CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-351

CROSS DISCIPLINE TEAM LEADER REVIEW

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II
Division of Anesthesia, Analgesia and Rheumatology Products

Cross-Discipline Team Leader Memorandum

Date	June 24, 2009
From	Jeffrey Siegel, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22-351
Applicant	Mutual Pharmaceutical Company
Date of Submission	September 30, 2008
PDUFA Goal Date	July 30, 2009
Proprietary Name / Established (USAN) names	Colcrys/colchicine
Dosage forms / Strength	Tablet / 0.6 mg
Proposed Indication(s)	Treatment of acute gout
Recommended:	*Approval*

TABLE OF CONTENTS

1. Introduction to Review

The Applicant, Mutual Pharmaceutical, submitted this new drug application (NDA) for colchicine (Colcrys) for the treatment of gout flares. Colchicine is an alkaloid originally derived from the autumn crocus, Colchicum automnale, that has been used since ancient times for the treatment of gout. Although colchicine has been used in the United States as a purified, single active ingredient since before 1938, it has been approved only as part of a combination with probenecid as ColBenemid - colchicine 0.5 mg/probenecid 500 mg. Thus, although colchicine has been widely available as a stand-alone product from many sources it has been a marketed, unapproved product.

The Applicant met with the Agency in a pre-IND meeting on July 31, 2006 to explore a clinical development program to gain approval for colchicine as 505 (b)(2) applications for treatment of acute gout, prevention of gout flares in chronic gout ——— ——————————, an orphan autoinflammatory disease. For the acute gout indication, the Division told the Applicant that since there was only a single randomized, controlled trial in the literature that they would have to conduct an additional adequate and well-controlled trial to file an NDA. b(4)

Mutual conducted a single randomized, placebo-controlled trial comparing two doses of colchicine to placebo in patients with acute flares of gout. This trial compared the standard colchicine regimen consisting of 1.2 mg orally at the first sign of a gout flare followed by 0.6 mg hourly until either pain relief or GI toxicity occurs. They also submit an article in the literature by Ahern et al describing a randomized controlled trial of acute gout comparing placebo with colchicine 1 mg followed by 0.5 mg hourly until pain relief or GI toxicity occurred. Mutual proposes a dose of colchicine of 1.2 mg at the onset of a gout flare followed by 0.6 mg one hour later. The safety database consists of the 125 patients enrolled in the new clinical trial, 126 healthy adults enrolled in a variety of pharmacokinetic studies, information from a search of the worldwide literature and an analysis of postmarketing adverse event reports from the FDA AERS database and the WHO database.

Review of this application had not revealed major issues that would preclude an approval. A major finding of the clinical review is that the low dose regimen has similar efficacy to the standard dose regimen with considerably less toxicity. This finding indicates that current medical practice should be changed to avoid unnecessary toxicity to patients. CMC review determined that colchicine contains photodegradant impurities, β- and γ-lumicolchicine. The Pharmacology/Toxicology review noted the lumicholchicine impurities and determined that there should be post-marketing commitments to 1) carry out carcinogenicity studies and 2) to improve detection methods for lumicolchicine and reduce the levels of the impurities. The Clinical Pharmacology review determined that there are important drug-drug interactions with a variety of other commonly used drugs. These interactions will require recommendations for dose adjustment when these products are used concomitantly with colchicine.

2. Background

Gout is a condition characterized by acute flares and chronic manifestations. The underlying predisposing factor for gout is elevated levels of uric acid. While many individuals with hyperuricemia never develop gout the likelihood of developing gout increases with increasing circulating levels of uric acid above 6 mg/dL. The first manifestation of gout is generally an acute, painful attack of monoarthritis, typically involving the great toe (termed podagra). Although some patients have a single episode of acute gout, many go on to develop chronic gout, which is manifest as recurrent episodes of acute gout as well as deposition of uric acid crystals in tissues, termed tophi. Acute attacks of gout are treated with anti-inflammatories, including non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids and ACTH. The goal of treatment of chronic gout is to reduce uric acid levels to below 6 mg/dL with urate-lowering drugs to reduce the risk of gout flares and to resolve tophi.

