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APPLICATION NUMBER:

22-353

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-353
Priority or Standard	Standard
Stamp Date	11/25/2008
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Division / Office	Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)/ODEII
Reviewer Name(s)	Jane L. Gilbert, MD, PhD
Review Completion Date	
Established Name	Colchicine
(Proposed) Trade Name	Colcrys™
Therapeutic Class	Alkaloid
Applicant	Mutual Pharmaceutical Company, Inc.
Formulation(s)	0.6 mg Tablets USP
Dosing Regimen	0.6 mg orally once or twice daily
Indication(s)	Prevention of gout flares
Intended Population(s)	Adults with chronic gout

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This review is for NDA 22-353: an application to approve colchicine for the prevention of acute gout. Two additional NDAs for approval of colchicine have recently been reviewed at the FDA: one is for treatment of acute gout (NDA 22-351) and the second is for treatment of Familial Mediterranean Fever (NDA 22-352). Since many issues in these NDAs overlap, I will quote extensively from reviews by Dr. Rosemarie Neuner (NDA 22-351) and Dr. Keith Hull (NDA 22-352). Both of these NDAs are now approved.

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends approval for this 505(b)(2) application for colchicine for prevention of gout flares. The recommendation is based upon both the evidence provided in the application as well as prior FDA actions that provide a regulatory basis for this approval.

Colchicine is an unapproved marketed product with a long history of use for the intended indication: prevention of gout flares. Numerous published studies, dating back approximately 50 years, describe the use of colchicine to prevent gout flares. While many of these are open label studies, there are two that have been identified as randomized controlled trials (RCTs).

The RCTs that support efficacy are smaller academic studies published in 1974 and 2004 in well known, peer-reviewed journals that are among the preeminent publications in the field of rheumatology. Nevertheless, they are consistent with the factors described in the Effectiveness Guidance which "increase the possibility of reliance on published reports alone to support approval of a new product..." These factors are:

a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.

b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.

c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily

interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.

d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or "evaluable" subset).

e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

Compared with drug trials that are commonly conducted today and designed expressly for the purpose of evaluating a new drug and gaining FDA approval for this, the two RCTs are academic studies published in preeminent peer-reviewed journals. Each summarizes the result of a study that was undertaken and completed by a small number of investigators at one (Borstad) or two (Paulus) institutions. The purpose of the studies was to analyze the relationship between colchicine (a marketed product) and the incidence of gout flares. Our ability to evaluate this type of a trial is limited by the fact that we do not have access to the original plans and, therefore, are unable to state that endpoints and/or statistical plans were specified prospectively. Nevertheless sufficient information appears to be contained within the body of each published paper to enable us to make reasonable judgements.

In terms of (a) above, in this reviewer's opinion both studies have *adequate* design and demonstrate consistent results. Both trials suffer from the fact that flares are identified retrospectively and are not verified by investigators. Though this feature is suboptimal, most physicians would acknowledge that patients with gout are generally able to identify a gout flare. The main design flaw of Paulus is that it excludes from analysis subjects (on placebo or colchicine) who did not achieve a decrease in uric acid. Thus, there is, in this study, an unconventional ITT population. However, as stated by the author in the first sentence of the paper's abstract: "The serum urate-lowering effect of probenecid was used to monitor compliance in a placebo-controlled study of prophylactic colcicine therapy for intercritical gout." It appears that this was a pre-specified design feature that was built in to take into consideration that the study population was likely to include a non-compliant group. In this regard, it should be noted that of the 14 subjects who were not analyzed, 5 came from the placebo group and 9 came from the group receiving colchicine. The exclusion of subjects who do not develop a decrease in uric acid also has the effect of excluding persons who would be less likely to experience a flare: thus, the analyzed population included those persons most likely to have a gout flare and to be able to identify whether or not a prophylactic drug such as colchicine would make a difference.

In terms of (b) above, the published reports provide clear and adequate descriptions of statistical plans, analytic methods, and study endpoints. As described above, given the nature of these publications, it is not possible to determine whether or not these were prospectively determined. However, there is no reason to suspect that they were defined post hoc. As described in section 5.3.1 and 5.3.2, the disposition of all subjects is covered adequately.

Factor (c) calls for appropriate endpoints and most would agree that gout attacks are unequivocal.

Factor (d) describes the need for robust results without post hoc subsetting. Both studies demonstrate this factor. And, Factor (e) calls for conduct of studies by well established groups; this is clearly seen in these two publications and further underscored by the fact that the papers were published in well-known and well-respected medical journals.

Though neither of the RCTs was designed to gain approval for a new drug and though neither of these RCTs has the degree of specificity that is more commonly seen in the studies submitted to the FDA at the current time, they do represent adequate and well-conducted studies whose results would be difficult to refute. In summary, as a total package the body of published literature that is submitted here, including RCTs and open-label studies, meets the standards outlined above and, therefore, supports the efficacy and safety of this drug for the proposed indication.

It is also important to note that, as a result of the DESI review of ColBenemid in 1971-1972, colchicine was previously found to be effective for prophylaxis of gout flares and was approved at that time as part of the combination product including probenecid and colchicine. Section 2 contains additional details about this DESI review.

It should be further noted, however, that the studies supporting the use of colchicine for prevention of gout flares were (with only a few exceptions) conducted in a setting where urate-lowering therapy was initiated simultaneously. Therefore, it is this reviewer's recommendation that the approved indication be stated more narrowly than is currently proposed by the applicant. Specifically, it is this reviewer's recommendation that colchicine should be approved for "prevention of gout flares during initiation of (and/or concomitant administration with) urate-lowering therapy."

1.2 Risk Benefit Assessment

The efficacy of colchicine to prevent gout flares at the time that urate-lowering therapy is initiated is well supported by the published literature. The adverse events associated with colchicine use are also well documented in the published literature. Adverse events recorded in the FDA and WHO postmarketing databases are consistent with the

published literature. Gastrointestinal toxicity, including abdominal pain, diarrhea and vomiting, is the major adverse event associated with colchicine when taken in therapeutic doses and this can be reduced by lowering the dose of colchicine.

Concomitant use of colchicine with the antibiotic clarithromycin is hazardous and has been associated with fatalitity. When colchicine and clarithromycin are used concomitantly, the dose of colchicine should be reduced. Since the medical community does not appear to be universally aware of this drug-drug interaction, it needs to be well publicized via communication to health care providers and pharmacists. This issue is being addressed in NDA 22-351 and NDA 22-352.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There is an extensive history of the use of colchicine in this country for prevention of gout flares as well as for treatment of acute gout attacks. The safety profile is well documented and no new safety signals have been identified in recent years, despite continued extensive use. Therefore, this reviewer does not recommend any changes to the Med Guide and REMS agreed to in the actions on NDA 22-351 and NDA 22-352.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirement or commitment is recommended beyond those agreed to for NDA 22-351 for acute gout and NDA 22-352 for FMF.

2 Introduction and Regulatory Background

Since many issues addressed in this section overlap extensively with those addressed by Dr. Neuner in her review of NDA 22-351 for acute gout, we draw heavily from Dr. Neuner's review where appropriate.

Gout is a chronic disease characterized by flares and remissions if untreated. It is the result of hyperuricemia and tends to predominate in men. Major symptoms include gouty arthritis. Flares of arthritis manifest themselves with one or more painful, swollen joints. Podagra, an erythematous, swollen metatarsophalangeal joint, is the hallmark and often the first symptom of this chronic disease. Definitive treatment of gout involves lowering serum uric acid (sUA) to a target that is usually defined as less than 6 or 6.5 mg/dL. If gout is not treated by lowering sUA, flares will become more frequent and a patient is likely to develop tophi, which are deposits of uric acid crystals that can become disabling.

Ironically, initiation of urate-lowering therapy, which is the definitive treatment for gout, often precipitates gout flares. This is due to the fact that uric acid stores in the body are mobilized and this can produce an inflammatory response. Since it is well known that flares commonly result after initiation of urate-lowering therapy, concomitant prophylactic treatment is often prescribed. Colchicine and non-steroidal anti-inflammatory drugs (NSAIDS) are the two medications most often prescribed to prevent gout attacks after beginning a urate-lowering drug such as allopurinol or probenecid.

Colchicine has been used for this purpose for decades and is now marketed in this country as an unapproved product. The NDA that is reviewed here seeks FDA approval of colchicine for prevention of gout flares. Given the long history of use, there are numerous published studies and the Applicant seeks approval with a 505(b)(2) application based on existing literature as well as other supportive data.

The efficacy of colchicine to prevent gout flares was previously acknowledged in 1971 when the combination product Colbenemid (probenecid 500 mg and colchicine 0.5 mg) underwent DESI (Drug Efficacy Study Implementation) review. The listed indication for this drug was "maintenance treatment of gout and gouty arthritis" and "the treatment of all stages of gout and gouty arthritis except a presenting acute attack." The report from the National Academy of Sciences – National Research Council, Drug Efficacy Study Group, states: "Probenecid is an effective uricosuric drug and colchicine is effective as a prophylactic agent." Therefore, reviewers acknowledged here that each component of the combination product Colbenemid was effective for a distinct purpose. The role of colchicine is further established in the label that was constructed at that time for Colbenemid which states: "The mode of action in gout is unknown. It is not an analgesic, yet produces dramatic relief of pain in acute attacks of gout. It is not a uricosuric agent and will not prevent progression of gout to chronic gouty arthritis. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks and to relieve the residual pain and mild discomfort that patients with gout occasionally feel. This is of particular importance in patients on prolonged therapy with Benemid..."

The agency's judgement that colchicine is efficacious for preventing gout flares is further evidenced by a recommendation to use concurrent colchicine to prevent gout flares in the approved labels for allopurinol, probenecid and febuxostat.

2.1 Product Information

As summarized in Dr. Neuner's review:

> Colchicine, a tricyclic alkaloid, was originally extracted from the autumn crocus (*Colchicum autumnale*). It was originally reported in the first century CE as an effective treatment for gout attacks. Colchicine interacts with beta-tubulin and

> acts to disrupt microtubules. It is commercially available in this country as 0.5 and 0.6 mg tablets produced by a number of different manufacturers. Mutual Pharmaceuticals wishes to obtain marketing approval for a 0.6 mg tablet of colchicine that will be marketed under the trade name Colcrys™ . . . .
>
> Colchicine's effectiveness as a treatment for gout has been postulated due to its ability to block neutophil-mediated inflammatory responses induced by monosodium urate crystals in synovial fluid by disrupting the function of the neutophils' cytoskeleton and interfering with microtubulin assembly. This results in the prevention of activation, degranulation, and migration of neutrophils to sites of inflammation. New evidence suggests that colchicine may interfere with the intracellular assembly of the inflammasome complex found in neutrophils and monocytes that mediate IL-1β activation.

Colchicine is proposed for the prevention of gout flares. The proposed dose is 0.6 mg once or twice daily. A dose adjustment is recommended for patients with impaired renal function based on the estimated creatinine clearance. It is not to be used when the Clcr < 30 mL/min. It is also contraindicated in patients with leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, or aplastic anemia.

As of July 29, 2009, Colcrys is an approved product so there are no issues about the product.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are a large number of nonsteroidal anti-inflammatory drugs (NSAIDS) that are currently available to prevent gout flares during urate lowering therapy. Prominent among these is indomethacin though numerous others such as naproxen or ibuprofen are also used. Oral and/or intramuscular injection of corticosteroids may also be used for this indication.

2.3 Availability of Proposed Active Ingredient in the United States

As summarized in Dr. Neuner's review:

> Colchicine has been available for use as a single active ingredient since prior to 1938 in the U.S. It has not been approved by the Agency as a single ingredient drug despite its extensive use primarily as both a treatment and prophylactic therapy for gout attacks. Currently, colchicine is marketed by several generic manufacturers as 0.5 mg and 0.6 mg tablets for oral administration as well as in combination with 500 mg of Probenecid for use in the treatment and prevention of gout flares.

As of July 29, 2009, Colcrys is an approved product.

