CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-353

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	October 15, 2009
From	Jeffrey Siegel, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22-353
Applicant	Mutual Pharmaceutical Company
Date of Submission	November 25, 2008
PDUFA Goal Date	September 25, 2009
Proprietary Name / Established (USAN) names	Colcrys/colchicine
Dosage forms / Strength	Tablet / 0.6 mg
Proposed Indication(s)	Prevention of gout flares
Recommended:	*Approval*

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1. Introduction to Review

The Applicant, Mutual Pharmaceutical, submitted this new drug application (NDA) for colchicine (Colcrys) for the prevention 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. Colchicine has been used in the United States as a purified, single active ingredient since before 1938. Colchicine was approved as part of a combination with probenecid as ColBenemid - colchicine 0.5 mg/probenecid 500 mg. However, colchicine as a single, active ingredient never underwent FDA review. Thus, despite the fact that colchicine has been widely available as a stand-alone product from many sources it was, until July, 2009, a marketed, unapproved product. This situation changed when, during the review of this current application, Colcrys (colchicine) was approved for two other indications: treatment of acute gout and treatment of familial Mediterranean fever (FMF).

Mutual submitted the results of two randomized controlled trials of colchicine for prevention of gout flares from the published literature. The first study, by Borstad et al, studied the frequency of gout flares at 3 and 6 months in 43 patients with crystal-proven gouty arthritis who were beginning urate-lowering therapy with allopurinol. The patients were randomized to receive colchicine 0.6 mg twice daily or placebo. The second study was a 6-month trial by Paulus et al that studied the number of gout flares per month in 51 patients with gout who were started on the uricosuric agent, probenecid. Patients were randomized to receive colchicine 0.5 mg three times daily or placebo. To support the safety of colchicine for the prevention of gout flares the Applicant submitted a review of the published literature, including the two randomized trials by Borstad and Paulus, data from a trial conducted by the Applicant for treatment of gout flares and a review of the postmarketing adverse event reports in the FDA and WHO databases. The Applicant's proposed dose is 0.6 mg once or twice daily.

The major issue for this application is the evidence base supporting efficacy. The panel that reviewed ColBenemid as part of the DESI process concluded that 1 tablet per day for one week followed by 1 tablet twice a day of probenecid 0.5 gm and colchicine 0.5 mg was effective in lowering serum urate levels and in reducing the frequency of recurrent acute attacks of gout. The two randomized, controlled trials from the published literature suggest that colchicine is effective for preventing gout flares. However, these two studies each have limitations due to the manner of their conduct and analysis. This review will consider the strengths and weaknesses of the various pieces of evidence relevant to a determination of efficacy of colchicine for preventing gout flares. There are no safety issues that would preclude approval of this application and no major issues were raised in the review by the other disciplines.

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. 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. Paradoxically, initiation of urate-lowering treatment for hyperuricemia has been shown to increase the risk of developing acute flares of gout. These gout flares are believed to be related to fluctuations in uric acid levels and to mobilization of urate from tissue stores. When tissue urate stores are depleted by urate-lowering therapies then patients stop experiencing gout flares. In order to avoid flares of gout upon initiation of urate-lowering therapies clinicians generally treat prophylactically with either a non-steroidal anti-inflammatory drug, corticosteroids or a course of colchicine until the risk of flare diminishes.

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.* 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.

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 was, however, approved in the pre-DESI era (NDA #12-383, June, 1960) as a component of ColBenemid, a combination product that contains colchicine 0.5 mg and probenecid 500 mg. Since approvals in the pre-DESI era did not require a finding of efficacy, ColBenemid was subsequently reviewed by a DESI panel for evidence of effectiveness. The DESI review panel concluded that ColBenemid was "effective, in lowering serum urate levels and in reducing the frequency of recurrent acute attacks of gout...Probenecid is an effective uricosuric drug and colchicine is effective as a prophylactic agent." At present, ColBenemid is no longer marketed. Colchicine has been marketed, though, as a stand-alone product but it has been a marketed, unapproved product. It is a current goal of the Agency to encourage pharmaceutical companies to file NDAs for marketed, unapproved products so they can be brought under the usual regulatory framework for pharmaceuticals. In July, 2009 the Agency approved Colcrys (colchicine) for treatment of acute attacks of gout and for FMF. The current application is for the additional indication of prevention of gout flares, which is the major use of colchicine.