The mechanism of action of colchicine in acute gout is not fully understood. Recent evidence suggests that uric acid crystals activate the inflammasome via NALP3, leading to activation of caspase-1 and release of the proinflammatory cytokine, interleukin-1. Colchicine is known to disrupt the assembly of microtubules. Evidence suggests several possible mechanisms that may mediate colchicine's anti-inflammatory effects.[1] At micromolar concentrations, colchicine inhibits urate crystal-induced activation of the inflammasome, activation of caspase-1 and release of interleukin-1. At nanomolar concentrations, colchicine inhibits urate crystal-induced release of chemotactic factors from neutrophils and adhesion of neutrophils to endothelium.

Clinicians use colchicine in two ways in the treatment of gout: as an acute treatment in the acute attack to reduce pain and inflammation and in the setting of chronic gout to prevent flares of gout, particularly when urate-lowering therapies are initiated. For the treatment of acute flares of gout, medical texts typically recommend colchicine 1.2 mg followed by 0.6 mg every hour until the attack resolves or until GI toxicity occurs. However, adequate studies to determine the optimal dose of colchicine in the treatment of acute gout have never been conducted. Despite the fact that colchicine is marketed and is widely used in the treatment of gout it has never been approved as a stand-alone product. Colchicine is, however, approved as ColBenemid, a combination product that contains colchicine 0.5 mg and probenecid 500 mg. ColBenemid was approved in the DESI process, but is no longer marketed. Thus, colchicine is currently a marketed, unapproved product. It is a current goal of the Agency to get pharmaceutical companies to file NDA's for marketed, unapproved products so they can be brought under the usual regulatory framework for pharmaceuticals.

Mutual Pharmaceuticals met with the Agency on July 31, 2006 in a pre-IND meeting to explore what would be required to get colchicine approved for acute flares of gout, for preventing flares of gout and for the orphan disease FMF. The Division told the Applicant that there were two randomized controlled trials in the literature for each of the indications of chronic gout and for FMF that could be used to support efficacy in

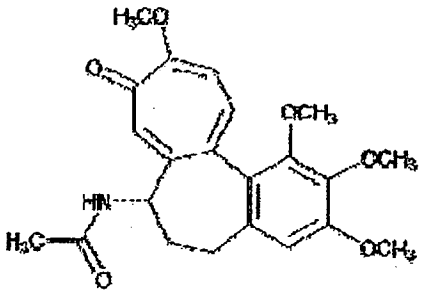
[1] Nuki G. Current Rheumatology Reports. 10(3):218-27, 2008.

505(b)(2) NDA applications, but for the acute gout indication there was only a single randomized, controlled study. Therefore, they would need to carry out an additional adequate and controlled trial. The Division said that the clinical trial in the literature by Ahern et al along with a new adequate and well-controlled trial could provide an adequate basis for filing a NDA for acute gout.

3. CMC/Microbiology/Device

3.1. General product quality considerations

The structure of colchicine is shown in Figure 1 (copied from the CMC review by Dr. Craig Bertha). The CMC review found no problems that would preclude approval. They initially made an approvable recommendation since the Office of Compliance had not yet issued a recommendation for this application. They did note in their review the presence of the photodegradant impurities β- and γ-lumicolchicine that will be discussed further under the discussion of the comments from the Pharmacology/Toxicology review team. The Office of Compliance issued a recommendation of Withhold in April, 2009 due to issues concerning a single site inspected, namely the ———. Subsequently, the ———. This site is the site that was intended to be used to prepare ——— of colchicine. The Applicant has stated that they ——— ——— of colchicine until a suitable site had been approved by FDA. Consequently, the CMC review team changed their recommendation to Approval on June 1, 2009. b(4)



Molecular formula: $C_{22}H_{25}NO_6$; Molecular weight: 399.44 g/mole

Figure 1

3.2. Facilities review/inspection

The Office of Compliance issued an recommendation of Acceptable, following ———, as described above in Section 3.1 b(4)

4. Nonclinical Pharmacology/Toxicology

The Applicant submitted no new toxicology studies under NDA 22-351. Pharmacology/Toxicology studies to support the approval of colchicine were submitted under NDA 22-352 and were reviewed under that NDA. In general, the

pharmacology/toxicology reviewer stated that findings of nonclinical toxicology closely mirror the known clinical toxicities of colchicine. The pharmacology/toxicology review team recommended approval of the application.