2.4 Important Safety Issues With Consideration to Related Drugs

As summarized by Dr. Hull:

> Colchicine is the only member of its pharmacologic class and has been used clinically as a single entity in the US for over 70 years; consequently, its safety profile has been well-documented over this period of time. Colchicine is generally well-tolerated at normal therapeutic doses with the most common side effects related to gastrointestinal symptoms, e.g., diarrhea, nausea and vomiting. However, colchicine has a narrow therapeutic index and toxic levels can result in serious life-threatening adverse events and death. Oral administration of colchicine generally limits the majority of patients from achieving toxic serum levels since the gastrointestinal adverse effects become rather severe and consequently dose-limiting.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

As summarized in Dr. Neuner's review:

> In the United States, colchicine has been available for the treatment of gout since prior to 1938. It is classified as a pre-DESI drug since there has never been a new drug application (NDA) approved for its use as a single entity in this country although it was approved for marketing as part of the combination drug product ColBenemid (colchicine 0.5 mg and Probenecid 500 mg) under NDA 12,383 for the treatment of gout in 1961. (Note: This combination product has been withdrawn from the market, however, the Applicant also owns this NDA.) Despite the numerous clinical trials which evaluated colchicine's safety and extensive clinical experience . . . it was subject to being removed from the market as an enforcement issue under the Compliance Policy Guide Section 440.100 Marketed New Drugs without Approved NDAs or ANDAs. Currently approved marketed combination drug products that contain colchicine with Probenecid include Col-Probenecid (NDA 84,279) manufactured by Watson Labs (the reference listed drug) and generic formulations of the latter manufactured by IVAX Pharmaceuticals (ANDA 40,618) and (ANDA 83,734) Concord Labs.
>
> A Pre-IND meeting between the Agency and the Applicant was held on July 31, 2006 to discuss requirements for approval of cochicine for prevention and treatment of acute gout attacks as well as for FMF. An IND was submitted and allowed to go into effect on March 14, 2007. A pre-NDA meeting was requested, a briefing package with questions was submitted and the review Division

responded in writing Since the Division's responses were clear to the Applicant, the pre-NDA meeting was canceled. However, the Division indicated that an NDA could be submitted for the prevention of gout on the basis of publicly available information as well as information regarding bioavailability relative to the approved Reference Listed Drug for the combination colchicine product, Col-Probenemid®.

On Novebmber 25, 2008, Mutual Pharmaceutical Company submitted this NDA for colchicine tablets USP, 0.6 mg (Colcrys™) under Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act.

2.6 Other Relevant Background Information

Colbenemid is a combination product that is composed of 0.5 mg of colchicine plus 500 mg of probenecid. As described above, it was approved in 1961 by the FDA. Colchicine as an individual product is marketed in 50 countries worldwide, according to the Applicant. It is also marketed in the U.S. as an unapproved product.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was appropriately organized and enabled the extraction of necessary information. Though there are inherent limitations associated with a literature-based 505(b)(2) submission the overall quality of this application is acceptable. The Applicant uses all available resources including postmarketing data from WHO and FDA to establish the safety and efficacy of colchicine for prevention of gout flares.

3.2 Compliance with Good Clinical Practices

A single trial was conducted to assess efficacy for treatment of acute gout. Though that trial was conducted primarily to support NDA 22-351, it is also provided as support for safety for this NDA (22-353). As summarized in Dr. Neuner's review:

> According to a statement included in the report for MCP-004-06-001, the Applicant certified that this trial was conducted in compliance with the following: good clinical practice standards as outlined in the Declaration of Helsinki or the International

> Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, with the institutional review board regulations as per 21 CFR (56), and the informed consent regulation as per 21 CFR (50).
>
> The Division of Scientific Investigation (DSI) inspected 3 clinical sites that participated in this pivotal Phase 3 trial and did not find any regulatory violations as a result of their efforts.

Good clinical practices were followed for the Applicant-initiated PK studies.

3.3 Financial Disclosures

As summarized by Dr. Neuner:

> The financial disclosure form signed by the Applicant certified that no financial arrangements had been made with any of the principal investigators or subinvestigators involved with the clinical studies where outcomes affected compensation as defined in 21 CFR 54.2(a). Additionally, none of the principal investigators or subinvestigators reportedly had a propriety interest as described in 21 CFR 54.2(b) in colchicine or a significant equity in Mutual Pharmaceuticals, who is commercially developing this drug for marketing in the United States.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

All issues related to other review disciplines are identical to those summarized by Drs. Neuner and Hull. Specifically, no new pharmacokinetic data were submitted for this NDA. Pharmacokinetic data submitted for the indication of familial mediterranean fever (FMF), NDA 22-352, are supportive of this NDA (22-353) as well.

5 Sources of Clinical Data

As discussed above (Section 2.5) the Division agreed, in principle, to allow the Applicant to submit the current NDA under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. Consequently the majority of data is derived from comprehensive searches of the worldwide literature using the following databases: Medline (1951 to present), Biosis Previews (1969 to present), Embase (1974 to present), and JICST-Eplus (1985 to present).

Additional safety data from a new Applicant-initiated trial: MPC- 004-06-001 is also included.

Additional data is derived from US and foreign labels, the prior DESI review of ColBenemid, and postmarketing safety databases from the FDA and WHO.

5.1 Tables of Studies/Clinical Trials

For a tabulation of clinical trials and pharmacokinetic studies, see Table 1 in Dr. Neuner's review, section 5.1. Specific studies relevant to this application will be discussed in the next section.

5.2 Review Strategy

The clinical efficacy data, submitted by the Applicant, for colchicine for prevention of gout flares is based solely upon the published literature. Multiple well-designed literature searches were conducted by Applicant and these identified two randomized controlled studies that were designed to evaluate the effect of oral colchicine on the prevention of gout flares during urate-lowering therapy. These two studies comprise the primary efficacy data for this application:

Borstad GC, Bryant LR, Abel MP, *et al.* Colchicine for prevention of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol 2004;31:2429-2432.

and

Paulus HE, Schlosstein LH, Godfrey RG, *et al.* Prophylactic colchicine therapy of intercritical gout. A placebo-controlled study of probenecid-treated patients. Arthritis Rheumatol 1974;17:609-614.

In addition to these two trials, which comprise the primary efficacy data, supportive efficacy data are also presented. Supportive data are derived from a number of sources including: (1) five open label studies supporting the use of colchicine for prevention of gout flare (see section 5.3.3), and, (2) "approved products recommending colchicine to prevent gout flares during urate lowering therapy." The category of approved products recommending colchicine for prevention of gout flares includes Benemid® and allopurinol as well as colchicine products approved in foreign countries. Additionally, the Uloric (febuxostat) package insert also recommends use of colchicine to prevent gout flares during initiation of treatment.

The safety data to support this application include: the results of the new Applicant-initiated trial (MPC-004-06-001) conducted to evaluate the role of colchicine in acute gout, the assessment of safety in the two randomized-controlled trials listed above, and,

the results of an extensive review of the literature for oral colchicine. In addition, the Applicant presents data from the postmarketing safety databases maintained by the FDA and WHO. Labeling for foreign colchicine products as well as safety data for the pharmacokinetic studies are also included as supportive data for safety. In this review, we emphasize the safety profile that is derived from the published literature including the randomized controlled trials. The results of the new study are only tangentially relevant for this indication, since, for the indication of acute gout, colchicine was administered over a 24 hour period only, whereas, for the indication of prevention of gout, it may be administered for ————————. b(4)

In this review, I will describe the two randomized-controlled trials that comprise the primary efficacy data, the 5 open label studies that are supportive of efficacy, and the new trial (MPC-004-06-001) in Section 5.3. I will also summarize there the two studies that were included in the DESI review of Colbenemid. Additional supportive data to establish efficacy and safety will be discussed in sections 6.1.10 and 7.7, respectively.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1. Borstad: Colchicine for prevention of gout flares when initiating allopurinol.

Overview and design:

The published study by Borstad is a randomized, placebo-controlled trial to evaluate the efficacy of colchicine to prevent gout flares during initiation of urate-lowering therapy with allopurinol. Colchicine and placebo tablets were not identical and the study was, technically, not double-blind. 51 subjects were randomized and 43 received study medication: 21 received colchicine (0.6 mg BID) and 23 placebo. Subjects were recruited from Wilford Hall USAF Medical Center. Inclusion criteria required crystal-proven gouty arthritis as well as criteria for allopurinol administration: tophi, uric acid overproduction, $\geq$ 3 attacks of gout per year, elevated serum urate with chronic renal insufficiency (CRI) and nephrolithiasis. Subjects were excluded if: < 19 years of age, had used colchicine within three months or had a history of allergic reaction to allopurinol or colchicine, had creatinine clearance < 20 ml/min, were female with childbearing potential, or had active hepatitis. Allopurinol was initiated for all subjects at 100 mg each day and was increased until the measured serum uric acid (sUA) was < 6.5 mg/dl. After attaining a sUA < 6.5 mg/dl, subjects continued to receive allopurinol plus either placebo or colchicine for three months. Acute flares were treated with NSAIDs. The study population included all subjects who received a study drug; subjects were evaluated at 3 and 6 months. The primary endpoint was defined as the

number of flares and this was recorded retrospectively by subjects, without investigator verification.

Demographics:

Baseline demographics for the Borstad study are displayed in Table 1 below. No clinically significant differences are noted that would nullify the results of the study.

Table 1: Baseline demographics and clinical characteristics of subjects in Borstad study. (n = 43 colchicine = 21, placebo = 22). Entries in % unless indicated.

Demographic	Colchicine	Placebo
Mean age	64 years	63 years
Male	81	91
Caucasian	67	73
Renal Insufficiency	14	9
Hypertension	90	77
Hypothyroidism	0.05	0.05
Coronary artery disease	29	27
Tophi	62	64
Alcohol use	33	18
Drugs affecting sUA	38	55
Diuretic use	57	27
Flares, prior year (mean #)	2.5	2.1

Subject Disposition:

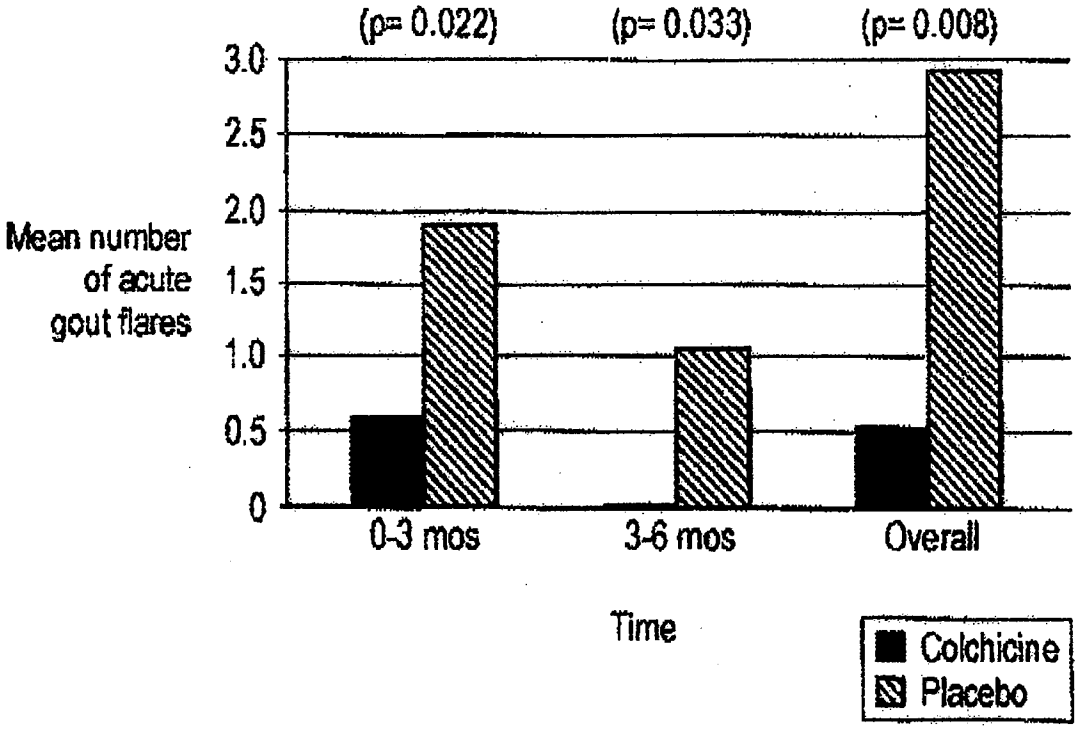
In the study by Borstad, 51 patients were enrolled but eight did not participate beyond the initial enrollment visit and did not, therefore, receive study drug. Of the 43 patients who comprise the ITT population, there were 7 withdrawals: 3 (14%)in the colchicine group and 4 (18%) in the placebo group. The three subjects in the colchicine group who discontinued did so for the following reasons: one had a stroke at 3 months, one had subjective muscle weakness at 2.5 months and one was lost to followup after 3 months. According to the author, the subject who experienced the stroke had significant comorbidities, and the stroke was not considered to be related to the study medication. The subject with muscle weakness had no objective or laboratory evidence of muscle weakness or damage and the symptoms resolved after discontinuation of the study drug. In the placebo group, 2 of the 4 withdrawals were due to the high frequency of flares, one was due to inadvertent discontinuation of medication and the last was due to a travel schedule that interfered with adequate followup. Therefore, overall, there was a

completion rate of 84%. Furthermore, there was no indication of either excess toxicity or irregularities in study management as an explanation for subjects not completing the study.

