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*APPLICATION NUMBER:*

**22-352**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type NDA  
Submission Number 22-352

Letter Date June 20, 2008  
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Reviewer Name Keith M Hull, MD, PhD  
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Established Name Colchicine  
(Proposed) Trade Name COLSTAT  
Therapeutic Class Tricyclic Alkaloid  
Applicant Mutual Pharmaceutical Co  
Priority Designation P

Formulation 0.6mg tablets  
Proposed Dosing Regimen Adults & Children >12 yo — 2.4 mg QD  
Children 6-12 yo: \_\_\_\_\_ mg QD  
Children ≥4 yo-6: 0.3 \_\_\_\_\_ mg QD

Indication \_\_\_\_\_ in  
patients with Familial  
Mediterranean Fever (FMF)

Intended Population Adults and children with FMF

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

This licensing application is for approval of colchicine (proposed trade name: COLSTAT) for \_\_\_\_\_ in adults and children  $\geq 4$  years of age with familial Mediterranean Fever (FMF). The application was filed under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act relying on publicly available information and received Orphan Drug Designation and Priority Review status. Three randomized, placebo-controlled, double-blinded, crossover studies provided the principal evidence of the efficacy of colchicine by reproducibly demonstrating a decrease in the number of acute attacks in patients with FMF while treated with colchicine compared to placebo. The primary evidence was further supported by sixteen open-labeled studies conducted in adults and children. Each of the studies enrolled patients with FMF and represented the targeted patient population. Safety analysis was provided based on data from the Applicant's pharmacokinetic (PK) studies, thorough searches for publications from four worldwide databases, postmarketing data from the FDA and World Health Organization (WHO) databases, and use of US and foreign labeling of colchicine-containing products. Overall there was substantial evidence of sufficient quality to adequately assess the safety and efficacy of colchicine for use in patients with FMF.

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This clinical reviewer recommends approval of colchicine for the \_\_\_\_\_ in adults and children  $\geq 4$  years of age with FMF. The Applicant was also seeking the additional claims for the \_\_\_\_\_; however, the data submitted in this marketing application was of insufficient quality to be able to provide substantial evidence of the effectiveness of colchicine for these claims; consequently, the latter two claims should not be granted.

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### 1.2 Risk Benefit Assessment

Currently, colchicine is the only known effective therapy for patients with FMF and fulfills an unmet medical need. Using the dosing recommendations outlined in this review, the clinical benefit of colchicine is greater than the potential risks, since the toxicity of colchicine at these doses is limited, and primarily consists of gastrointestinal symptoms.

### **1.3 Recommendations for Postmarketing Risk Management Activities**

Given the long history of clinical use of colchicine, which includes over 30 years of experience in FMF, the well documented and well known adverse event (AE) profile associated with the drug, and the lack of identification of additional safety signals in this review, no additional postmarketing risk management activities are required for the present indication.

### **1.4 Recommendations for other Post Marketing Study Commitments**

Given the long history of clinical use of colchicine, the well-documented AE profile associated with the drug, and the lack of identification of additional safety signals in this review, no clinical postmarketing study commitments are required for the present indication.

## 2 Introduction and Regulatory Background

Mutual Pharmaceutical Company, Inc. has submitted the present NDA under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act relying on publicly available information for colchicine tablets USP, 0.6 mg (trade name COLSTAT) for the treatment of adults and children  $\geq 4$  years of age with Familial Mediterranean Fever (FMF). The Applicant was granted Orphan Drug Designation status for this indication since the prevalence of FMF in the US is less than 5000 patients.