4.1. Carcinogenicity

Genetic toxicology studies showed that colchicine treatment leads to aneuploid cells through non-disjunction, although colchicine is not considered mutagenic or clastogenic. Carcinogenicity studies were not requested because of the long history of human use. However, upon review of the available data concerning the association between aneuploidy and cancer, the pharmacology/toxicology review team determined that carcinogenicity studies should be performed post-marketing.

4.2. Reproductive toxicology

There have not been GLP studies of reproductive toxicology. However, there is sufficient information in the published literature to convey potential risks in the product label. Recent reports of clinical epidemiologic studies of the outcomes of pregnancies of pregnant women exposed to colchicine have not found detrimental effects, although only limited numbers of pregnancies were available for analysis. The pharmacology/toxicology reviewer recommends an observational epidemiologic study of male and female reproductive problems, pregnancies, and their outcomes to further assess reproductive effects of colchicine in patients. I agree with Dr. Leshin that an observational epidemiologic study to assess the effects of colchicine on the reproductive system would be desirable. However, I am not convinced that such a study is either necessary or chievable. First, most women with gout are post-menopausal. In addition, gout is seen predominantly in older men. It is not clear to me that it would be possible to amass a large enough cohort of men who father children when exposed to colchicine to reach meaningful conclusions. I have spoken with Dr. Leshin and explained these concerns. He says he is OK with not requiring an observational epidemiology study.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review team determined that the submission was acceptable.

5.1. General clinical pharmacology/biopharmaceutics considerations

Systemic exposure to colchicine with the standard and low-dose regimens were derived from studies #1002 and #1003 from NDA 22-352. With the low-dose regimen (1.2 mg followed by 0.6 mg after 1 hour), peak plasma concentrations of colchicine were observed approximately 1.8 hours after the initial dose. With the standard-dose regimen (1.2 mg followed by 0.6 mg hourly for 6 hours), peak concentrations were observed at approximately 4.5 hours. The $T_{1/2}$ was at approximately 24 and 31 hours for the low-dose and standard-dose regiments, respectively.

5.2. Drug-drug interactions

The Clinical Pharmacology review team determined that there are a number of important drugs that interfere with the metabolism of colchicine. They formulated recommendations for the modification of dosing with colchicine when used concomitantly with such drugs that would maintain the average Cmax and AUC at levels in between those seen with the low-dose and standard-dose colchicine dose regimens.

For strong CYP3A4 inhibitors (such as ritonavir), the systemic exposure of colchicine is increased by 3- to 4-fold. Moderate CYP3A4 inhibitors (such as verapamil) cause a 2-fold increase in colchicine AUC. For weak CYP3A4 inhibitors (such as azithromycin), little change in the pharmacokinetics of colchicine is observed. P-glycoprotein (P-gp) inhibition increased the Cmax and AUC of colchicine 3.5 fold. The Clinical Pharmacology review team recommends dose adjustment of colchicine accordingly when it is given concomitantly with these types of drugs.

5.3. Pathway of Elimination

In healthy volunteers, 40-65% of a 1 mg oral dose of colchicine was recovered unchanged in urine. Enterohepatic recirculation and biliary excretion also play a role in elimination of colchicine. In addition, it is also a substrate of P-gp.

5.4. Demographic interactions/special populations

The Applicant did not conduct pharmacokinetic studies to assess the influence of age, race, body weight, pregnancy and organ dysfunction. Studies of these factors from the published literature were previously assessed by Clinical Pharmacology during review of the FMF submission. The Applicant submitted one study from the published literature exploring the effect of age on the pharmacokinetics of colchicine that suggested that mean peak plasma concentrations and AUC were higher in the elderly. That study assessed 4 elderly women with a mean age of 83 (range 75-93) and 6 healthy males. That study found that peak plasma concentrations and AUC were approximately 2-fold higher in the elderly patients. These data suggest that colchicine should be used with caution in the elderly due to potentially high plasma concentrations. The higher exposure in the elderly may be due to reduced renal function.

5.5. Thorough QT study or other QT assessment

Colchicine is not an NME. It has been previously approved in combination with probenecid as ColBenemid. A thorough QT study was not required for this submission because of the previous human experience with colchicine

5.6. Notable issues

The drug-drug interaction information and recommended dose adjustments should be included in the product label.