Efficacy Endpoints:

In Borstad's study the primary objective was to see if "colchicine administration during administration of allopurinol therapy ...reduces acute gout flares." A secondary endpoint was defined as the time to achieve a benefit. To assess these endpoints, the study evaluated: the number of flares at 0-3 months, 3-6 months, and overall. The results are displayed below (Figure 1). These clearly demonstrate the relationship between study drug and the number of gout flares and further demonstrate the strength of the relationship in all time periods analyzed. .

Figure 1: Mean number of gout flares at 0-3 and 3-6 months and overall, n = 21 for colchicine, n = 22 for placebo



Additionally, of the 77 acute gout flares, 12 were experienced by subjects receiving colchicine compared with 65 among subjects receiving placebo. Thus acute flares

occurred in 33% of colchicine subjects and 77% of placebo subjects. Analysis of subjects experiencing multiple flares revealed that 14% of those in the colchicine group experienced multiple flares compared to 63% in the placebo group.

In terms of the "time to benefit" Borstad concludes that patients who continued to take colchicine for as long as 6 months derived a greater benefit compared with those who took colchicine for only 3 months. He, therefore, recommends that patients, in general, be treated for 6 months.

Safety Evaluation:

Borstad reports that colchicine was well tolerated. One subject experienced muscle weakness (subjective) that resolved after the medication was discontinued. A number of subjects developed diarrhea that resolved after the dose was reduced to once (rather than twice) each day. The table below summarizes these results. A detailed description of withdrawals was discussed above in the section on disposition.

Table 2: Treatment effects, side effects/withdrawals (colchicine: n= 21; placebo: n = 22)

Treatment/Side Effects	Colchicine	Placebo	p
Allopurinol dose (mean QD dose, mg)	265	245	0.453
Study drug QD instead of BID, %	62	36	0.094
Withdrawals, %	14.3	18.2	0.729
Any side effect, %	43	36	0.760
Diarrhea as side effect, %	38	4.5	0.009

5.3.2 Paulus: Colchicine for the prevention of gout glares when initiating probenecid.

The study by Paulus was published in 1974. It was a randomized, placebo-controlled double-blind, parallel group study involving 51 males with gout. It was conducted in two

locations, Los Angeles (LA) and Kansas City and was carried out for six months. Inclusion criteria required a sUA > 7.5 mg/ dL and a history of typical attacks of gouty arthritis that had responded to colchicine previously. Of the 51 subjects, 18 had crystal-proven gout and 13 had tophaceous gout. Subjects were excluded with renal disease associated with a creatinine > 1.2 mg/dL.

The study designs in LA and Kansas City were slightly different: in LA urate lowering agents were withdrawn two weeks before treatment began; in Kansas City, subjects received probenecid for two weeks before treatment. Treatment involved either 500 mg of probenecid three times each day or a combination tablet of 500 mg of probenecid plus 0.5 mg of colchicine three times each day. Tablets in both arms were identical in appearance; similar to Borstad's study, attacks were recorded by patients and discussed with investigators at monthly visits. Investigators then rated attacks as mild, moderate or severe depending upon patients' description; for observed attacks (19 of the 58) the same grading scale was used as well. The primary endpoint was the number of attacks of gout per month of therapy for each patient. The only subjects included in the anlysis were those who achieved a lowering of sUA. By excluding patients who did not achieve urate lowering, the investigators were able to optimize the probability that subjects were compliant with the protocol.

Demographics:

Baseline demographics for the Paulus study are displayed in Table 3 below

Table 3: Baseline demographics and characteristics of subjects in Paulus study

	Colchicine/probenecid	**Placebo/probenecid**
Number enrolled	29	23
Age (years): mean (range)	53 (34-77)	52 (43-73)
Number with Tophi	3	4
Duration gout (years), mean ± SE	10.5 ± 2.3	10.5 ± 1.8
Gout attacks, prior 12 months, mean ± SE	4.2 ± 1.1	3.2 ± 0.4
Number treated with urate lowering drug for 12 months prior to study	12	12
Months of therapy	108	94
Serum urate before study (mg/dL)	8.4	9.2

There are no clinically significant differences between arms that would change the interpretation of the results of the study.

Subject Disposition:

In the study by Paulus, there were 28 patients studied in LA (12 randomized to placebo and 16 to colchicine) and 24[1] in Kansas City (11 receiving placebo and13 receiving colchicine). Among patients at the LA site, only 11 of the 12 subjects receiving placebo were analyzed, and, of these, only 8 completed the entire 6 months while three others failed to return after 1,2 and 4 months, respectively. Of the 16 patients receiving colchicine medication, 15 were analyzed but only 12 completed the entire 6 months: one did not return after 3 months and 2 did not return after 4 months. One patient from each group was not analyzed because there had not been the required decrease in sUA. At the Kansas City site, only 12 subjects were included in the analysis. Seven of the 13 on colchicine and 4 of the 11 on placebo were not analyzed because they **"probably did not take the drug regularly or as prescribed"** [2] and failed to show a decrease in sUA as required in the study. In addition, one patient on colchine was not included in the analysis because of alopecia. Thus, a total of 38 subjects were analyzed (out of 52 enrolled): 18 received placebo and 20 who received colchicine. These data are summarized in Table 4.

Table 4: Disposition of Subjects in Paulus Study

LA site

	Placebo	Colchicine	Total
Number enrolled	12	16	28
Not analyzed	1	1	2
Number analyzed	11	15	26

Kansas City site

Number enrolled	11	13	24
Not analyzed, alopecia		1	1
Not analyzed, high Urate	4	7	11
Number analyzed	7	5	12

Total, both sites	18	20	38

[1] There is a discrepancy with regard to the number of subjects at the Kansas City site: in one instance the publication states that there were 23 subjects at this site, in another instance it describes 24 subjects. I have chosen to use the latter number because it is generally consistent with other analyses in the publication.
2 Paulus, p. 611.

Efficacy Endpoints:

In the Paulus study, the primary endpoint was the number of gout attacks per month of therapy for each patient. The final group of subjects analyzed included 20 patients who received colchicine-probenecid and 18 who received placebo-probenecid. In brief, there were 35 attacks during 94 months of therapy among patients in the placebo-probenecid group and there were 23 attacks during 109 months in the colchicine-probenecid group. This is equivalent to 0.19 attacks per patient per month for patients on study drug compared to 0.48 attacks per patient per month for patients on placebo. These results, demonstrating that treatment with colchicine reduces by more than 50% the number of gout attacks, are summarized in Table 5.

Table 5: Effects of Therapy, Paulus

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)

Safety Evaluation:

Table 5 also provides information about the number of patients who experienced side effects while receiving colchicine or placebo. Some patients experienced more than one side effect. A total of 15 patients in the colchicine and 8 patients in the placebo group experienced gastrointestinal side effects but these were mild to moderate in severity, according to the author, and did not cause dehydration, hypokalemia or weight loss. The specific side effects in the colchicine group included 9 subjects with diarrhea, 22 with nausea, vomiting or anorexia and one with increasing transaminases that returned to prestudy levels after completion of the study. Of an additional 9 subjects who were not included in the analysis, 3 varied their dose to control diarrhea and 1 was discontinued after 2 months because of alopecia that continued for six months.

5.3.3 Open-Label Studies

There are five published open-label studies that the Applicant considers supportive of the application for the use of colchicine for prevention of gout flares. These will be summarized in this section of the review and include:

Yü TF. The efficacy of colchicine prophylaxis in articular gout—a reappraisal after 20 years. Seminar Arthritis Rheum 1982;12:256-264.

Becker MA, Schumacher HR, Wortmann RL, *et al.* Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase. A twenty-eight day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. Arthritis Rheum 2005;52:916-923.

Becker MA, Schumacher HR, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005;353:2450-2461.

Karimzadeh H, Nazari J, Mottaghi P, *et al.* Different duration of colchicine for preventing recurrence of gouty arthritis. J Res Med Sci 2006;11:104-107.

Schumacher HR, Becker MA, Wortmann RL, *et al.* Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008;59:1540-1548.

The study by Yu considers the experience of 540 patients who took colchicine for up to 20 years. The study population included 53% of subjects with a sUA > 10 mg/dL, 69% with tophi present and 30% with a history of renal calculi. Approximately 75% had other medical problems; 48% had hypertension, CAD or cerebrovascular disease, and, 24% had other medical conditions. Some, but not all, patients received concomitant hypouricemic therapy. Analysis of results, displayed in Table 6, shows an association between colchicine prophylaxis and reduction in the recurrence of acute gout attacks. This study is limited by the fact that it was not randomized and was retrospective. Nevertheless the results are compelling and supportive of efficacy of colchicine for prevention of gout flares.

Table 6: Recurrent Acute Attacks Before and After Colchicine Prophylaxis

Attacks/Year During Colchicine Prophylaxis	Attacks/Year Before Colchicine Prophylaxis									
	1-2		3-4		5-9		10-12		Total	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Hardly Any Attacks	89	(88)	143	(76)	57	(54)	74	(50)	363	(67)
Gradually Decreased to 0-1	6	(6)	20	(11)	25	(24)	32	(22)	83	(15)
1-2	1	(1)	19	(10)	16	(15)	29	(20)	65	(12)
Milder, Not Less	5	(5)	5	(3)	6	(6)	9	(6)	25	(5)
Unchanged	0	(0)	0	(0)	1	(1)	3	(2)	4	(1)
Total No. (%)	101	(19)	187	(35)	105	(19)	147	(27)	540	

The study by Becker et al. (Arthritis and Rheumatism, 2005) summarizes a Phase 2 trial designed to evaluate febuxostat (a hypouricemic drug recently approved by the FDA). One hundred and fifty-three patients were randomized to placebo or one of three doses of febuxostat. The primary efficacy endpoint was a sUA < 6 mg/dL at day 28. Prophylactic colchicine was prescribed for all subjects for two weeks after randomization. For the placebo, 40 mg/day, 80 mg/day and 120 mg/day arms, the incidence of gout flares was: 11%, 8%, 8% and 13%, respectively, when subjects were taking concomitant colchicine. When subjects were on study drug alone, i.e. after colchicine was discontinued, the incidence of flares increased to: 34%, 30%, 40% and 42%, respectively. This study is limited by both size and design. Nevertheless, the incidence of gout flares was clearly lower during the time that colchicine was administered along with the study drug. Thus, it would appear supportive of efficacy for colchicine for prevention of gout flares during administration of urate lowering therapy.