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

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

preventing flares of gout and for the orphan disease FMF. The Division told the Applicant that for the prevention of gout flares indication that the two randomized controlled trials in the literature could be used to support filing a 505(b)(2) NDA application.

3. CMC/Microbiology/Device

The CMC review team recommends approval of this application. No new CMC information was submitted in this application. The Office of Compliance provided a recommendation of Acceptable.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review team recommends approval. No new nonclinical studies were submitted in this application. The pharmacology/toxicology review team recommends two nonclinical studies be conducted that were required as postmarketing requirements for the recent approval of Colcrys for acute gout and FMF.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review team determined that the submission was acceptable. No new clinical pharmacology information was submitted in this NDA.

6. Clinical/Statistical

6.1. General Discussion

As stated above, a combination of colchicine and probenecid was approved as ColBenemid, but until very recently colchicine was not approved as a stand-alone product. 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 it was only in July, 2009 that Colcrys (colchicine) was approved for the treatment of acute attacks of gout and FMF. The current application is for the additional indication of prevention of attacks of gout.

In their application, Mutual submitted the results of two randomized controlled trials of colchicine for prevention of gout flares from the published literature: a study by Borstad et al of 43 patients with crystal-proven gouty arthritis who were beginning urate-lowering therapy with allopurinol and a 6-month trial by Paulus et al of 51 patients with gout who were started on the uricosuric agent, probenecid.

In support of safety for the chronic gout indication, the Applicant submitted data from their randomized, placebo-controlled trial of 126 patients with acute gout, 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. The data are all consistent with the well-known side effect profile of colchicine. The major toxicities are gastrointestinal (GI) in nature in the proposed dose of 0.6-1.2 mg daily. Significant adverse events are often the result of inappropriate dosing in patients with renal or

hepatic insufficiency, concomitant drug interactions, or intentional/unintentional overdosing.

6.2. Efficacy

6.2.1. Dose identification/selection and limitations

The randomized controlled studies in the literature (Borstad et al and Paulus et al) studied doses ranging from 0.6 mg/d to 1.5 mg/d. Data from those studies suggest that higher doses may not be well tolerated. In the Borstad study patients were treated blindly with colchicine 0.6 mg twice daily with the option of reducing the dose to 0.6 mg once daily for adverse effects. A total of 62% of patients randomized to colchicine reduced their dose to 0.6 mg once daily.

Formal dose ranging studies have not been conducted for colchicine for prevention of gout flares. However, colchicine has been widely used for many years for the prevention of gout flares at the dose proposed by the Applicant. Based on the well-characterized safety profile of colchicine the side effects experienced by patients who cannot tolerate the proposed dose consist of reversible gastrointestinal adverse events that are not serious (nausea, vomiting and diarrhea). Therefore, the proposed dose is a reasonable starting dose with dose reduction or discontinuation for patients who develop gastrointestinal toxicity.

6.2.2. Phase 3/ clinical studies essential to regulatory decision

No Phase 3 trials were conducted for this submission.

6.2.3. Other efficacy studies

The Applicant submitted two randomized controlled trials from the literature to support the efficacy of colchicine for the prevention of gout flares. The first study, by Borstad et al (Borstad GC et al. J Rheum. 31:12, 2429, 2004) was a randomized, placebo-controlled trial of 43 patients with crystal-proven gouty arthritis who had criteria for initiating allopurinol including 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. Patients with renal insufficiency received 0.6 mg colchicine once daily. The study was technically double-blind, but the colchicine and placebo tablets were not identical. Subjects initiated allopurinol therapy at a dose of 100 mg daily and increased allopurinol dosing by 100 mg/d increments until 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 3 and 6 months 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, as assessed by T-test, the number of patients with at least one flare by chi-square test and the number of patients with more than one flare by chi-square test. The mean pain score per flare by visual analog scale (VAS) and the average length of flares were analyzed by Mann-Whitney test for nonparametric data because of the non-normal distribution of the data.