6. Clinical/Statistical

6.1. General Discussion

A combination of colchicine and probenecid (ColBenemid) has been previously approved for the treatment of gout based on the DESI process. Colchicine as a stand-alone product has been widely marketed in the US and prescribed for the treatment of acute flares of gout and for prevention of gout flares, but colchicine has never been approved. It is an important goal of the Agency to elicit NDAs from pharmaceutical companies for marketed, unapproved products such as colchicine to bring these products under the usual regulatory framework.

Mutual Pharmaceutical approached the Division in a pre-IND meeting seeking to submit 505(b)(2) marketing applications for colchicine for the treatment of acute flares of gout, prevention of gout flares in patients with chronic gout and in the orphan indication, FMF. The Division reviewed the company's proposal and informed the company that for submission of an NDA for acute gout that the clinical trials from the published literature proposed would not be sufficient for filing since there was only a single, randomized controlled trial in that indication. Rather, the company would need to conduct a single adequate and well-controlled clinical trial in acute gout. A successful result, along with the single randomized, controlled trial in the published literature would provide an adequate evidence base to file an NDA.

Mutual Pharmaceutical conducted a single, randomized, placebo-controlled trial of colchicine in patients with acute flares of gout. The trial randomized 575 patients in the US to standard-dose or low-dose colchicine or placebo. Of these, 185 patients had a flare and received treatment. A statistically significantly greater proportion of patients in both the standard-dose and low-dose arms achieved a 50% reduction in target joint pain at 24 hours compared to placebo. There were no major issues regarding efficacy for this trial.

The Applicant also submitted a randomized, placebo-controlled trial of colchicine in acute gout from the literature by Ahern et al. This trial enrolled 43 patients with acute gout who received either placebo or 1 mg colchicine followed by 0.5 mg every 2 hours until they achieved a clinical response or experienced toxicity. A greater proportion of patients receiving colchicine achieved a 50% reduction in pain and clinical scores than patients who received placebo. Limitations for this trial include the fact that the original datasets were not available for analysis by the FDA so the Agency could not independently verify the results. In addition, some patients receiving colchicine could have been unblinded by the GI side effects that were commonly seen with colchicine.

The safety database for patients with acute gout contains a total of 126 patients who received colchicine in the Applicant's randomized, controlled trial. In addition, a total of 126 healthy subjects received single and multiple doses of colchicine in pharmacokinetic studies. The Applicant also submitted an analysis of safety from the published medical literature and from post-marketing adverse event reports from the FDA AERS database and from the WHO database. In the clinical trial, the major toxicities were gastrointestinal (GI) in nature and were similar to those previously reported. The rate of

GI adverse events was considerably higher in the standard-dose regimen than with the low-dose regimen. Given that efficacy was similar in the two groups this suggests that prior practice may have subjected patients to increased toxicity with no greater efficacy than with the low-dose regimen. Review of the postmarketing adverse event experience did not reveal any unexpected toxicities compared to what has been previously reported.