The second study by Becker et al. (NEJM) describes a Phase 3 randomized, double-blind, 52 week trial also with febuxostat compared with allopurinol (the active comparator). Due to what the authors claimed was the known association of increases in gout flares with initiation of urate-lowering therapy, prophylaxis with either naproxen or colchicine (0.6 mg/day) was administered to all patients during the washout period as well as the first eight weeks of treatment. Though the primary endpoint of the study was a sUA < 6 mg/dL, the authors analyzed the number of gout flares and concluded that there was an increased incidence of flares after withdrawal of prophylaxis. (These data are displayed in Table 7 below.) This study appears supportive of efficacy of colchicine for prevention of gout flares during urate lowering therapy.

Table 7: Gout Flares with Colchicine and Febuxostat

End Point	Febuxostat, 80 mg/day	Febuxostat, 120 mg/day	Allopurinol, 300 mg/day
Incidence of gout flares			
Day 1–wk 8 (prophylaxis)			
No./total no. (%)	55/255 (22)	90/250 (36)	52/251 (21)
P value	<0.001‖	<0.001¶	
Wk 9–52			
No./total no. (%)	147/228 (64)	150/215 (70)	150/234 (64)
Wk 49–52			
No./total no. (%)	13/167 (8)	9/153 (6)	20/185 (11)

The next study, by Karimzadeh, evaluated the optimal duration of prophylactic colchicine during urate lowering therapy. The study was performed in Iran and included 190 subjects randomized to one of three groups. All received allopurinol and colchicine (1 mg/day) but the groups differed in terms of the length of time colchicine was administered: 3-6 months, 7-9 months and 10-12 months. Colchicine was then discontinued and patients were followed for one year for evidence of recurrence of gouty arthritis. At the end of six months, the probability of recurrence, by order of length of time the drug was received, was 46%, 11% and 6 %. At the end of one year, in the same order, the probability of recurrence was **54%, 28% and 23%. This study is identified in support of Applicant's conclusion that** increasing duration of treatment reduces the probability of recurrence of gout flares. By demonstrating that gout flares decrease with duration of colchicine use, this study suggests that colchicine, if used for a lengthy period of time after initiation of urate lowering therapy, may be efficacious for prophylaxis of gout flares during urate lowering therapy. The reason that a longer duration of treatment (with colchicine) may be beneficial is due to the fact that continued treatment with the concomitant urate-lowering agent, such as febuxostat, is likely to lead to more complete depletion of total body urate stores. Thus, when colchicine is discontinued after longer treatment with a urate-lowering agent, there is a decreased likelihood of a flare. This is likely, however, to reflect the efficacy of urate-lowering therapy and not the efficacy of a longer duration of use of colchicine.

The final study, selected by the Applicant as providing evidence to support the application, is by Schumacher et. al. (Arthritis and Rheumatism, 2008). Similar to the studies above, authored by Becker et. al., it was conducted as part of the development program for febuxostat. The trial itself was a Phase 3, randomized, double-blind, allopurinol and placebo-controlled trial conducted at 167 U.S. sites and carried out for 28 weeks. Colchicine (0.6 mg each day) or naproxen were administered as prophylaxis during the washout period as well as for the first 8 weeks of the study. The issue of treatment for gout flares is minimally addressed in this article. It appears that during the 8 weeks of treatment with colchicine, more subjects on the higher doses of febuxostat required treatment for gout flares compared with subjects on lower doses, allopurinol or placebo. In contrast, after the 8 week period of treatment with colchicine, the need to treat gout flares was the same in the

different arms of the study. It was also noted that the need for treatment of acute gout attacks appeared to diminish as treatment with the hypouricemic febuxostat continued. This reviewer would not deem this study to be supportive of the efficacy of colchicine for prevention of gout flares during urate lowering therapy.

5.3.4 MPC-004-06-001

To further support the safety of the use of colchicine for prevention of gout, the Applicant supplies data from a new trial: MCP-004-06-01 - 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. The primary objective of this trial is to assess the efficacy of colchicine in an acute gout attack based on pain reduction after 24 hours. Secondary objectives include evaluation of two dose regimens as well as an evaluation of the safety of colchicine.

The study design is thoroughly described in Dr. Neuner's review of NDA 22-351. In brief, this was a 1-week multicenter, randomized, double-blind, placebo-controlled, parallel group dose comparison Phase 3 trial. Enrollment of 390 patients was planned. Subjects were randomized to one of three arms: standard-dose colchicine (4.8 mg total over a 24 hour period), low-dose colchicine (1.8 mg over a 24 hour period) or placebo.

Efficacy was derived from diary entries recorded by subjects as well as by joint examination and phone calls received at the study call center. Safety was similarly monitored via AE information that patients recorded in their diaries, as well as changes noted on physical examination. As described by Dr. Neuner:

> The study had a number of safety variables as follows:
> - Analysis of adverse events (SAEs) – the treatment emergent period was defined as the active treatment period up to Visit 5 (7 $\pm$ 2 days post-flare onset) or longer in the event of unresolved AEs
> - Clinical lab tests
> - Vital signs and body weight – as measured at each study visit (Visits 1-4 or 5).
> - Physical exam – performed at Visit 1 and the final visit (Visit 4 or 5).

Discussion of efficacy variables can be found in Dr. Neuner's review. In brief, the primary endpoint was defined as a $\geq$ 50% improvement in target joint pain score at 24 hours post-initiation of treatment. The primary endpoint for the standard and low dose regimens was achieved by 33% and 38% of subjects, respectively; in the placebo group only 16% of subjects achieved the primary endpoint. Though this trial does demonstrate the efficacy of colchicine for acute gout flares, it is only tangentially related

to the indication proposed here. Furthermore, it is not submitted as evidence of efficacy for the proposed indication.

In terms of the conduct of the study, Dr. Neuner and the statistical reviewer (David Petullo) have assessed the study to be adequate for purposes of evaluation of safety and efficacy. However, Dr. Neuner does raise a concern about the adequacy of blinding. She writes as follows:

> Patients were to have been dosed until they developed either a complete response or symptoms of colchicine toxicity (i.e., nausea, vomiting, or diarrhea). All patients in the colchicine group reportedly developed diarrhea and/or vomiting at a median time of 24 hours (range: 12-36 hours) or after ingesting a mean dose of 6.7 mg of colchicine. A total of five placebo treated patients reportedly developed nausea during the trial. These results raise questions regarding maintenance of the blind given that the blinded clinical evaluators may have been aware of patients' clinical manifestations of toxicity since they were acting as rheumatology consultants to an inpatient population cared for by hospital staff.

In terms of safety, Dr. Neuner writes:

> The overall safety profile of colchicine generated from the adequate and well controlled Phase 3 trial MPC-004-06-001, which compared a standard high dose regimen (4.8 mg over 6 hours) versus a low dose regimen of the drug (1.8 mg over 1 hour), was consistent with what has been reported in the medical literature for the past 70 years, mainly gastrointestinal toxicity manifested by diarrhea, nausea, and vomiting. Approximately twice as many subjects randomized to the standard dose colchicine treatment group (77%) experienced treatment-emergent adverse events (TEAEs) as compared to subjects in the low-dose colchicine group (37%) or placebo group (27%) that were predominantly gastrointestinal in nature. The majority of these AEs were mild to moderate in nature, however, almost all of the severe AEs occurred in patients treated with the standard dose regimen of colchicine. Both of these findings are consistent with a definitive dose-response relationship for gastrotoxicity and decreasing tolerability with increasing dose of colchicine. There were no serious adverse events or deaths reported in the safety database associated with colchicine therapy that may be related to the limited exposure to the drug (i.e., one treatment of an acute gout flare) during this trial.

It should be noted that the colchicine dose proposed in this NDA (for prevention of gout flares) is closer to that used in the low dose regimen in study MPC 004-06-001 for treatment of acute gout. However, the duration is extended over as many as ——— compared with the dose in the treatment of acute gout which is less than one day. b(4)

5.3.5 DESI REVIEW

The DESI review of the combination product, colbenemid, included descriptions of two publications:

Gutman AB. Treatment of primary gout: the present status. Arthritis Rheum 1965; 8:911-920.

Yü TF, Gutman AB. Efficacy of colchicine prophylaxis in gout. Prevention of recurrent gouty arthritis over a mean period of five years in 208 gouty subjects. Ann Intern Med 1961;55:179-192.

The 1965 paper by Gutman summarizes his experience treating patients with gout. He writes:

> The ideal double-blind, long-term, large-scale study of the efficacy of prophylaxis has yet to be reported. Nevertheless, there is now a considerable experience with colchicine prophylaxis by a number of observers, and when the frequency and severity of acute attacks with colchicine prophylaxis are compared to the course anticipated without such treatment,in the gouty population at risk and in the individual patient, there can be little question as to the value of the preventive program.

To support these statements he presents data drawn from 734 of his patients who he deems reliable in giving their history before starting colchicine prophylaxis. From this group, Gutman further summarizes the experience of 260 with severe (marked incapacitation by four or more disabling attacks a year) or moderately severe (repeated interruption of work by one or two fulminating and protracted seizures [sic] and/or multiple minor attacks a year). These data are presented in Table 8 below.

Table 8: Effect of Colchicine Prophylaxis, with or without Conjoint Uricosuric Therapy, on the Course of Recurrent Acute Arthritis in 260 Gouty Subjects Followed at Least 2 years (Mean: 6.4 Years)

	Before		After	
	No.	%	No.	%
Severe	101	39	6	2
Moderately severe	159	61	32	12
Mild			82	32
Virtually no attacks			138	53

Gutman further describes the good patient acceptance of colchicine prophylaxis in 0.5-2.0 mg daily and the very low incidence of side effects.

> The second study included in the DESI review was published in 1961 by Yu and Gutman. This study is based upon 208 patients who had an established pattern of recurrent gouty arthritis. A total of 76 of these were identified as severe cases and unable to work steadily because of 4 or more attacks each year. The remaining 132 patients had moderately severe disease with several attacks a year and interruption of work resulting from this. Colchicine prophylaxis was maintained for at least two years with a mean of 5.4 years. The initial dose of colchicine was usually 1 or 1.2 mg daily and was maintained at this level in 66% of subjects. In other subjects it was possible to reduce the dose to 0.5 mg daily and in 4 subjects the dose was reduced to 0.5 mg on alternate days. Of the 208 patients, 89 were given uricosuric medication as well. Results are displayed in
>
> Table 9 below. These data generally support the efficacy of colchicine in preventing recurrent gout flares. The data in

Table 9 further show that responses are similar regardless of whether or not a uricosuric agent is being administered. This underscores the fact that the reduction in recurrent attacks is due to colchicine and not to the uricosuric agent.

With regard to safety, Yu reports that "in the lower dosages employed prophylactically, albeit every day for years, there is no indication of a cumulative toxic effect .... Other than the initial hypersensitivity, usually of the bowel, already mentioned in 4% of our patients, we have seen no untoward reactions to colchicine prophylaxis: there has been no evidence of toxicity of the bone marrow, nerves, skin, liver, or kidney."

Table 9: Colchicine Prophylaxis and Recurrent Gouty Arthritis

	A. Colchicine Alone			B. Colchicine and Uricosuric Agents		
Response	Severe Cases	Moderately Severe Cases	All Cases	Severe Cases	Moderately Severe Cases	All Cases
Excellent	29(66%)	60(80%)	89(75%)	23(72%)	41(72%)	64(72%)
Satisfactory	10(23%)	12(16%)	22(18%)	7(22%)	13(23%)	20(22%)
Unsatisfactory	5(11%)	3(4%)	8(7%)	2(6%)	3(5%)	5(6%)

Taken together these studies provide support for the efficacy and safety of colchicine when used to prevent recurrent gouty arthritis attacks.

6 Review of Efficacy

Efficacy Summary

Data supporting the efficacy of colchicine for prevention of gout flares is derived from the published literature and includes two RCTs published in preeminent rheumatology journals plus five open label supportive studies.