FMF is an autosomal recessive, autoinflammatory disease caused by mutations in the gene *MEFV* (MEditerranean FeVer), which encodes for the protein pyrin. Clinically, FMF is characterized by relatively discrete, usually 1 to 3 day episodes of fever with serositis, synovitis, or skin rash. In some patients attacks begin in infancy or very early childhood, and the large majority of patients experience their first episode by age 10. Young children sometimes present with fever alone. The frequency of FMF attacks is highly variable, both among patients and for any given patient, with the interval between attacks ranging from days to years. Moreover, the type of attack (abdominal, pleural, arthritic) may also vary over time. Some patients relate attacks to physical or emotional stress, although in many cases there is no obvious provocative event. There is a slight predominance of males in most series, possibly the result of under-reporting in women for social reasons or under-recognition because of confounding gynecologic diagnoses. In some women attacks may occur at a specific point in the menstrual cycle, and sometimes remit during pregnancy.

Attacks comprised of fever and abdominal pain occur at some time in nearly all FMF patients, and range from a dull aching pain to full-blown peritonitis, with board-like rigidity, absent bowel sounds, and rebound tenderness. Constipation is usual during the attacks, sometimes with a diarrhea at the very end of the episode. Plain films may demonstrate air-fluid levels, and CT scanning may show thickened mesenteric folds, lymphadenopathy, splenomegaly, or a small amount of ascites. Repeated episodes may lead to peritoneal adhesions.

Pleurisy may occur alone with fever, or concurrently with abdominal pain. Pleuritic episodes are usually unilateral, with sharp, stabbing chest pain and, in some cases, diaphragmatic pain referred to the ipsilateral shoulder. Radiographic findings may include atelectasis due to splinting and, in a minority of cases, pleural effusion. Thoracentesis, when performed, yields a neutrophil-laden exudate. Pleural thickening sometimes develops after multiple attacks. Other forms of serosal inflammation may also be seen in FMF. Nonuremic pericarditis is much less common than peritoneal or pleural involvement. Although small subclinical effusions are more frequent than symptomatic

pericarditis, there have been rare reports of tamponade. Unilateral acute scrotum occurs in about 5% of prepubertal boys with FMF resulting from inflammation of the tunica vaginalis, an embryologic remnant of the peritoneal membrane.

Joint involvement in FMF is particularly common among North African Jews and has been related to the M694V homozygous genotype which is very frequent in this population. Acute monoarticular arthritis is most characteristic in FMF, often affecting the knee, ankle, or hip. Such attacks tend to last somewhat longer than serosal episodes, sometimes with large effusions, extreme pain, and inability to bear weight. Synovial fluid often appears septic but cultures are sterile. Soft tissue swelling may be apparent on X-rays taken during attacks, but erosive changes do not develop. A number of other less common oligo- or polyarticular patterns of arthritis may occur, especially in children. Arthralgia is also very common in FMF. In the pre-colchicine era, about 5% of patients with acute monoarticular arthritis went on to develop protracted arthritis, usually affecting the hip. In such cases, symptoms could last for several months, sometimes leading to secondary osteoarthritic radiographic changes and/or osteonecrosis, and requiring total hip replacement surgery. Chronic sacroiliitis may also occur in FMF, regardless of the HLA-B27 status or colchicine therapy.

The most characteristic cutaneous lesion of FMF is erysipeloid erythema, a sharply demarcated, erythematous, warm, tender, swollen area 10 to 15 cm in diameter occurring unilaterally or bilaterally usually on the dorsum of the foot, ankle, or lower leg. On skin biopsy, there is a mixed perivascular infiltrate of polymorphonuclear leukocytes, histiocytes, and lymphocytes. As is the case for arthritis, the frequency of erysipeloid erythema may be increased among M694V homozygotes.

Children with FMF frequently develop myalgia of the legs related to vigorous exertion. Much less commonly, FMF patients may experience attacks of febrile myalgia, with excruciating muscle pain unrelated to exertion that can last from a few days to several weeks. During these episodes the creatine kinase is normal, the erythrocyte sedimentation rate is prolonged, and the electromyogram shows nonspecific myopathic changes. Histologic data suggest that febrile myalgia is a form of vasculitis. Other forms of vasculitis, including Henoch-Schönlein purpura and polyarteritis nodosum, are also seen at increased frequency in FMF.