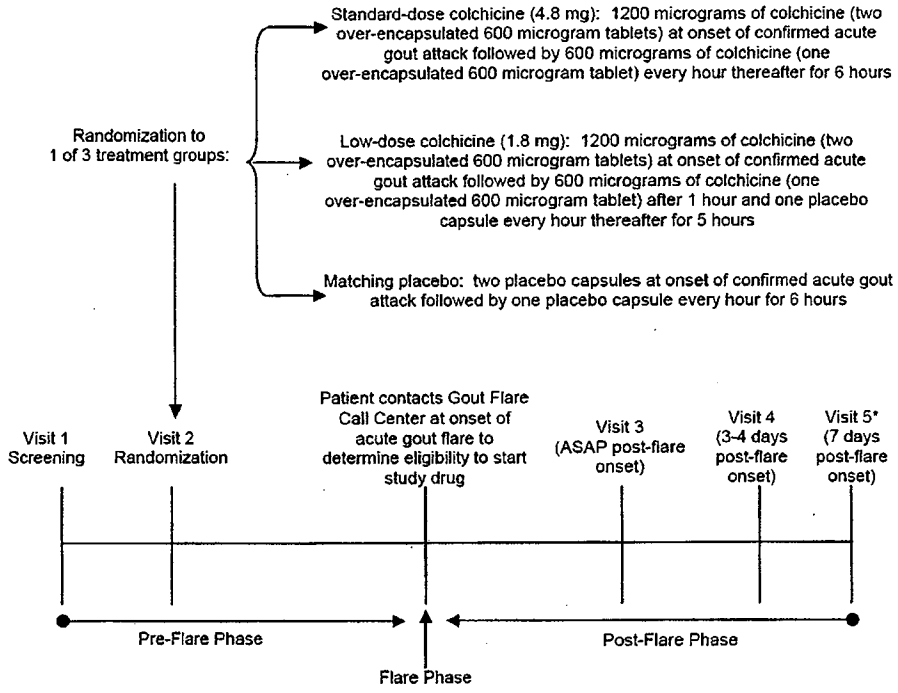
6.2. Efficacy

6.2.1. Dose identification/selection and limitations

Previous dosing recommendations for colchicine in the treatment of acute gout have been 1.2 mg orally followed by 0.6 mg orally every hour until relief of symptoms or toxicity occurred. In their Phase 3 trial, Mutual compared a lower dose of 1.2 mg followed by 0.6 mg at 1 hour to the standard-dose regimen. They found that a similar proportion of patients achieved 50% relief of pain at 24 hours in the low-dose arm (38%) as in the high dose arm (33%). Both colchicine regimens provided better responses than placebo (16%). Toxicity, consisting mostly of GI toxicity, was greater with the standard-dose arm. These data indicate that the low-dose regimen provides similar efficacy to the standard-dose regimen with less toxicity.

6.2.2. Phase 3/ clinical studies essential to regulatory decision

The Applicant conducted a single Phase 3 trial of colchicine in the treatment of acute gout, MPC-004-06-001. MPC-004-06-001 was a randomized, double-blind, placebo-controlled, parallel-arm trial of two doses of colchicine vs. placebo (Figure 1; this and all other figures and tables in this section copied from the clinical review of Dr. Rosemarie Neuner). Study MPC-004-06-001 enrolled patients with a confirmed diagnosis of crystal-proven gout per ACR criteria who had experienced at least 2 attacks of acute gout in the prior 12 months. Patients were excluded who had acute polyarticular gout involving 4 or more joints or who had arthritis due to any other cause. Patients with chronic renal or hepatic toxicity were also excluded.



*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.

Figure 2: Schema of Study MPC-004-006-001

Following screening, patients were randomized to either placebo or low-dose (1.2 mg followed by 0.6 mg at 1 hour) or high-dose (1.2 mg followed by 0.6 mg hourly for 6 hours). Patients were not treated until they experienced what they believed was a gout flare. At that time, patients were to contact a call center where trained personnel established whether the patient had the swelling, redness, marked tenderness and pain characteristic of a gout flare. When a flare was confirmed patients were to take their randomized study medication. The primary endpoint for the clinical trial was response to treatment in the target joint based on patient self-assessment at 24 hours. 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. The analysis was based on the intent-to-treat population. The study had 90% power based on the prespecified assumptions, using the Mantel-Haenszel chi-square test. No adjustment was specified in the protocol for multiple comparisons since the protocol specified the standard-dose colchicine arm as the comparison of interest.

Subject disposition for the randomized patients who experienced a gout flare and received study drug treatment in study MPC-004-06-001 is shown in Table 1. Of the 575 patients randomized, approximately 30% experienced a flare and received blinded study medication. Similar proportions of patients completed the study in the placebo and low-

dose colchicine arms (approximately 95%), while a smaller proportion completed the study in the standard-dose colchicine arm. The major reason for withdrawal was "Other." Patients enrolling in the trial were typical of the gout population in the US. The mean age was 52 and patients were overwhelmingly male (95%). The majority of patients were Caucasian (83%), although 14% were African American. Mean body mass index was 33. In the prior year, the mean number of gout attacks was approximately 4. The mean uric acid was approximately 9 mg/dL. A MPC-004-06-001