The first study, by Borstad, was published in 2004. The primary endpoint was the number of flares and the study population was defined as all who received a study drug. Subjects were evaluated at 3 and 6 months. Results are shown graphically in Figure 1: there is a significant difference in the mean number of gout flares at 0-3 months, 3-6 months and overall. A total of 33% of subjects receiving colchicine experienced gout flares compared with 77% of those receiving placebo.

The second study, by Paulus, was published in 1974. In this study, the serum urate-lowering effect of probenecid was used to determine whether or not subjects were compliant with study medication. It should also be noted that those who did not manifest serum urate-lowering would constitute a group that is less likely to have flares. The primary endpoint was the number of attacks of gouty arthritis per patient per month. A significant difference was identified with 0.19 attacks per month in subjects receiving colchecine and probenecid compared to 0.48 attacks per month in subjects receiving placebo plus probenecid.

In addition, five open-label studies are submitted by the Applicant as supportive evidence of efficacy. Of these, four appear to be of adequate design and scope so that they do provide supportive evidence of the efficacy of colchicine for prevention of gout flares. The first paper, by Yu, includes 540 patients and is a followup to the paper authored by Yu and Gutman that was reviewed in the DESI process in 1971. Compaing the quantity of attacks before and after starting colchicine prophylaxis, Yu demonstrates a rather dramatic difference For example, of 147 subjects who reported 10-12 attacks per year before starting colchicine, 50% reported "hardly any attacks" afterwards, 32% reported that attacks gradually decreased to 0-1 per year, and so on. (SeeTable 6.)

There are two additional papers by Becker that summarize data from recent Phase 2 and Phase 3 trials used to gain approval of febuxostat (a new urate lowering agent) for gout. In both papers, data are presented comparing the incidence of flares while subjects were receiving febuxostat plus colchicine (first 8 weeks) with the incidence after colchicine was discontinued. In both papers the incidence of flares increses dramatically after colchicine is discontinued: 22% vs 64% for subjects taking 80 mg/day of febuxostat. (SeeTable 7.)

The final paper which is supportive is the one by Karimzadeh demonstrating that flares are reduced to a greater extent when colchicine prophylaxis is continued for a longer period of time.

The fifth paper, not included here as supportive, was also part of the development program for febuxostat. It only minimally addressed the issue of the efficacy of colchicine to prevent flares.

In summary, the totality of evidence generated by these papers is consistent and supports the conclusion that colchicine prevents gout flares when concomitant urate lowering therapy is administered.

6.1 Indication

The Applicant proposes that colchicine be approved for prevention of gout flares.

6.1.1 Methods

This is a 505 (b)(2) application. Accordingly, primary efficacy data for this application are derived from the two published randomized, controlled trials described in section 5.3. Supportive efficacy data are derived from five additional published open-label studies also described in section 5.3.

In addition, the Applicant cites the DESI review of Colbenemid® which followed the approval of this combination product in 1961 (NDA 12-383). The data in that review were derived from ten investigators and included a total of 43 patients. ColBenemid efficacy was evaluated on a scale of "excellent", "good", "fair", "insufficient", and "none" for 37 of the 43 patients. The results were "excellent" for 21 patients, "good" for 8 patients, "fair" for 3 patients, "insufficient" for 2 patients and one patient with "no results."

The DESI review also based its conclusion on two additional published studies:

Gutman AB. Treatment of primary gout: the present status. Arthritis Rheum 1965;8:911-920.

Yü TF, Gutman AB. Efficacy of colchicine prophylaxis in gout. Prevention of recurrent gouty arthritis over a mean period of five years in 208 gouty subjects. Ann Intern Med 1961;55:179-192.

Further supportive evidence for efficacy for colchicine is identified in the labels for currently approved products. Benemid® is a uricosuric agent approved in 1951 "for treatment of the hyperuricemia associated with gout and gouty arthritis." In the Warnings section of the approved label, it is stated that "exacerbation of gout following therapy with probenecid may occur; in such cases colchicine or other appropriate therapy is advisable."

Similarly, the Precautions section of the allopurinol label includes advice to use colchicine prophylactically when allopurinol is begun. Additionally, the label for Uloric (febuxostat), which was recently approved for treatment of hyperuricemia in gout, also recommends concomitant treatment with colchicine during the first six months after initiation of therapy.

Finally, the Applicant has reviewed labels from foreign countries and presents data from six labels where Colchicine has received an indication for prevention of gout flares.

6.1.2 Demographics

As described in detail in section 5.3, the demographic composition of subjects in the two published trials used to establish efficacy is acceptable. In each study, the subjects appear to be representative of patients who have gouty arthritis and who could be expected to use colchicine. There are no meaningful differences between placebo and drug arms.

Likewise, for the new trial, MCP-004-06-001, Dr. Neuner reports that baseline characteristics and gout history were similar for all three treatment groups.

6.1.3 Subject Disposition

The disposition of subjects in the two publications used to support this application (Borstad and Paulus) is discussed in detail above. It does not appear that there were disproportionate dropouts or discontinuations among colchicine-treated subjects compared to placebo-treated subjects.

The disposition of patients in MPC-004-06-001 is well summarized in Dr. Neuner's review. She points out there that, overall, 92% of subjects who flared completed the trial and this varied from 87% in the "standard-dose group" to 96% in the low-dose group.

Protocol violations are not specifically addressed in the Borstad and Paulus studies. However, since the Paulus study only analyzes subjects who achieve a reduction in sUA, this excludes, for practical purposes, subjects who may have violated the protocol by virtue of incorrect use of the study drug. In MPC-004-06-01, Dr. Neuner refers to protocol violations as minor and describes that none of the violations resulted in withdrawal of a subject from the trial.

6.1.4 Analysis of Primary Endpoint(s)

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 reducing the number of gout flares in subjects with gout who

are initiating urate lowering therapy. See Figure 1 (Borstad) and Table 5 (Paulus) reproduced below.

Figure 2: Mean number of gout flares at 0-3 and 3-6 months and overall, n = 21 for colchicine, n = 22 for placebo

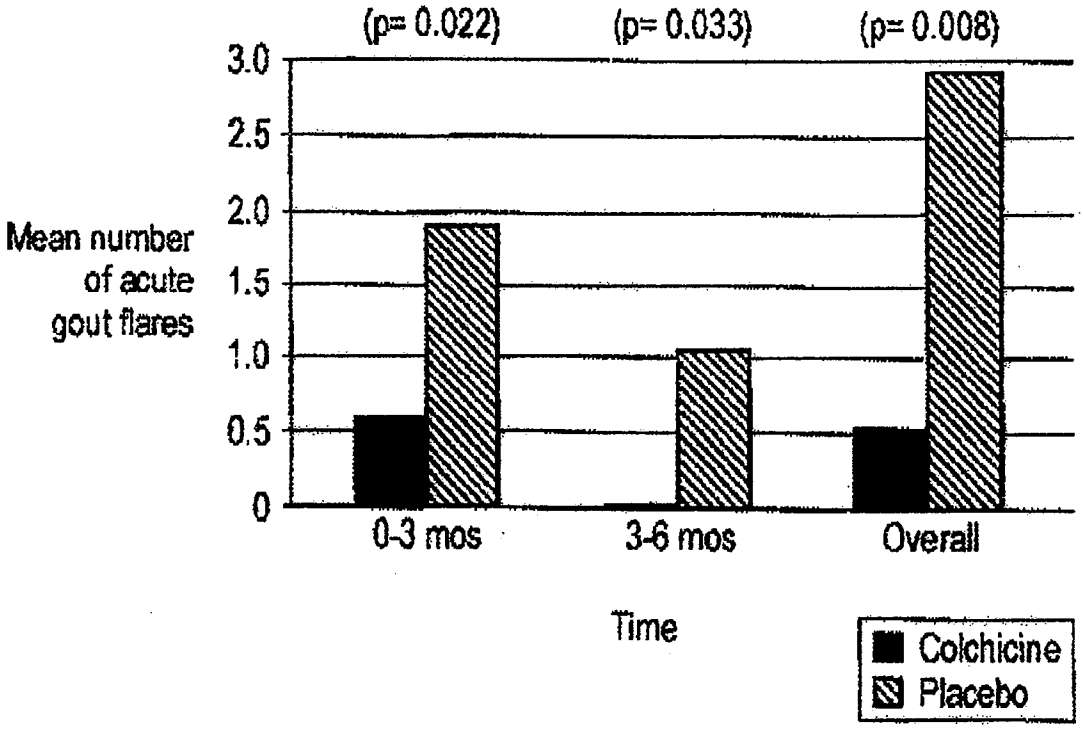


Table 10: Effects of Therapy, Paulus

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)

As summarized in section 5.3, the primary endpoint for Borstad's study is the number of gout flares at 0-3 months, 3-6 months, and overall. Analysis of this endpoint supports the efficacy of colchicine to prevent gout flares when used with concomitant urate-lowering therapy which in this case was allopurinol. (See Figure 1.) In the Paulus study, the primary endpoint is the number of gout attacks per month of therapy for each patient. Again, analysis of this endpoint provides good support for the efficacy of colchicine to prevent gout attacks when used with concomitant urate-lowering therapy which in this case was probenecid. (See Table 3.)

6.1.5 Analysis of Secondary Endpoints

By dividing his analysis of the number of flares into two time periods (0-3 months and 3-6 months), Borstad attempts to analyze, as a secondary endpoint, the "time to benefit," or optimal duration of treatment. The data (see Figure 1) show that the mean number of flares decreases to close to zero during the 3- 6 month period. Though this is inconclusive, it does suggest that treatment with colchicine for up to six months may be appropriate.

There are no secondary endpoints in the Paulus publication.

6.1.6 Other Endpoints

Borstad reports results for three other endpoints: severity of flares, length of flares and frequency of multiple flares. Paulus does not discuss additional endpoints.

Severity of flares is measured with a visual analog scale (VAS) in Borstad's study. He reports that severity as measured by VAS averaged 3.64 in the colchicine group compared to 5.08 in the placebo group.

Borstad also reports the average length of flares (6 days for colchicine versus 5.56 for placebo) and concludes there is no significant difference between treatment arms.

Finally, Borstad considers and reports on the number of subjects who experienced multiple gout flares: 14% in the cholchicine group and 63% in the placebo group.

The results therefore suggest that colchicine may be helpful in reducing the severity of a flare (as measured by VAS but not by length of time) and also in reducing the likelihood of a patient experiencing multiple flares.

6.1.7 Subpopulations

Borstad's study excludes severe renal insufficiency which is defined as a creatinine clearance < 20 ml/min. Paulus also excludes subjects with renal disease: his cutoff is

a serum creatinine greater than 1.2 mg/100 ml. Therefore results are only applicable to subjects without renal insufficiency.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Neither Borstad nor Paulus conducted dose ranging studies. Therefore efficacy as related to dose cannot be firmly established. Despite this fact, dosing information can be extrapolated. In Borstad's study subjects were given colchicine, 0.6 mg BID, or placebo; they remained on this medication for 3 months after attaining a sUA < 6.5 mg/dL. Though side effects are only identified in 43% of patients receiving colchicine, and, though only 38% of colchicine-treated patients reported diarrhea, a total of 62% reduced their dose to once rather than twice daily. (See Table 2.) This suggests that a dose of colchicine starting at 0.6 mg twice daily is acceptable with reduction to once daily as a modification that helps reduce side effects.

In Paulus' study, patients received (as part of a combination product with a urate lowering drug) Colchicine 0.5 mg TID. Though Paulus does not report the number of subjects who may have reduced the dose, there were a large number of subjects who were not analyzed due to the fact that sUA was not adequately reduced. This raises the question of whether subjects discontinued the combination product due to side effects from colchicine and, therefore, did not experience the benefit of the urate lowering component of the pill. Paulus does report that 3 of the 9 subjects who were assigned to the colchicine-probenecid group and who were not analyzed (because sUA was not adequately reduced) did vary their dosage to control diarrhea. One could speculate that the larger dropout rate in Paulus (31%) compared with Borstad (14%) is due to the larger dose in that protocol: 1.5 mg vs. 1.2 mg daily.