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 Figure 1, 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. A smaller 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%).

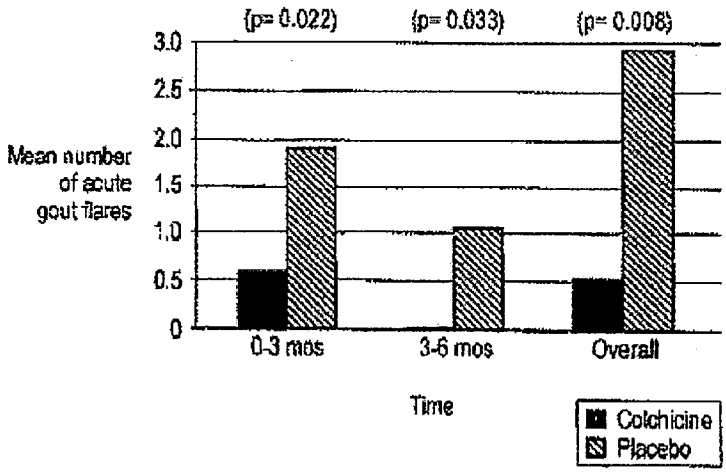

Figure 1: Mean number of acute gout flares in 0-3 and 3-6 month time periods and overall (source: Borstad et al, 2004)

The second study, by Paulus et al (Arthritis & Rheumatism, 17:5, 609, 1974), was a 6-month, randomized, double-blind, placebo-controlled study of colchicine for the prevention of gout flares in patients with gout starting 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 sites – Los Angeles and Kansas City – and there were some differences between sites in terms of study conduct. At the Los Angeles site all urate lowering therapies were discontinued 2 weeks before therapy while in Kansas City patients were to be on a stable dose of probenecid 2 weeks before beginning therapy. Patient reports on gout flares were recorded on a monthly basis.

Gout flares that were moderate or severe were included in the analysis with "moderate" or "severe" defined as definite pain accompanied by swelling and tenderness.

Before unblinding the data the investigators examined the serum urate levels to determine whether urate lowering therapy was successful. Only patients who successfully lowered their urate levels were included in the analysis. 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.

To assess the effect of colchicine on preventing gout flares Paulus et al analyzed the number of gout flares per month. As shown in Table 1, 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). The table also illustrates that the probenecid lowered serum urate in both groups to a similar extent. More patients in the colchicine arm experienced adverse events, including 9 patients with diarrhea, 11 with nausea, vomiting or anorexia and reversible increases in SGOT and SGPT.

Table 1: Effects of Therapy (Paulus, 1974)

Treatment Group	Serum Urate mg/100 ml ± SE		Attacks of Gouty Arthritis per Patient per Month ± SE	No. of Patients with (Drug-related) Side Effects
	Before	After		
Colchicine-Probenecid	8.4 ± 0.4	6.3 ± 0.4†	0.19 ± 0.05*	15
Placebo-Probenecid	9.2 ± 0.6	6.2 ± 0.4†	0.48 ± 0.12*	8‡

*$P < 0.05$
†$P < 0.01$
‡$0.1 > P > 0.05$ (chi square analysis)

The Applicant also included in their submission several open-label studies in the literature in support of the efficacy of colchicine in preventing gout flares. The study by Becker et al (Becker MA *et al.* Arthritis Rheum 2005;52:916-923) 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. To prevent gout flares patients took colchicine 0.6 mg twice daily for the first two weeks

then colchicine 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. In contrast, when colchicine was stopped, the proportion with gout flares rose to 34%, 30%, 40% and 42%, respectively. The increase in the rate of flares suggests that colchicine was preventing gout flares during the period when it was administered.