Systemic amyloidosis develops in a subset of FMF patients, due to the deposition of a fragment of serum amyloid A (SAA) in the kidneys, adrenals, intestine, spleen, lung, and testes. SAA is an acute phase reactant produced by the liver and found at high levels in the serum during FMF attacks. Patients with amyloid deposition in the kidneys progress from albuminuria to the nephrotic syndrome to renal failure, usually over the course of 3 to 5 years. Amyloid

deposits in the gastrointestinal tract may cause malabsorption, and deposits in the testis may cause azoospermia and infertility. Cardiac involvement, neuropathy, and arthropathy are very uncommon with the amyloidosis of FMF. The diagnosis is usually established by renal or rectal biopsy.

The amyloidosis of FMF usually occurs after the onset of inflammatory attacks (Phenotype I), but rarely can occur as the first manifestation of FMF (Phenotype II), perhaps due to subclinical elevations in the SAA. The overall risk of amyloidosis in FMF is the product of a complex interaction of factors. Prior to the cloning of *MEFV*, epidemiologic data indicated that, among Jewish subpopulations, the risk was highest for North African Jews, intermediate for Iraqi Jews, and very low for Ashkenazi Jews. This gradient has subsequently been found to parallel the frequency of the M694V/M694V genotype, which, in most studies, is associated with an increased risk of amyloidosis, although not in a large recent series from Turkey. Other risk factors for amyloidosis include male gender, the SAA1- $\alpha$  genotype, and a positive family history for amyloidosis. There are also geographical and secular effects on amyloid susceptibility, perhaps reflecting improvements in general medical care that may modify the SAA load from intercurrent illness.

To date over 35 disease-associated mutations have been identified. Research on the function of pyrin, the *MEFV* gene product, has focused on interactions mediated by the N-terminal 92 amino-acid domain encoded by exon 1. This motif, which has variously been denoted the PYRIN domain has now been recognized in a total of over 20 human proteins involved in the regulation of inflammation and apoptosis. Computational modeling and subsequent NMR spectroscopy have demonstrated that the PYRIN domain is the fourth member of the death domain-fold superfamily, which also includes death domains, death effector domains, and caspase-recruitment domains (CARDs). All four assume a six alpha-helix three-dimensional structure that facilitates homotypic interactions through electrostatic charge interactions. Thus, the PYRIN domain of pyrin is a docking motif that facilitates cognate interactions with other PYRIN domain proteins.

The PYRIN domain of pyrin interacts specifically with the homologous domain of a protein called ASC (apoptosis-associated specklike protein with a CARD). Both proteins are located in the inflammasome, a complex of proteins found in neutrophils and monocytes that have distinct roles in the innate defense system. Through its CARD, ASC binds caspase-1 (also known as IL-1 $\beta$  converting enzyme [ICE]) and other adaptor proteins, leading to the catalysis of caspase-1 into enzymatically active p20 and p10 subunits. Activated caspase-1, in turn, cleaves IL-1 $\beta$  from its 31 kDa precursor form to its 17 kDa biologically active fragment, which is a potent mediator of fever and inflammation. Data from mice

expressing a hypomorphic pyrin mutant indicate that wild type pyrin plays an important role in regulating the ASC-ICE-IL-1 $\beta$  cascade.

Although less completely understood, the interaction of pyrin with ASC also appears to regulate leukocyte apoptosis. Peritoneal macrophages from the aforementioned pyrin-deficient mice exhibit a defect in apoptosis through a caspase-8-dependent, IL- $\beta$ -independent pathway, suggesting a role for wild type pyrin in limiting the duration of the innate immune response through cell death. Nevertheless, underscoring the complexity of the process, in some transfection systems wild type pyrin exerts an anti-apoptotic effect.

Finally, the pyrin-ASC interaction has also been shown to modulate NF- $\kappa$ B activation, another important component of the innate immune response. ASC has been shown to bind to components of the I $\kappa$ B kinase complex, which regulates NF- $\kappa$ B through the phosphorylation of I $\kappa$ B. Depending on the cellular context, cotransfection of wild type pyrin with ASC may potentiate or suppress NF- $\kappa$ B activation.