Therefore, a recommended dose of 0.6 mg BID with reduction as needed for gastrointestinal side effects appears to be supported by these studies.

Additional dosing information concerns the length of time during which patients will continue colchicine. In both the Paulus and the Borstad studies, initiation of urate lowering therapy (with either allopurinol or probenecid) occurred concomitantly with intiation of colchicine. The reason is that urate-lowering therapy alone is known to precipitate gout attacks. Therefore, colchicine was initiated to prevent these attacks. Since with continuation of urate lowering therapy, total urate stores may be eventually depleted, there may be a time period after which a prophylactic medication such as colchicine is not needed. Though different treatment periods were not selected at the outset, information concerning this issue can be extrapolated from Borstad's study. In Figure 1 we have displayed data suggesting that therapy for 3-6 months may be superior to therapy for 0-3 months.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

These issues are not addressed in the literature that supports this application. However, in Dr. Hull's review of colchicine for treatment of Familial Mediterranean Fever (FMF), he concludes that the clinical benefit of colchicine is durable and that tolerance does not develop to the drug. Though his conclusion is based upon an analysis of the population with FMF there does not appear to be an inherent reason why the persistence of efficacy or the tolerance to the medication would be different in patients with gout.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 U.S. Labels

Additional evidence to support the efficacy of colchicine for prevention of gout flares during initiation of urate-lowering therapy is derived from the fact that it is recommended in currently-approved labels for specific urate-lowering drugs: allopurinol, probenecid and febuxostat.

The label for allopurinol (section on precautions), states:

> An increase in acute attacks of gout has been reported during the early stages of administration of allopurinol, even when normal or subnormal serum uric acid levels have been attained. Accordingly, maintenance doses of colchicine generally should be given prophylactically when allopurinol is begun. . . . . The use of colchicine or anti-inflammatory agents may be required to suppress gouty attacks in some cases. The attacks usually become shorter and less severe after several months of therapy. The mobilization of urates from tissue deposits which cause fluctuations in the serum uric acid levels may be a possible explanation for these episodes. Even with adequate therapy with allopurinol it may require several months to deplete the uric acid pool sufficiently to achieve control of the acute attacks.

Under Dosage and Administration the label additionally states:

> While adjusting the dosage of allopurinol in patients who are being treated with colchicine and/or anti-inflammatory agents, it is wise to continue the latter therapy until serum uric acid has been normalized and there has been freedom from acute gouty attacks for several months.

The label for the uricosuric agent probenecid similarly states:

> Exacerbation of gout following therapy with probenecid may occur; in such cases colchicine or other appropriate therapy is advisable.

It further advises:

> However, if an acute attack is precipitated *during* therapy, probenecid may be continued without changing the dosage, and full therapeutic dosage of colchicine, or other appropriate therapy, should be given to control the acute attack.

Uloric (febuxostat) was approved in February 2009 as a new urate-lowering drug for treatment of hyperuricemia in gout. The recently drafted label also includes the recommendation to use colchicine as a prophylactic medication for gout flare. In the section on Warnings and Precautions, it states:

> Gout Flare: An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents, including ULORIC. If a gout flare occurs during treatment, ULORIC need not be discontinued. Prophylactic therapy (i.e., non-steroidal anti-inflammatory drug (NSAID) or colchicine upon initiation of treatment) may be beneficial for up to six months.

In the section on Dosage and Administration it further states:

> Flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended upon initiation of ULORIC. Prophylactic therapy may be beneficial for up to six months.

In summary, there are three urate-lowering drugs that are currently approved in the U.S. Approved labels for each of these drugs include recommendations for the use of colchicine to prevent gout flares when initiating urate-lowering therapy.

6.1.10.2 Foreign Labels

The Applicant states that colchicine is currently marketed in numerous other countries worldwide. Included with the application is a table showing the labeling for colchicine in a number of other countries. This table is reproduced below as Table 11:

Table 11: Colchicine Labeling from Foreign Sources

Country	Product / Manufacturer	Indications	Dosage
Argentina	Xuric / Craveri S.A.I.C.	Chronic gout, for prevention of an acute attack, especially during treatment with hypouricemics	1 × 1-mg tablet (daily) at bedtime
Australia	Colgout / Aspen Pharmacare	Prevention of acute attacks	Not given (insert only describes dose for gout flare)
Britain	Generic / Westward	Prevention of acute gout attacks	Mild to moderate cases: 1 × 0.6 mg tablet 1 to 4 times per week Severe cases: 1 to 2 times a day
	Wockhardt, Ashton Pharma, Boots Company Ltd.	Prevention of gout flare-ups when treatment is started with other drugs such as allopurinol, probenecid, and sulfinpyrazone	2 or 3 × 0.5-mg tablets daily
France	Colchimax / Laboratoires de l'Opocalcium	Prevention of acute gout attack in chronic gout sufferers, especially when irritating hypouricemic therapy	1 × 1-mg tablet (daily) in evening
Mexico	Quimica Y Farmacia	Chronic gout	1 × 1-mg tablet 5 days each week
Uganda	Goutnil / Inga Laboratrories (Mumbai, India)	Prevention of acute gout; long-term maintenance of chronic gout	Up to 1.5 mg a day

Therefore, colchicine to prevent gout attacks is recommended, not only in U.S. labels for urate-lowering drugs, but, also, in foreign labels for marketed colchicine.

7 Review of Safety

Safety Summary

This application includes a number of sources of data to support the safety of colchicine. Data sources include the published literature which includes two randomized-controlled trials, data from the Applicant-initiated trial MPC-004-06-001, as well as data from large postmarketing databases managed by the FDA and the WHO.

These data are consistent with the well-known side-effect profile of colchicine and demonstrate that this drug is generally well tolerated when orally administered 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.

7.1 Methods

There is a long history of use of colchicine in this country and worldwide. The combination product Colbenemid was initially approved in 1961 and subsequently in 1972 with the DESI reviews. The safety profile is well-documented and well known. No new safety signals have been identified in the data supplied by the Applicant to support this or other NDAs that have been submitted to the FDA: NDA 22-351 for treatment of acute gout and NDA 22-352 for treatment of FMF. Important new information about drug-drug interactions has, though, been identified: for example, there is significant toxicity when used concomitantly with clarithromycin, a relatively new macrolide antibiotic.

The safety of colchicine as treatment for acute gout and FMF has been thoroughly reviewed by Drs. Neuner and Hull in their clinical reviews of NDA 22-351 and 22-352, respectively. The review of NDA 22-351 for treatment of acute gout focuses upon the results of MPC 004-06-001, a new study conducted by the Applicant. The review of NDA-22-351, for FMF, includes an assessment of the literature as well as postmarketing experience.

Since much of the information that is presented vis-à-vis safety in this application overlaps extensively with the information already reviewed by Drs. Neuner and Hull, I will not duplicate their analyses here. The population of patients receiving colchicine for acute and chronic gout overlaps extensively, though, the treatment for acute gout is of a much shorter duration than is the case for chronic gout. The population of patients receiving colchicine for FMF may be different from that of patients receiving colchicine for chronic gout, but the chronicity of these illnesses makes the safety data for FMF relevant to chronic gout.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 12 summarizes the sources of safety data which support this NDA.

Table 12: Safety Data

Source	Population	N	Data Source / Study Design
Mutual-Sponsored Studies			
Adequate and Well Controlled Study MPC-004-06-001	Adults with Gout	185 (126 colchicine)	Multicenter, randomized, double-blind, placebo-controlled, parallel group, 1-week, dose comparison study in gout flare
Mutual-Sponsored Pharmacokinetic Studies	Healthy Adults	167	Single- and multiple-dose pharmacokinetic and drug-drug interaction studies (131 subjects single dose/1-day regimen and 43 subjects 10- to 14-day steady state regimen)
Medical Literature			
Randomized, placebo-controlled study	Adults with Gout	43 (22 colchicine)	Ahern *et al.*, 1987
Other case reports	--	--	Additional reports of adverse effects
Postmarketing Safety Data			
U.S. Food and Drug Administration	Primarily U.S. but includes foreign reports	--	751 adverse event reports from 1969 through 30 June 2007
World Health Organization	79 countries including the U.S.	--	1380 adverse event reports from 1968 – March 2006
Labeling			
Col-Probenecid (Watson—US; ANDA 84-279)	--	--	FDA-approved probenecid and colchicine combination product (500 mg-0.5 mg), providing for a maximum daily colchicine dose of 2 mg
Other Countries	--	--	Labeling from oral colchicine obtained from Argentina, Australia, Britain, Germany, Mexico, France, Singapore, and Uganda

In addition to what is listed in the table above, the data from the medical literature includes data from the two RCTs submitted to support efficacy: Borstad and Paulus.

7.1.1.1: MPC-004-06-001

Dr. Neuner summarizes the safety profile revealed in this study as follows:

> The overall safety profile of colchicine generated from the adequate and well controlled Phase 3 trial MPC-004-04-001, which compared a standard high dose regimen (4.8 mg over 6 hours) versus a low dose regimen of the drug (1.8 mg over 1 hour), was consistent with what has been reported in the medical literature for the past 70 years, mainly gastrointestinal toxicity manifested by diarrhea, nausea, and vomiting. Approximately twice as many subjects randomized to the standard dose colchicine treatment group (77%) experienced treatment-emergent adverse events (TEAEs) as compared to subjects in the low-dose colchicine group (37%) or placebo group (27%) that were predominantly gastrointestinal in nature. The majority of these AEs were mild to moderate in nature, however, almost all of the severe AEs occurred in patients treated with the standard dose regimen of colchicine. Both of these findings are consistent

> with a definitive dose-response relationship for gastrotoxicity and decreasing tolerability with increasing dose of colchicine. There were no serious adverse events or deaths reported in the safety database associated with colchicine therapy that may be related to the limited exposure to the drug (i.e., one treatment of an acute gout flare) during this trial. The short duration of exposure to colchicine in this trial is a limitation, since no information was gathered to assess the time interval necessary for safe retreatment with colchicine of patients who have repeat gout flares. . . . Additionally, there was no evidence of colchicine having an adverse effect on clinical lab test parameters or vital signs, but this again may be a result of the short duration of exposure to the drug which is known to have toxic effects on the hematopoietic, hepatic, and renal systems as well as on muscles. (. . . Although a QTc prolongation study was not required for this application, the Applicant did submit the results of a failed study in which adequate prolongation in the control arm was not achieved.)
>
> Another limitation of the safety data reviewed in support of colchicine as a treatment for acute gout, were the small numbers of patients involved in the demographic subanalyses for gender, age, and race as well as concomitant allopurinol use and creatinine clearance which made it impossible to draw any valid conclusions from these analyses regarding the possibility of increasing risk for gastrotoxicity associated with these factors .

Extrapolation of safety information from study MPC-004-06-001 is limited by the significant difference in duration of treatment in this study from that which is anticipated in the use of colchicine for chronic gout. Nevertheless, the study does provide additional data that characterize the side effect profile of colchicine and it does not identify any new safety signals.

Additional details of the safety results for MPC-004-06-001 can be found in Dr. Neuner's review.

7.1.1.2: Pharmacokinetic Studies

There were 167 healthy subjects exposed to at least one dose of oral colchicine (0.6 mg). Table 13 displays AEs reported by more than two subjects in all of the pharmacokinetic (PK) studies that were conducted. The Applicant additionally summarizes other adverse events as follows:

> Other adverse events reported in only 1 subject each were...: abdominal pain upper, cardiac flutter, cold sweat, decreased appletite, dry mouth, dyspepsia, Epistaxis, flatulence, hot flush, muscle spasm, nasal congestion, palpitations, pharyngeal pain, rash, rhinorrhea, sinus congestion, sinus headache, skin laceration, vessel puncture site hematoma and vessel puncture site pain.