A second trial by Becker et al (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 to prevent gout flares then colchicine was stopped. As shown in Figure 2, the proportion of patients experiencing gout flares increased when colchicine prophylaxis was stopped. These data again suggest that colchicine prophylaxis during the first 8 weeks reduced the incidence of gout flares.

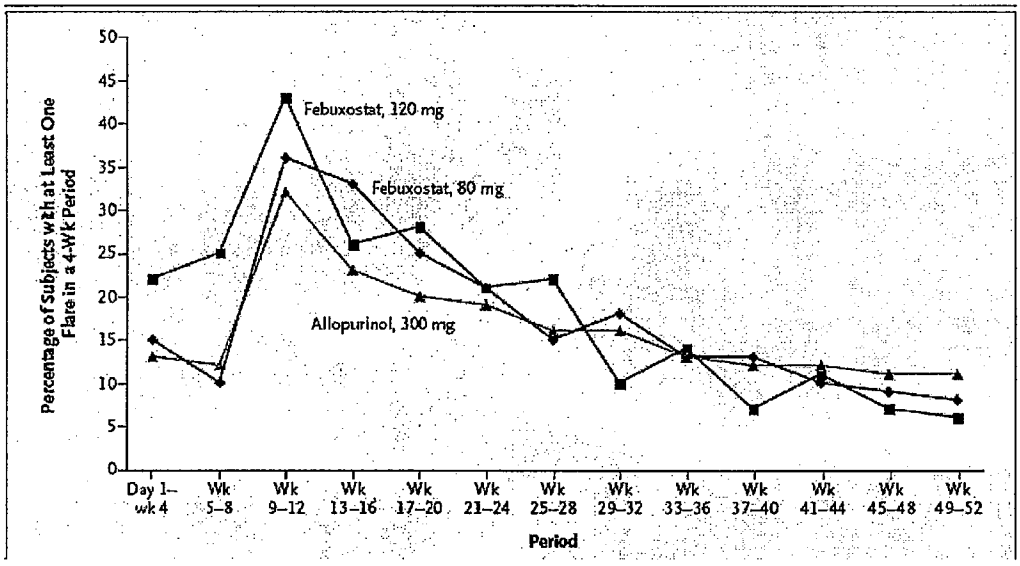

Figure 2: Subjects requiring treatment for gout flares in randomized trial of febuxostat

The Applicant also submitted the results of their randomized, placebo-controlled trial of colchicine for the treatment of gout flares. Study MPC-004-06-001 (reviewed as part of the clinical review of NDA 22351) was a randomized, placebo-controlled, double-blind trial that compared standard dose colchicine (4.8 mg total over 24 hrs) to low-dose colchicine (1.8 mg over 24 hrs) to placebo for the treatment of acute gout flares. That study showed efficacy of colchicine based on the primary endpoint of a 50% or greater improvement in target joint pain at 24 hours. A total of 33%, 38% and 16% of patients achieved the primary endpoint in the standard-dose colchicine, low-dose colchicine and placebo groups, respectively. These data demonstrate the efficacy of colchicine in the

treatment of gout flares, although they do not directly demonstrate efficacy of colchicine for prevention of gout flares.

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

The clinical reviewer, Dr. Jane Gilbert, recommends approval of this NDA. She concludes that the two randomized controlled trials from the published literature provide adequate evidence of efficacy and that prior FDA actions (i.e., approval of the combination product ColBenemid under DESI and recommendations in the product labels of approved urate-lowering drugs to use concomitant colchicine to prevent gout flares) demonstrate that the Agency has previously concluded that colchicine is efficacious for the prevention of gout flares. She notes that the two randomized controlled trials in the literature submitted as evidence of efficacy have certain limitations. For example, the Paulus study excluded from analysis subjects who did not achieve a reduction in serum uric acid. However, she concludes that "despite the inherent limitations of using previously published studies to establish efficacy, both the Borstad and the Paulus studies provide convincing evidence" that colchicine is effective in preventing gout flares.