While the interaction of the N-terminal domain of pyrin with ASC sheds new light on the regulation of inflammation, it does not yet explain the molecular mechanism by which missense mutations in pyrin, many of which are at the C-terminal end of the protein, lead to autoinflammatory disease. Possibly, these mutations indirectly influence the effect of pyrin on IL-1 $\beta$  processing, apoptosis, and/or NF- $\kappa$ B activation, perhaps conferring a selective advantage by pushing the balance, under some circumstances, towards heightened innate immunity.

## 2.1 Product Information

Colchicine is a tricyclic alkaloid derivative originating from the plant *Colchicum autumnale*, more commonly known as "Autumn Crocus" or "Morning Saffron". There is evidence that the bulb of the plant was already used to treat pain and articular disease as early as the first century CE, and by the eighteenth century, colchicum was specifically used as a treatment for gout. The active ingredient, (-) colchicine, was isolated in 1821 by Pelletier and Caventou and has been used in the US to treat disease since the early 19<sup>th</sup> century. Colchicine is currently available from several different manufactures as tablets for oral administration containing colchicine 0.6 mg but none of these single-ingredient products have yet been approved by FDA.

The exact mechanism whereby colchicine decreases inflammation is not fully understood, however, it has been long believed that colchicine disrupts the function of the cytoskeleton by interfering with microtubulin assembly; this in turn is thought to prevent the activation, degranulation, and migration of neutrophils to

sites of inflammation. Recent evidence however now suggests that colchicine may derive its mechanism of action by interfering with the intracellular assembly of the inflammasome complex found in neutrophils and monocytes that mediate IL-1 $\beta$  activation.

Mutual Pharmaceutical Company is proposing to license colchicine 0.6 mg USP in the form of a purple, film coated, capsule-shaped, immediate-release tablet that is debossed 'AR 374' on one side and scored on the other. In addition to the 0.6 mg of colchicine, each tablet contains standard compendial pharmaceutical excipients that raise no safety concerns.

Colchicine is the established drug name and the Applicant has proposed using "COLSTAT" for the product's trade name. The Applicant has proposed the following indications for the use of colchicine in adults and children ( $\geq 4$  years of age) with FMF:

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- \_\_\_\_\_
- \_\_\_\_\_
- \_\_\_\_\_

The Applicant's proposed dosing of colchicine for use in patients with FMF is proposed as follows:

- Children ages 4 to 6 years: 0.3 mg to — mg of colchicine daily
- Children ages 6 to 12 years: — mg to — mg of colchicine daily
- Adults and children  $>12$  years: — mg to 2.4 mg of colchicine daily

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## 2.2 Tables of Currently Available Treatments for Proposed Indications

Colchicine is currently the only known effective therapy for patients with FMF. Several recent publications from the scientific literature have reported efficacy using interleukin-1 antagonists or interferon; however, these therapies are still experimental and have not been shown to be effective in well-controlled, double-blinded studies. Narcotics and NSAIDs are typically used for the symptomatic relief of the acute attacks associated with FMF but do not alter the frequency, duration, or severity of the attacks.

### **2.3 Availability of Proposed Active Ingredient in the United States**

Colchicine was originally approved as part of the combination product ColBenemid (colchicine 0.5 mg and probenecid 500 mg) in 1961. However, since its approval predated the requirement for the demonstration of efficacy, it was reviewed again in 1972 by the National Academy of Sciences as part of the Drug Efficacy Study Implementation (DESI) reviews and was deemed effective for "chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout". Currently, colchicine is available from several manufacturers as a 0.6 mg tablet for oral administration but none of the products are FDA approved.

### **2.4 Important Safety Issues with Consideration to Related Drugs**

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**

Colchicine was originally approved under NDA 12-383 as part of the combination product ColBenemid (colchicine 0.5 mg and probenecid 500 mg) in 1961. However, since its approval predated the requirement for the demonstration of efficacy, it was reviewed again in 1972 by the National Academy of Sciences as part of the DESI reviews and was deemed effective for "chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout". The current FDA approved colchicine products are colchicine in combination with probenecid (Col-Probenecid from Watson Labs and Probenecid and Colchicine from IVAX Pharmaceuticals).