Table 1: Study Disposition for Study mpc-004

	Colchicine		Placebo (N=189)	Total (N=575)
	Standard Dose (N=193)	Low Dose (N=193)		
Number of Subjects Randomized	193	193	189	575
Number of Subjects with Qualifying Flare	52 (27%)	75[1] (39%)	58 (31%)	185 (32%)
Number of Subjects with No or Non-Qualifying Flare	141	118	131[2]	390[2]
Number of Subjects Treated (ITT)	52	74	58[2]	184[2]
Number of Subjects who Completed the Study	45 (87%)	71 (96%)	55 (95%)	171 (92%)
Number of Subjects who Withdrew from the Study:				
Lack of Efficacy	7 (13%)	3 (4%)	4 (7%)	14 (8%)
Withdrew Consent	0 (0%)	1 (1%)	1 (2%)	2 (1%)
Lost to Follow-Up	1 (2%)	0 (0%)	1 (2%)	2 (1%)
Other	1 (2%)	1 (1%)	1 (2%)	3 (2%)
	5 (10%)	1 (1%)	1 (2%)	7 (4%)

As stated above, the primary endpoint for study MPC-004-06-001 was the proportion of patients with a reduction of 50% or more in pain in the target joint at 24 hours. 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. Response rates in the standard- and low-dose colchicine groups were similar, although the point estimate was somewhat higher with low-dose colchicine (38% vs. 33%).

Table 2: Treatment Response at 24 Hours (Primary Endpoint) for Study MPC-004-06-001 (ITT Population)

Number (%) Responders			Treatment Comparison (Odds Ratio and 95% Confidence Interval)		
Colchicine		Placebo (N=58)	Standard vs Placebo	Low vs Placebo	Standard vs Low
Standard Dose (N=52)	Low Dose (N=74)				
17 (33%)	28 (38%)	9 (16%)	2.64 (1.06, 6.62)	3.31 (1.41, 7.77)	0.80 (0.38, 1.68)
			p = 0.0343[1]	p = 0.0046[1]	p = 0.5529[1]

For the primary endpoint, a responder is defined as a patient who achieved a ≥ 50% reduction in pain score and did not take rescue medication prior to the 24-hour post dose assessment.
[1]P-value is from the unstratified Pearson chi-square test.
Sponsor's Table 11:10; p. 79.

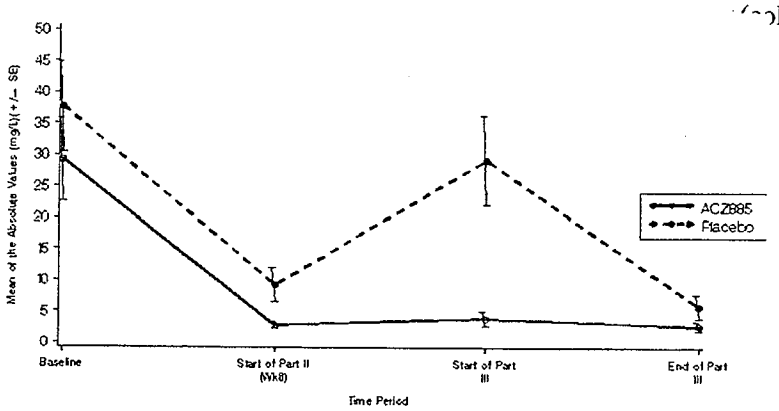


Figure 3: CRP levels in Study D2304

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.

6.2.3. Other efficacy studies

The Applicant submitted results of an additional randomized, controlled trial from the published literature in support of efficacy of colchicine for acute gout. The study by Ahern et al[2] was a randomized, double-blind, placebo-controlled study in 43 patients with crystal-proven gout. Randomized patients who met criteria for an acute flare were admitted to the hospital and received either placebo or colchicine 1 mg, followed by 0.5 mg every 2 hours until toxicity or until a complete response occurred. The protocol specified a response to be a 50% or greater decrease from baseline in patient-assessed pain based on a visual analog scale (VAS). Investigator assessments were obtained using blinded assessors who evaluated pain, tenderness on palpation, swelling and redness to generate a compound clinical score with a range of 0-12.

A total of 43 patients were randomized in a 1:1 ratio. Pain scores and clinical scores showed moderate to severe gout flares.

[2] 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

Table 3: Baseline Demographic and Disease Characteristics: Ahern Study

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

Table reproduced from published article by Ahern et al[1]
*No significant differences between the groups were detected using Student's t-test
**Large = knee, ankle, wrist; small = metatarsophalangeal, metacarpophalangeal, interphalangeal

Based on the prespecified endpoint of 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. A difference was first apparent as early as 12 hours post-treatment and became more pronounced over time. Nominal p values were less than 0.05 at the 36 and 48 hour time points.