Table 13: Number (%) of Healthy Volunteers with AEs Following Exposure to Colchicine; Reported in > 2 Subjects

MedDRA System Organ Class / Preferred Term	Single Dose[1]		Low Dose[3]	High Dose[4]	Multiple Dose[5]	All Exposure
	Fasted[2]	Fed				
	N=111	N=27	N=13	N=15	N=37	N=167
General Disorders and Administration Site Conditions						
Cold sweats	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5.4%)	2 (1.2%)
Pallor	4 (3.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (2.4%)
Gastrointestinal Disorders						
Diarrhoea	3 (2.7%)	0 (0%)	2 (15.4%)	15 (100%)	6 (16.2%)	26 (15.6%)
Hypoacusis	2 (1.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.2%)
Nausea	3 (2.7%)	0 (0%)	1 (7.7%)	7 (46.6%)	3 (8.1%)	14 (8.3%)
Stomach discomfort	2 (1.8%)	1 (3.7%)	0 (0%)	0 (0%)	4 (10.8%)	7 (4.2%)
Vomiting	1 (< 1%)	1 (3.7%)	0 (0%)	9 (60.0%)	0 (0%)	11 (6.6%)
Musculoskeletal and Connective Tissue Disorders						
Pain in extremity	5 (4.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (3.0%)
Nervous System Disorders						
Dizziness	5 (4.5%)	1 (3.7%)	0 (0%)	1 (6.7%)	1 (2.7%)	8 (4.8%)
Headache	13 (11.7%)	1 (3.7%)	2 (15.4%)	1 (6.7%)	0 (0%)	17 (10.2%)
Syncope	4 (3.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (2.4%)
Respiratory, thoracic and mediastinal disorders						
Nasopharyngitis	2 (1.8%)	0 (0%)	0 (0%)	1 (6.7%)	0 (0%)	3 (1.8%)
Eye disorders						
Vision blurred	3 (2.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.8%)

[1] Single dose = 0.6 mg
[2] Subjects pooled from five studies (MPC-004-07-1001 [N=28]; MPC-004-07-1004 [N=13]; MPC-004-07-1006 [N=24]; MPC-004-08-1011 [N=24]; MPC-004-08-1013 [N=24])
[3] MPC 004-07-1003, low dose = 2 × 0.6 mg (1.2 mg) followed by 0.6 mg after 1 hour (total: 1.8 mg / 2 hours)
[4] MPC 004-07-1002, high dose = 2 × 0.6 mg (1.2 mg) followed by 0.6 mg q1h for 6 hours (total: 4.8 mg / 6 hours)
[5] Multiple dose = 0.6 mg b.i.d. × 10 days in MPC-004-07-1006 and × 14 days in MPC 004-07-1005

Applicant's Table 26, Integrated Summary of Safety

The multiple dose group is most comparable (in terms of dose and duration) to patients who can be expected to use colchicine for prevention of gout flares. In this group, gastrointestinal disorders predominate. In general the adverse events in the PK studies are consistent with the known GI toxicity of colchicine.

7.1.1.3 Medical Literature: Dr. Hull's review of NDA 22-352

Between 2006 and 2007, the Applicant conducted three database searches to identify publications related to the safety of colchicine. These searches involved four databases: Biosis Previews (1969 to present), Embase (1974 to present), JICST-Eplus (1985 to present) and MEDLINE (1951 to present). An additional search was conducted in 2008 to identify any publications pertaining to the safety of colchicine within a group of specific organ systems. The Applicant reports that as of May 2008, their database

holds more than 1200 articles. This database was offered to support NDA 22-352 for FMF as well as this one.

In his review of NDA 22-352 for FMF, Dr. Hull undertakes a system-by-system analysis of the literature reviewed by the Applicant. He reports as follows:

Cardiovascular system: No AEs with therapeutic doses were identified.

Gastrointestinal system: Gastrointestinal side effects are the most common side effect seen in patients receiving colchicine. These include abdominal pain, cramping, diarrhea and vomiting. Symptoms are usually transient and reverible with discontinuation.

Hepatotoxicity: No serious hepatotoxic AEs were identified with therapeutic doses of colchicine. Transaminase elevations were reported in FMF patients treated with colchicine.

Hematologic and Lymphatic Systems: "**Myelosuppression is a known dose-related AE** associated with colchicine and life- threatening granulocuytopenia and/or thrombocytopenia generally occur 24 to 48 hours after an acute overdose.Several published reports of leucopenia and granulocytopenia were identified from the literature search as well as one report each of thrombocytopenia, pancytopenia, and aplastic **anemia with colchicine use in typical doses....**"

Leukopenia: three cases were identified. One case appeared to be related to a CMV infection as when the patient recovered from this she was able to receive colchicine without leukopenia. In the remaining two cases, colchicine may have been administered in doses that were likely inappropriate given their medical status.

Agranulocytosis: This developed in an 86 year old female with end-stage renal disease; her colchicine level was two-times the upper limit of normal. Her neutrophil count reached a nadir of < 500 cells / mm^3 but returned to normal after colchicine was discontinued.

Thrombocytopenia and Leukopenia (simultaneiously) in a 69 year-old male. Even after discontinuation of colchicine a bone marrow biopsy revealed a hypocellular marrow. The patient remained stable.

Pancytopenia: This developed in a 46 year old female with hepatic and renal insufficiency. A Bone marrow aspirate revealed drug-induced marrow suppression. Colchicine was discontinued; the patient received G-CSF and after 7 months made a full recovery.

Metabolic and Nutritional Disorders: NoAEs with therapeutic doses of colchicine were identified.

Musculoskeletal System: Dr. Hull describes neuromuscular toxicity (i.e. myopathy) and writes as follows:

> Colchicine-induced neuromuscular toxicity is a rare adverse event associated with short- and long-term use. Patients have generally received standard oral doses of colchicine but frequently have renal impairment or are elderly and may have received excessive doses. The typical presentation is that of proximal muscle weakness and pain that may also include mild sensory polyneuropathies. The effects are typically reversible within weeks to months following the discontinuation of colchicine.

Two reviews were identified in the published literature that described cases of colchicine-related myopathies. Renal impairment seemed to be common among patients identified in these reviews. The database search "also identified two novel manifestations of colchicine-induced neuromuscular toxicity which included a case of severe bilateral optic neuromyopathy and one case of involvement of respiratory muscles. Both patients recovered following discontinuation of colchicine."

In addition, several cases of colchicine-associated rhabdomyolysis were identified. In one publication 8 of 475 cases of rhabdomyolysis were attributed to colchicine, but additional information is not available.

Nervous System: According to Dr. Hull, a mild sensory polyneuropathy may accompany myopathy. He describes that the "neuropathy typically improves following discontinuation of colchicine."

Respiratory System: No respiratory AEs with therapeutic doses of colchicine were identified.

Urologic System: Two cases of Peyronie's disease, in patients receiving cholchicine for FMF, were reported in the literature. The clinical significance of these is not known.

Though serious colchicine adverse events have been reported in the literature, these are rare when colchicine is taken at a therapeutic dose. However, as pointed out by Dr. Hull, colchicine overdosing has resulted in additional instances of adverse events. This will be discussed in: 7.6.4.

7.1.1.4 Placebo-Controlled Studies in the Medical Literature: Ahern, Borstad, Paulus

Table 14 summarizes the data from the three RCTs and demonstrates that gastrointestinal AEs predominate.

Table 14: Adverse Events in the Published Double-Bind, Placebo-Controlled Studies in Patients with Gout

	Colchicine	Placebo
Treatment of Acute Gout		
Ahern *et al.*, 1987	1 mg followed by 0.5 every 2 hours until response or toxicity	
N	22	21
Nausea, Vomiting, Diarrhea	22 (100%)	5 (23.8%) [1]
Prevention of Acute Gout		
Borstad *et al.*, 2004	0.6 mg once or twice daily × 3 months	
N	21	22
Any AE	9 (43%)	8 (36%)
Diarrhea	8 (36%)	1 (4.5%) [2]
Paulus *et al.*, 1974	0.5 mg t.i.d. × 6 months [3]	
N	20	18
Any AE	15 (75.0%)	8 (44.4%) [2]
Gastrointestinal AEs	15 (75.0%)	8 (44.4%)
Diarrhea	9 (45.0%) [4]	6 (33.3%)
Nausea, vomiting, or anorexia	11 (55.0%)	5 (27.8%)
Steadily increasing SGOT / SGPT	1 (5.0%)	0

[1] Nausea only
[2] $P < 0.05$
[3] Patients randomized to colchicine or placebo as add-on treatment to probenecid
[4] Episodic and mild-moderate in intensity; did not cause weight loss, dehydration or hypokalemia nor did any subject discontinue as a result. Of the 9 additional patients who were not included in the efficacy analysis, diarrhea resulted in variation of the dose in 3; 1 patient discontinued after 2 months due to alopecia.

Applicant's Table 27, Integrated Summary of Safety.

7.1.1.5 Postmarketing Databases

The safety data derived from postmarketing databases that are submitted to support NDA 22-353 are identical to those submitted in support of NDA 22-353 for FMF and reviewed by Dr. Hull.

In brief, the Applicant obtained a complete summary of the marketing experience with colchicine using the FDA's reporting systems: the ADRA database (1969-1997) and the AERS Database (1977-2008). Approximately 751 Med Watch reports were obtained in which colchicine was either the primary or secondary suspected drug. Additional reports of AEs were obtained from WHO and this database included 1380 reports from 79 countries between 1968 and 2006.

Table 15 and Table 16 summarize these reports. As noted by Dr. Hull,

Data from the ADR database demonstrate that diarrhea, myopathy, and pancytopenia were the most commonly reported AEs priot to 1997...the AERS database showed that diarrhea, drug interactions, vomiting, acute renal failure and nausea have been the most common events since 1997.

The WHO database reports a similar pattern: gastrointestinal events predominate but renal failure and cytopenia are also observed.

Table 15: Adverse Events from FDA Databases

FDA ADR Database (1969-1997)	# Reports (n=241)	FDA AERS Database (1997-2007)	# Reports (n=510)
Diarrhea	29	Diarrhea	69
Myopathy	21	Drug interaction	69
Pancytopenia	19	Vomiting	65
Overdose	18	Renal failure acute	59
CK elevation	17	Nausea	54
Hypotension	17	Gout	50
Neuropathy	17	Diarrhea NOS	49
Intentional overdose	15	Blood creatinine increased	44
LFT abnormality	12	Abdominal pain	43
Acute kidney failure	11	Pyrexia	41
Asthenia	11	Rhabdomyolysis	40
Leukopenia	10	Completed suicide	35
Sepsis	10	CK elevation	34
Thrombocytopenia	10	Myopathy	32
Agranulocytosis	9	Pancytopenia	31
Shock	9	Vomiting NOS	31
Apnea	8	Dehydration	30
Dehydration	8	Asthenia	28
Kidney function abnormal	8	AST elevation	27
Marrow depression	8	Renal Failure NOS	27
Myasthenia	8		
Peripheral neuritis	8		

Table 16: Adverse Events Reported from the Who Database

WHO 1968 – March 2006 Adverse Event Term	No. Reports
Total	1380
Diarrhea	382
Vomiting	117
Nausea	80
Rash	78
Pruritus	62
Renal Failure Acute	56
Abdominal Pain	54
Thrombocytopenia	54
Death	48
Leukopenia	43
Creatine phosphokinase increased	41
Rash maculo-papular	41
Myopathy	39
Fever	38
Granulocytopenia	36
Rash erythematous	36
Renal function abnormal	34
Dehydration	32
Pancytopenia	31
Dyspnea	30
Rhabdomyolysis	30
SGOT increased	30
SGPT increased	30

7.1.2 Categorization of Adverse Events

For the studies conducted by the Applicant: MPC-004-06-001 and the pharmacokinetic studies, Adverse Events (AEs) are reported by MedDRA System Organ Class and preferred term. Standardized coding is not used for the variety of published studies nor for the postmarketing databases reviewed.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from different studies have not been pooled.

7.2 Adequacy of Safety Assessments

Safety assessments are based upon a number of discrete sources of data as outlined in Table 12. The adequacy of MPC-004-06-001 and the Mutual-Sponsored pharmacokinetic studies has been addressed in reviews by Drs. Neuner and Hull.