A Pre-IND meeting between the Division and the Applicant was held on July 31, 2006 to discuss the requirements for development and approval of colchicine tablets, 0.6 mg, for the \_\_\_\_\_ treatment of acute attacks of gout and FMF. An IND was submitted on February 9, 2007 regarding PK studies to support the Applicant's development of colchicine for use in gout and FMF.

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On September 25, 2007, the Applicant's request was granted for Orphan Drug Designation status for colchicine in the treatment of patients with FMF since the prevalence of the disease in the US is <5000 patients.

A pre-NDA meeting was requested by the Applicant on October 3, 2007 and a briefing package in support of the meeting was submitted on December 21, 2007. The Division responded in writing on February 1, 2008 addressing the Applicant's questions proposed in the briefing package. The Applicant cancelled the pre-NDA meeting as they deemed the Division's written responses adequate and their concerns addressed. It was confirmed in the Division's responses to the Applicant that a thorough review of the publicly available information was all that was necessary to submit this NDA.

On June 20, 2008, Mutual Pharmaceutical Company submitted the current NDA under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act relying on publicly available information for colchicine tablets USP, 0.6 mg (trade name COLSTAT) for the treatment of adults and children  $\geq 4$  years of age with FMF.

Incidentally, in February 2008, the FDA took enforcement action and ordered unapproved injectable colchicine products to be withdrawn from the market for safety reasons.

## **2.6 Other Relevant Background Information**

Colchicine is currently approved for use in 50 countries. The Applicant was able to obtain safety data contained in the colchicine product labels from 8 of the countries: Argentina, Australia, France, Germany, Mexico, Singapore, Uganda, and United Kingdom.

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

Given the inherent limitations of a literature-based 505(b)(2) submission, the overall quality of the submission was acceptable. The Applicant used all available resources to provide efficacy and safety data to support their application including Applicant-initiated pharmacokinetic (PK) studies, a thorough search of the scientific literature using four large databases which emphasize different publication types and sources were utilized to ensure identification of all relevant publications, postmarketing data obtained from FDA and World Health Organization (WHO) databases, and US and foreign labels for products containing colchicine. The application was complete, well-organized, and uncomplicated in hyperlinking references as necessary.

#### **3.2 Compliance with Good Clinical Practices**

Compliance with good clinical practices was followed for the Applicant-initiated PK studies. The remainder of the submission was derived from publicly available sources of information and not subject to the review of good clinical practice

#### **3.3 Financial Disclosures**

All studies were either directly performed by the Applicant or derived from publicly available source of information. Consequently, the Applicant has adequately disclosed their finances.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

This portion of the application was reviewed by Craig M Bertha, PhD who recommended approval of the application from the perspective of Chemistry, Manufacturing, and Controls (CMC). Dr. Bertha noted however that the recommendation from the Office of Compliance is currently pending. Additionally, the CMC review team commented that a \_\_\_\_\_ expiration dating period is not appropriate at the present time for the \_\_\_\_\_ drug product and an \_\_\_\_\_ expiration dating period is granted for this presentation of the product. Further details can be found in Dr. Bertha's review.

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### 4.2 Clinical Microbiology

Not applicable to this application.

### 4.3 Preclinical Pharmacology/Toxicology

The nonclinical portion of this application was reviewed by Lawrence S Leshin, PhD who recommended approval of the application from the perspective of Preclinical Pharmacology/Toxicology. In his review, Dr. Leshin concluded that the doses of colchicine for the proposed indication are at or below those for which there is extensive clinical pharmacological and toxicological knowledge and clinical experience. Additionally, he noted that the nonclinical pharmacology was well characterized, but the nonclinical toxicology lagged behind the knowledge of clinical toxicology and that the vast majority of previous studies were not conducted to meet today's regulatory standards nor performed according to GLP. Repeated dose studies of at most a few weeks, cited in the literature, indicated a low threshold between adverse effects and mortality, although the colchicine used in these older studies was unlikely to be as pure as the Applicant's drug. These factors, together with the more widely known clinical experience and clinical toxicity of colchicine, contributed to the decision that further nonclinical studies, including carcinogenicity studies would be of limited usefulness or difficult to accomplish.