The biostatistics review, Mr. David Petullo, had concerns about the two randomized controlled trials from the published literature. For the Paulus et al study, he noted that:

1. there were differences in the way urate-lowering drugs were handled at the two study sites: in the Los Angeles site urate-lowering drugs were removed prior to starting the study while in the Kansas City site patients were stabilized on probenecid prior to beginning colchicine. Since he did not have the data themselves he was unable to investigate what effect this difference might have had.

2. the investigators excluded from their analysis patients who did not demonstrate a reduction in urate levels. Consequently, the study population is not intent-to-treat introducing the potential for bias.

3. the publication did not specify how the mean flare rate was calculated. He assumed the overall flare rate was calculated based on the average of the monthly flare rate for individual patients; however, alternatively it may have been calculated by dividing the total number of flares in the group by the number of subjects. Without the data, he was unable to verify the method for calculation.

4. it was not clear how the investigators accounted for patients who did not complete the study. In addition, the authors did not provide complete information on the cause of withdrawal for all patients who withdrew.

5. there may have been differences in the patient-reported flares and the investigator-reported flares. Without the data, he was unable to determine the impact of any potential differences on the results.

For the Borstad trial, Mr. Petullo had the followed concerns:

1. The trial was not completely blinded as colchicine tables and placebo tablets had a different appearance.

2. It was uncertain how the analyses accounted for patients who had multiple flares.

3. It was uncertain how the analyses accounted for patient withdrawals.

Mr. Petullo concluded that "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," he was not able to confirm the authors' conclusions. Shortcomings in the studies additionally raised concerns regarding the design, conduct, and statistical analyses of the data.

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

While I share the concerns of the biostatistics reviewer that there are limitations to the two randomized controlled studies from the published literature, because of the consistency of effect in those studies, the large effect size they show and their consistency with other evidence of efficacy these two studies do provide supportive evidence of the efficacy of colchicine in preventing gout flares. In approving colchicine as part of a combination product with probenecid, ColBenemid, for "all stages of gout and gouty arthritis" the FDA already made the determination that colchicine was effective for prevention of gout flares. The evidence that colchicine is efficacious in preventing gout flares and support the approval of this NDA is as follows:

1. *The FDA approval of ColBenemid (colchicine in combination with probenecid) reflected a finding of efficacy of colchicine for preventing gout flares.* ColBenemid was approved by the FDA in 1960 based on safety considerations alone. ColBenemid was subsequently approved under the DESI process. It was approved for treatment of "all stages of gout and gouty arthritis except a presenting acute attack." Treatment of all stages of gout includes prevention of gout flares. 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 efficacy for the colchicine moiety. In approving ColBenemid under the DESI process the Agency relied on the findings of the DESI panel, which found that "probenecid is an effective uricosuric drug and colchicine is effective as a prophylactic agent." The DESI panel raised concerns about the combination product but they are not relevant to the finding of efficacy of colchicine for prevention of gout flares. The objections of the DESI panel to the combination

were that the fixed combination would not allow separate adjustment of the probenecid dose without also changing the colchicine dose.

It should be noted that the situation with colchicine as a component of ColBenemid is unusual; it does not indicate that the approval of a combination product generally indicates efficacy of each component. What is special about the ColBenemid combination is that each component has 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.

Of note, the labels for each of the approved urate-lowering therapies (e.g., allopurinol, probenecid, febuxostat) contains a recommendation to treat patients with colchicine when initiating urate-lowering therapy to prevent gout flares. This recommendation is consistent with our finding that colchicine is safe and effective for prevention of attacks of gout but it is not essential to our finding. When this recommendation was included in these other labels colchicine was not approved as a single ingredient product and had not been reviewed as such.

2. *Two randomized controlled trials in the literature provide important supportive evidence for the efficacy of colchicine at preventing gout flares.* The studies by Borstad et al and by Paulus et al are consistent in suggesting the efficacy of colchicine in reducing the frequency of gout flares in patients with chronic gout. However, in view of the issues identified with the published trials it is clear that these trials do not rise to the level of evidence expected for clinical trials that stand alone in providing evidence of efficacy for new therapeutic agents. Nonetheless, these studies provide important supportive evidence of efficacy of colchicine.