The review of published literature appears to have been thorough and comprehensive. It was based upon four different literature searches and used four well-known databases. The strategy for the database searches is outlined in the Integrated Summary of Safety and appears to have been adequately designed. The literature review itself identifies a variety of adverse events such as leukopenia and myopathy which are uncommon but generally well known.

The two randomized-controlled trials (Borstad and Paulus) assessed the use of colchicine for prevention of acute gout. Together the studies evaluated 81 subjects who received colchicine concomitantly with another uric acid-lowering therapy: either allopurinol (Borstad) or probenecid (Paulus). **In Borstad's study, subjects received colchicine 0.6 mg twice daily; in Paulus' study** they received colchicine 0.5 mg three times each day as part of the combination medication with probenecid. In both cases, the doses were at or above levels recommended in NDA 22-353. In the Borstad study, subjects continued colchicine for up to 6 months (at least 3 months beyond the point at which their sUA < 6.5 mg/dL and they were evaluated at 3 and 6 month intervals. **Paulus' study was ongoing for 6** months as well though not all subjects completed the full 6 months. Patients were evaluated at monthly visits. Taken together these studies evaluated colchicine: (1) in a population of individuals comparable to that which is expected to use colchine if this NDA is approved, and, (2) in doses similar to those anticipated, and, (3) for a duration of time that is also similar to what would be expected in this NDA.

Taken together, the sources of data submitted by the Applicant are adequate to assess safety in terms of range of doses, exposure and patient population.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in MCP-004-001 or in the pharmacokinetic studies conducted by the Applicant.

Dr. Hull summarizes the data regarding deaths in other sources as follows:

There were 234 deaths reported from the estimated 751 total reports obtained from the ADR and AERS databases for colchicine. A total of 169 of the 234 (72%) deaths were associated with oral colchicine with the remaining deaths due to either an unspecified (19%) or intravenous (9%) route administration. The disproportionate number of reported deaths with oral colchicine likely reflects the far greater use of oral colchicine compared to intravenous route of administration. Of the 169 reports of death associated with oral administration, 96 (57%) reported actual dosages of colchicine but overall 117 (69%) of the reports were not reported as overdoses and the majority reported colchicine doses were in the therapeutic range of ≤2 mg/day. No information was obtained regarding patients' renal or hepatic function which may increase colchicine toxicity. It is interesting to note that 60 of the 117 (51%) patients who died while receiving therapeutic doses of colchicine were receiving concomitant clarithomycin, which has been shown to dramatically increase serum concentrations of colchicine. This potentially life-threatening drug interaction is discussed in greater detail in Section 7.5.5.3.

Deaths reported in the published literature were generally associated with acute or chronic overdoses of colchicine or drug interactions with concomitant potent P-gp inhibitors. Overdoses are discussed further in Section 7.6.4. No deaths were reported in the Applicant-initiated PK studies

7.3.2 Nonfatal Serious Adverse Events

There were no treatment-emergent serious adverse events (SAEs) associated with the use of colchicine in study MCP-004-06-001 nor in the pharmacokinetic studies referenced in Table 12.

Serious and other adverse events identified in the pharmacokinetic studies are summarized in 7.1.1.2 . Serious and other adverse events identified in the published literature are summarized in 7.1.1.3. and 7.1.1.4. Serious and other adverse events identified in postmarketing databases are summarized in 7.1.1.5.

7.3.3 Dropouts and/or Discontinuations

For Borstad's study, this subject is covered in detail in section 5.3.1. The completion rate, overall, was 84%.

For Paulus' study, this subject is covered in detail in section 5.3.2. The overall completion rate here was 73% but this obscures the fact that 13 of the 14 patients who were not included in the final analysis were excluded because they did not manifest a decrease in uric acid. An additional subject discontinued because of alopecia (which resolved after discontinuation of colchicine).

In the Paulus study, patients in both the placebo and colchicine arms received probenicid. If a subject had been compliant, in either arm, uric acid should have decreased. By excluding subjects who did not manifest a decrease in uric acid, the author effectively excluded subjects who were not compliant. Furthermore, gout flares are most likely to occur when uric acid declines. Therefore, by excluding patients who did not manifest this decline, Paulus selected for those who were most likely to have flares and potentially benefit from colchicine.

Neither the Borstad nor the Paulus study reveal an unusual pattern of discontinuation or non-completion.

7.3.4 Significant Adverse Events

Section 7.3.2 identifies where significant adverse events are described.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The most common adverse event involves gastrointestinal toxicity and the well known fact that this is dose dependent is noted in a number of the publications supporting this NDA. Dose reduction was a common strategy to reduce GI toxicity.

Serious adverse events are not often seen when therapeutic doses are used but may be seen when colchicine is taken in excess of that which is normally prescribed.

7.5.2 Time Dependency for Adverse Events

Not applicable for this application.

7.5.3 Drug-Demographic Interactions

As described by Dr. Hull:

> Several literature publications noted that the elderly may be more sensitive to toxic effects of colchicine, which may reflect age-related impairments in renal and hepatic function.

In the adequate and well-controlled study MPC-004-06-001, the Applicant reports "no apparent difference in attributable risk of experiencing gastrointestinal events based on demographics" but also states that "given the small number of elderly, female and non-caucasian patients, this conclusion should be interpreted with caution."

7.5.4 Drug-Disease Interactions

As described by Dr. Hull:

> Significant adverse events are associated with the use of therapeutic doses of colchicine in patients with renal and hepatic impairment. Hepatic impairment may significantly decrease the clearance of colchicine and increase its plasma half-life compared to healthy subjects. Although colchicine has been used safely in patients with liver cirrhosis, no PK data have are available for patients with hepatic impairment. One meta-analysis (Rambaldi A and Gluud C. Cochrane Database of Systematic Reviews, 2005) evaluating colchicine in alcoholic and non-alcoholic liver fibrosis and cirrhosis that included 11 randomized trials with 443 colchicine-exposed patients. Patients were treated with colchicine 1 mg QD for 5 days/week to 7 days/week. Eight of 443 (2%) patients developed a serious AE compared to none in the control group. Similarly, 39 of 443 patients experienced a non-serious AE compared to 5 out of 420 (1%) patients in the control groups.
>
> Ben-Chetrit et al. (1994) reported significantly reduced clearance and prolonged plasma half-lives of colchicine administered to patients with renal impairment. The authors recommended a reduction of the colchicine dose in patients with FMF having an estimated creatinine clearance of <50 mL/min, and even a possible cessation of cochicine in patients with creatinine clearance <10 mL/min. . . . significant AEs are also associated with the use of therapeutic doses of colchicine in patients with renal impairment including neuromyotoxicity and hematological AEs.

7.5.5 Drug-Drug Interactions

As described by Dr. Hull:

> A major route of elimination for colchicine includes its elimination via P-gp mediated biliary excretion. Additionally, colchicine is demethylated into two major metabolites by the CYP3A4 pathway. Thus concomitant medications that inhibit P-gp or CYP3A4 decrease the metabolism and excretion of colchicine resulting in increased serum concentrations of colchicine. Thus, even therapeutic doses of colchicine can result in toxic serum levels when in the presence of concomitant drugs that inhibit P-gp or CYP3A4.

Table 17, from Dr. Hull's review lists established and potentially significant drug interactions with colchicine. Additional detail can also be found in his excellent summary, sections 7.5.5.1 – 7.5.5.7.

Table 17: Established and Potential Drug Interactions with Colchicine

Drug Class or Substance	Drugs within Class		Comment
	Reported	Potential	
Immunosuppressive Agents	Cyclosporine	Tacrolimus	Increased colchicine plasma levels and toxicity
Macrolide Antibiotics	Clarithromycin Erythromycin	Dirithromycin Telithromycin	Produces colchicine toxicity, including fatalities
HMG-CoA Reductase Inhibitors	Simvistatin Fluvastatin Pravastatin Atorvastatin	--	Produces acute myopathy or rhabdomyolysis including a reported fatality
Other Lipid Lowering Agents	Fenofibrate Benzafibrate Gemfibrozil	--	Produces acute myopathy or rhabdomyolysis
Calcium Channel Blockers	Diltiazem Verapamil	--	Produces colchicine toxicity
Digitalis Glycosides	Digoxin	--	Produces rhabdomyolysis
Protease Inhibitors	--	Atazanavir Amprenavir Darunavir Fosamprenavir Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir Tipranavir	Potential to produces colchicine toxicity
Azole Antifungal Agents	--	Ketoconazole Itraconazole Voriconazole	Potential to produces colchicine toxicity
Antiarrhythmic Agents	--	Quinidine	Potential to produces colchicine toxicity
Antidepressant Agents	--	Nefazodone	Potential to produces colchicine toxicity
Antiemetic Agents	--	Aprepitant	Potential to produces colchicine toxicity
Antihypertensive Agents	--	Reserpine	Potential to produces colchicine toxicity
Foods	Grapefruit Juice	Grapefruit	Produces colchicine toxicity

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No reports of malignancies have been identified in the data submitted by the Applicant either in this NDA or NDA 22-352.

7.6.2 Human Reproduction and Pregnancy Data

No new data are submitted regarding reproduction and pregnancy. The proposed label specifies that this will be pregnancy category C and acknowledges that there are no adequate and well-controlled studies with colchicine in pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

Colchicine is not intended to be used for this indication (prevention of gout) in the pediatric population. A pediatric waiver has been granted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Colchicine is a narrow therapeutic index drug and the exact dose that produces toxicity is unknown. Fatalities have occurred after ingestion of a dose as low as 7mg over four days yet other patients have survived after ingesting 60 mg. A review of 150 patients, described by the Applicant, found that there was 100% mortality for those who overdosed and ingested >0.8 mg/kg. For overdoses involving less than 0.5 mg/kg, all survived with GI symptoms. For those who took between 0.5 and 0.8 mg/kg, symptoms were severe, such as myelosupression.

According to one author (Ben-Chetrit and Levy, 1998), colchicine toxicity develops in three sequential and overlapping stages. The first stage begins within 24 hours and includes GI symptoms. Life-threatening complications may occur during the seond stage (24-72 hours after ingestion) and death is usually the result of respiratory depression and cardiovascular collapse. A third, recovery, stage ensues if the patient survives and this stage involves alopecia and leukocytosis.

Putterman et al (1991) published a review of colchicine intoxication. This includes: cardiovascular collapse and cardiogenic shock, respiratory distress due to a variety of causes including neuromuscular weakness, hematological manifestations, mental status changes, renal complications, rhabdomyolysis, metabolic acidosis, hypocalcemia, hypophosphatemia, and hypomagnesemia. Less commonly one sees liver damage, pancreatitits and/or fever. Alopecia is a common effect of toxicity usually appearing

during the late recovery phase. Skin findings, **including toxic epidermal necrosis –like** rash have been rarely reported.

According to the Applicant, treatment of an overdose is accomplished with aggressive bowel decontamination with gastric lavage and activated charcoal. Otherwise, treatment is supportive. Hemodialysis and hemoperfusion are not effective due to the large volume of distribution. [3]

8 Postmarket Experience

Postmarketing data are discussed in Section 7.

9 Appendices

9.1 Literature Review/References

Not applicable for this review.

9.2 Labeling Recommendations

The two published randomized-controlled studies, as well as 4 of the 5 open-label studies that are identified as providing supportive information, are conducted in a setting where urate-lowering therapy is concomitantly initiated. No evidence is provided to support the use of colchicine as a single agent for use long term in the prevention of gout flares. Therefore, in the final label, the indication should be modified to be: prevention of gout flare during initiation of/or concomitant administration with urate-lowering therapy.

[3] These statements seem to be based upon: Jayaprakash, Vikram et. al. Colchicine overdose; the devil is in the detail. Journal of the New Zealand Medical Association. January 26, 2007. Vol 120. No. 1248.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22353	ORIG 1		COLCHICINE TABLETS USP 0.6MG

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/s/

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08/05/2009

JEFFREY N SIEGEL
08/05/2009