Dr. Leshin noted for nonclinical studies that the photodegradant impurities contain structural alerts for mutagenicity and therefore he recommended specifications set to maintain daily intake at less than 1.5 µg/day. If that is not possible, qualification studies (genetic toxicology and a 28-day repeated dose

study) are necessary. These photodegradants are not detected in the clinical product at the current levels of impurity detection. The currently marketed approved generics of Colbenemid, and the numerous marketed, but unapproved colchicine-only products have the same potential of containing these impurities, and should all be limited with regards to these impurities. Since these have been on the market for years, Dr. Leshin recommends that lowering of specifications or qualification studies could be done postmarketing. Further details can be found in Dr. Leshin's review.

#### **4.4 Clinical Pharmacology**

The Clinical Pharmacology portion of this application was reviewed by Srikanth C Nallani, PhD who recommended approval of the application.

##### **4.4.1 Mechanism of Action**

The exact mechanism whereby colchicine decreases inflammation is not fully understood, however, it has been long believed that colchicine disrupts the function of the cytoskeleton by interfering with  $\beta$ -tubulin assembly; this in turn is thought to prevent activation, degranulation, and migration of neutrophils to the sites of inflammation. Recent evidence however now suggests that colchicine affects the intracellular assembly of the inflammasome complex found in neutrophils and monocytes that mediate IL-1 $\beta$  activation.

##### **4.4.2 Pharmacodynamics**

Data pertaining to the effect of colchicine on QTc prolongation can be found in Section 7.4.4

#### 4.4.3 Pharmacokinetics

The Applicant conducted six separate PK studies which are reviewed in detail by Dr. Nallani in his review. Table 1 summarizes the PK parameters of colchicine obtained from the Applicant's studies (study numbers: 1002, 1003, and 1004).

**Table 1. Summary of PK Parameters for Colchicine**

	$C_{max}$ (ng/mL)	$T_{max}$ (h)	$AUC_{0-t}$ (ng·h/mL)	$AUC_{\infty}$ (ng·h/mL)	Vd/F (L)	CL/F (L/hr)	$Ke^{-1}$ (h)	$t_{1/2}$ (h)
<b>Colchicine 0.6-mg Single Dose (N=13) from study # 1004</b>	2.45 (28.7)	1.50 (1.0 – 3.0)	10.5 (33.8)	12.3 (36)	341 (54.3)	54.05 (31)	0.183 (32.4)	4.95 (89.5)
<b>Colchicine 1.8 mg Single Dose (N=13) from study # 1003</b>	6.19 (39.3)	1.81 (1 – 2.5)	43.79 (26.1)	52.07 (26.3)	1188 (26.9)	36.95 (27)	0.0326 (31)	23.6 (39)
<b>Colchicine 4.8 mg over 6 hours (N=15) from study # 1002</b>	6.84 (19)	4.47 (3.12- 7.5)	104.95 (23.45)	118.2 (22)	1876 (24.3)	43 (29.8)	0.0242 (36.6)	31.38 (26.6)

## 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 relying on publicly available information as the primary source of data necessary to demonstrate the clinical safety and efficacy of colchicine for the treatment of FMF. Consequently, the majority of data in this application is derived the comprehensive searches of the worldwide literature using the following databases:

- Biosis Previews (1926 to present)
  - Worldwide coverage of research in the biological and biomedical sciences citing from approximately 5000 primary journal and monograph titles, books, reviews, meeting abstracts, book chapters, notes, letters, and selected reports.
- EMBASE (1974 to present)
  - Worldwide coverage of literature regarding clinical medicine and related disciplines with a stronger emphasis on European studies and cites from approximately 4500 primary journals.
- JICST-Eplus (1985 to present)
  - Provides coverage of the Japanese and Asian literature in the fields of science, technology, and medicine. Includes citations from approximately 6000 journals and serials, conference papers, preprints, technical reports, and other nonperiodicals published by the Japanese government.
- MEDLINE (1950 to present)
  - Major source of biomedical literature from the National Library of Medicine and includes citations and abstracts from approximately 4800 journals published in the US and 70 other countries.

