)	0
Melena	1 (2)	0	1 (1)	0
Nausea	1 (2)	0	1 (1)	0
Musculoskeletal and Connective Tissue Disorders				
Pain in extremity	1 (2)	0	1 (1)	0
Metabolism and Nutrition Disorder				
Gout	0	0	0	1 (2)

The case of melena consisted of a 41-year-old male who experienced melena 3 days after taking his first dose of study medication. It was also noted that approximately 4 hours after taking his study medication he had ingested 16 mg of methylprednisolone as rescue medication. A colonoscopy and esophagogastroduodenoscopy (EGD) performed 6 weeks later was consistent with small hemorrhoids, irritable bowel syndrome, erosive duodenitis, erosive gastritis, gastroesophageal reflux disease, and a hiatal hernia. Dr. Neuner concurred with the Applicant's assessment that the gastrointestinal bleeding was probably due to the methylprednisolone, which seems a plausible hypothesis.

In the study published by Ahern, et. al., gastrointestinal toxicity was also prevalent. All patients in the colchicine group developed diarrhea or vomiting at a median time of 24 hours, corresponding to a mean dose of 6.7 mg of colchicine. A total of 5 placebo-treated patients developed nausea.

#### Post-Marketing Experience

Review of the post-marketing data did not identify any new adverse event signal, with most of the adverse events reported involving the gastrointestinal, hematologic, and renal organ systems.

## 5. 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 (treatment of acute flares of gout), and the lack of any specific issues identified in the application that would warrant discussion at an advisory committee meeting.

## 6. 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.

## 7. 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 identified.

There are no other unresolved relevant regulatory issues.

## 8. Labeling

The Applicant had originally requested the name “Colstat” as the proprietary name, but it was found to be unacceptable because it contained the United States Adopted Names (USAN) Council stem ‘-stat’. This particular USAN stem has the USAN definition of “enzyme inhibitors,” and since the product is not an enzyme inhibitor, the use of this stem in the proposed proprietary name would be inconsistent with the USAN definition. The Applicant had also submitted the name “Colcrys” as an alternative; this was found to be acceptable.

## 9. Decision/Action/Risk Benefit Assessment

- Regulatory Action  
Approval

- Risk Benefit Assessment

The Applicant has presented information to demonstrate that colchicine therapy is effective in the treatment of acute flares in patients with gout. I concur with Drs. Neuner and Siegel that, overall, when colchicine is taken in therapeutic doses, and when the prescriber exercises vigilant monitoring with respect to the appropriate reduction of dosage in susceptible populations, or with potentially interacting drugs, colchicine is generally safe and well-tolerated.

The study conducted by the Applicant in support of this indication, MPC-004-006-001, also demonstrated that a dose lower than what has conventionally been used for this indication had comparable efficacy, with less adverse events. This finding is important enough to warrant the Agency to issue a communication to healthcare professionals.

- Recommendation for Post marketing Risk Management Activities  
None.
- Recommendation for other Post marketing Study Requirements  
None.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22351	ORIG 1	MUTUAL PHARMACEUTICA L CO INC	COLCHICINE TABLETS USP 0.6MG

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/s/

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RIGOBERTO A ROCA  
07/30/2009