6.3. Safety

No new safety data were submitted in this application. Colcrys (colchicine) is currently approved for chronic use in FMF and for acute use for the treatment of gout flares. The data submitted by the Applicant in support of the safety of colchicine in the prevention of gout flares include a review of the published literature, including the two randomized trials by Borstad and Paulus, data from a trial conducted by the Applicant for treatment of gout flares and a review of the postmarketing adverse event reports in the FDA and WHO databases. These data were previously reviewed in the review of the FMF and acute gout applications.

The submitted safety data are consistent with the well-known side effect profile of colchicine and demonstrate that it is generally well tolerated when it is given in the proposed dose of 0.6 mg once or twice daily. Serious adverse events have been seen most frequently 1) in the setting of intentional or unintentional overdose; 2) when it is used without appropriate dose modification in patients with renal or hepatic

insufficiency; 3) when it is used with concomitant medications with which it has a significant interaction. Each of these situations is covered fully in the current product labeling with appropriate warnings and precautions.

6.3.1. Discussion of primary reviewer's comments and conclusions

The primary clinical reviewer, Dr. Jane Gilbert, concluded that colchicine was generally well tolerated when given orally at a dose of 0.6 to 1.2 mg daily. She said the safety data were consistent with the well-known side effect profile of colchicine. I concur with her assessment.

7. Advisory Committee Meeting

No advisory committee meeting was convened to discuss this application. Colchicine is not an NME and it is now approved as a stand-alone medication. An advisory committee meeting was not deemed necessary to judge whether the data were adequate to establish the efficacy of colchicine in the prevention of gout flares.

8. Financial Disclosure

Not applicable. No new clinical trial data were reviewed for this application.

9. Labeling

9.1. Physician labeling

At this time, the review of the Applicant's proposed product labeling is ongoing.

10. DSI audits

Not applicable. No new clinical trial evidence was submitted in this application.

11. Conclusions and recommendations

11.1. Regulatory action

Recommend approval of Colcryst (colchicine) for the prevention of gout flares.

11.2. Risk-benefit assessment

The evidence for the efficacy of colchicine for the prevention of gout flares in patients with chronic gout is derived from the previous Agency finding of effectiveness of colchicine that was reflected in the previous approval of ColBenemid (colchicine/probenecid combination) and from important supportive evidence from the positive results of two randomized, controlled trials in the published literature

Colchicine has been marketed and prescribed as a stand-alone agent for prevention of gout flares for decades as a marketed but unapproved product. Therefore its safety for this indication in a dose of 0.6 mg once or twice daily is well understood. The most

common adverse events are gastrointestinal in nature and may be managed by reducing the dose or discontinuing the drug. The risk-benefit relationship is favorable for prevention of gout flares. Serious adverse events, including deaths, are seen uncommonly and have been associated with use with drugs with which colchicine has an important drug-drug interaction. Serious adverse events are also seen in patients with hepatic and renal insufficiency who do not have appropriate dose adjustments. These specific situations, and the uncommon serious adverse events, are fully described in the current product label for Colcrys.

Overall, the use of colchicine for the prevention of gout flares demonstrates a favorable benefit:risk ratio. A dose of 0.6 mg once or twice daily is an appropriate dose, with dose reduction for patients who develop adverse events. This 505(b)(2) NDA application should be approved with appropriate modifications to the proposed package insert.

11.3. Safety concerns to be followed postmarketing

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

11.4. Postmarketing studies

11.4.1. Required studies

None

11.4.2. Commitments (PMCs)

None.

11.4.3. Other agreements with Sponsor

None.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22353	ORIG-1	MUTUAL PHARMACEUTICAL CO INC	COLCHICINE TABLETS USP 0.6MG

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEFFREY N SIEGEL
10/15/2009