Table 4: Percentage of Patients with Joint Response Defined as a 50% Reduction in Pain and Clinical Scores: Ahern et al Study

	12 Hrs. Post-Treatment	24 Hrs. Post Treatment	36 Hrs Post-Treatment	48 Hrs. Post Treatment
Clinical Score:				
Colchicine	5%	23%	50%**	64%*
Placebo	0%	0%	5%	23%
Pain Score:				
Colchicine	23%	41%	73%*	73%*
Placebo	9%	9%	32%	36%

*unadjusted p< 0.05; **unadjusted p<0.01 by chi-square test

In the Ahern study, GI toxicity was highly 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. The clinical reviewer noted that the common GI adverse events raise questions about whether the clinical assessors who were blinded may have nonetheless figured out the study assignment given the well-known GI toxicity of colchicine.

6.2.4. Discussion of primary and secondary reviewers' comments and conclusions

The primary clinical reviewer, Dr. Rosemarie Neuner, concluded that Study MPC-004-06-001 demonstrated the clinical efficacy of colchicine based on a 50% or greater improvement in target joint pain at 24 hours post-dosing. She concluded that the Ahern study had shown efficacy of colchicine based on the greater proportion of patients with improvement in pain and clinical scores. She noted that there were limitations to the

study, including the inability of the Agency to verify the findings since the datasets were unavailable and the possibility of unblinding of investigators due to characteristic adverse events among the colchicine-treated patients. The statistical reviewer concluded that there is statistical evidence to support the efficacy of the low-dose and standard-dose colchicine regimens to treat acute attacks of gout as measured by a reduction in pain. I concur with the clinical and statistic reviewers that the MPC-004-06-001 and Ahern studies together demonstrate the efficacy of colchicine in the treatment of acute flares of gout.

6.2.5. Pediatric use/PREA waivers/deferrals

Gout is quite rare in children and it would not be possible to conduct studies in children due to the small number of patients available. Therefore, the Applicant was granted a waiver to conduct studies in children under PREA. The PeRC Committee concurred with this decision.

6.2.6. Discussion of notable efficacy issues

There are no notable efficacy issues.

6.3. Safety

6.3.1. General safety considerations

The safety database for patients with acute gout contains a total of 126 patients who received colchicine in the Applicant's randomized, controlled trial. In addition, a total of 126 healthy subjects received single and multiple doses of colchicine in pharmacokinetic studies. The Applicant also submitted an analysis of safety from the published medical literature and from post-marketing adverse event reports from the FDA AERS database and from the WHO database. In view of the extensive prior postmarketing experience the size of the clinical trial safety database is adequate.

There were no deaths in the randomized, controlled trial and no serious adverse events. The major toxicities in the randomized, controlled trial were GI and included diarrhea, nausea and vomiting. Review of the postmarketing experience did not demonstrate new safety signals compared to what has been previously reported.

6.3.2. Safety findings from submitted clinical trials

Exposure to colchicine in the randomized Phase 3 trial is shown in Table 5. Approximately 90% of patients in the low dose and placebo arms received all 7 doses of blinded study medication. Fewer patients in the standard dose arm (73%) received all 7 doses. Although no patient was reported to have withdrawn prematurely due to an adverse event associated with the use of study medication, the Applicant examined the study diaries to see if patients missing a dose of medication may have had a drug-related safety issue. A total of 16 patients missed study medication due to a possible safety reason. Eleven of these 16 patients had a GI adverse event. Seven of these 11 were in

the standard dose group, 1 was in the low-dose group and 3 were in the placebo group. These findings are consistent with the well-known GI toxicity of colchicine.

Table 5: Study Drug Exposure in MPC-004-06-001

	Colchicine		Placebo (N=59)	Total (N=185)
	Standard Dose (4.8 mg) (N=52)	Low Dose (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[1]:	14 (27%)	6 (8%)	7 (12%)	27 (15%)
Took at Least the First 2 Doses of Study Medication:	49 (94%)	71 (96%)[2]	56 (95%)	176 (95%)
Did Not Complete the last 6 Doses:	3 (6%)	2 (3%)	0	5 (3%)

There were no deaths in the Phase 3 trial and no serious adverse events. Severe adverse events (AEs) were more frequent in the standard-dose colchicine group (10 events, 19% of patients) than in the low-dose colchicine (zero events) or placebo groups (1 event, 2% of patients). All 10 severe AEs in the standard-dose group were GI in nature and consisted of diarrhea, melena (1 case) and nausea. The case of melena may have been related to use of methylprednisolone as rescue medication. The most common AEs were also GI in nature. No clinically meaningful changes in laboratory values were observed in the Phase 3 trial.

With respect to review of the postmarketing experience with colchicine, the most common AEs seen in the AERS database since 1997 were diarrhea, drug interaction, vomiting, acute renal failure and nausea. Prior to 1997, the most common AEs were diarrhea, myopathy, pancytopenia, overdose and increased CPK. The most common laboratory abnormalities reported in the AERS database include increased creatinine, increased CPK, increased AST and ALT and increased BUN.

6.3.3. Safety update

The 120-day safety update showed no new safety signals.

6.3.4. Immunogenicity

Not applicable.

6.3.5. Discussion of primary reviewer's comments and conclusions

The primary clinical reviewer, Dr. Rosemarie Neuner, concluded that most common adverse events were GI in nature. She concluded that GI toxicity was greater with the standard dose than with the low dose of colchicine. I concur with her assessment.

6.3.6. Discussion of notable safety issues

Treatment of acute flares of gout with colchicine appears to be reasonably safe. The major toxicities appear to be GI in nature and are not serious or life-threatening. Surprisingly, the majority of GI toxicities can be avoided by administering the low-dose regimen of colchicine without sacrificing efficacy.

7. Advisory Committee Meeting

No advisory committee meeting was convened to discuss this application. Colchicine is not an NME. It was judged that the data submitted were adequate to determine whether the risk/benefit relationship was favorable for colchicine in the treatment of acute flares of gout. Furthermore there were no serious issues in dispute with respect to efficacy or safety of colchicine for acute flares of gout.

8. Financial Disclosure

Based on the information submitted by the Applicant there were no financial conflicts of interest that would have the potential to bias the data.

9. Labeling

9.1. Proprietary name

DMEPA determined that the proposed proprietary name, Colcrys, was acceptable.

9.2. Physician labeling

At this time, the review of the Applicant's proposed product labeling is just beginning. I agree with the Applicant's proposal to recommend only the low-dose colchicine regimen. The label should include information on drug-drug interactions and appropriate recommendations for dose adjustment.

10. DSI audits

DSI inspected 3 clinical sites and found no regulatory violations.

11. Conclusions and recommendations

11.1. Regulatory action

Data from the Phase 3 clinical trial of colchicine, along with the randomized controlled trial in the published literature by Ahern and the prior approval of colchicine as a component of ColBenemid together provide substantial evidence of efficacy for colchicine in the treatment of acute flares of gout. In the Phase 3 trial conducted by the Applicant, MPC-004-06-001, a greater proportion of patients in the low-dose (38%) and standard-dose (33%) colchicine arms achieved a 50% reduction in patient-assessed target joint pain as compared to controls (16%). Assessment by investigators demonstrated improvement in signs and symptoms of inflammation.

Data from the Phase 3 clinical trial and prior reported trials in the literature demonstrate the well-known GI toxicities associated with colchicine. None of the AEs were serious. GI toxicity was much more common with standard-dose than with low-dose colchicine. Other toxicities of colchicine based on postmarketing data are consistent with the well-known toxicites associated with this product.

Overall, the use of colchicine in the setting of acute flares of gout demonstrates a clearly favorable benefit:risk ratio. Given the lower toxicity and similar efficacy, the low-dose regimen is the preferred regimen. This 505(b)(2) NDA application should be approved with appropriate modifications to the proposed package insert.

11.2. Safety concerns to be followed postmarketing

Given the well-known safety profile of colchicine there are no safety concerns that require following postmarketing.

11.3. Postmarketing studies

11.3.1. Required studies

None

11.3.2. Commitments (PMCs)

None.

11.3.3. Other agreements with Sponsor

None.

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/s/

Jeffrey N Siegel
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MEDICAL OFFICER