A total of eight searches were performed by a trained research associate between December 2005 and May 2008 using a search strategy that combined drug name or synonyms, specific indication terms, and general clinical and clinical trial terms without restriction of publication date, type or language. Available titles and abstracts from each search output were reviewed by an experienced healthcare professional.

Additionally, the Applicant has submitted data from the FDA and WHO adverse event reporting safety databases, labeling from colchicine-containing products from the US and foreign markets, and six Applicant-initiated PK studies.

### 5.1 Tables of Clinical Studies

Seventy-four of the more than 1200 published articles obtained as a result of the database searches were included in the Applicant's application to contribute information supporting the clinical efficacy of colchicine for the efficacy treatment of FMF. Only nineteen of the publications were considered to be of adequate quality to be used in the efficacy and dosing determination for the use of colchicine to \_\_\_\_\_ in patients with FMF in adults and children (Table 2 and Table 3).

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**Table 2. Studies Used to Support the Efficacy of Colchicine**

Reference	N	Study Design	Treatment Dose & Duration	Primary Efficacy Outcome
<b>Randomized, Controlled Trials</b>				
Dinarello et al., 1974	11	R, DB, PC C/O (28 d periods)	Colchicine 0.5 mg or Placebo BID	Frequency of Acute Attacks Severity of Acute Attacks
Goldstein et al., 1974	15	R, DB, PC C/O (90 d periods)	Colchicine 0.6 mg or Placebo TID	Frequency of Acute Attacks
Zemer et al., 1974	22	R, DB, PC C/O (60 d periods)	Colchicine 0.6 mg or Placebo TID	Frequency of Acute Attacks
<b>Non-Randomized, Open-Label Trials, Adults</b>				
Barakat & Menon, 1977	43	NR, OL	Colchicine 0.5 mg BID followed by an off-treatment period	Frequency of Acute Attacks
Barakat et al., 1986	175	NR, OL	Colchicine 0.5 to 1.5 mg/day	Frequency of Acute Attacks
Ben-Chetrit & Levy., 1991	45	NR, OL	Colchicine 1 to 3 mg/day	Frequency of Acute Attacks
Levy et al., 1977	47	NR, OL	Colchicine 0.5 to 1.5 mg/day	Frequency of Acute Attacks
Minialawi et al., 1973	22	NR, OL	Colchicine 0.5 mg BID	Frequency of Acute Attacks
Minialawi et al., 1974	85	NR, OL	Colchicine 0.75 to 1.5 mg/day	Frequency of Acute Attacks
Peters et al., 1983	85	NR, OL	Colchicine 1-2.4 mg/day	Frequency of Acute Attacks
Zemer et al., 1976	84	NR, OL	Colchicine 1 to 3 mg/day	Frequency of Acute Attacks

R: Randomized; DB: Double-blind; PC: Placebo-controlled; C/O: cross-over; NR: Non-randomized; OL: Open-label

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**Table 3. Studies Used to Support the Efficacy of Colchicine**

Reference	N	Study Design	Treatment Dose	Primary Efficacy Outcome
<b>Non-Randomized, Open-Label Trials, Children</b>				
Gedalia et al, 1977	101	OL, OL	Colchicine 0.5 to 2 mg/day	Frequency of Acute Attacks
Lehman et al, 1986	14	NR, OL	Colchicine 0.6 to 1.8 mg/day	Frequency of Acute Attacks
Majeed et al, 1989	45	NR, OL	Colchicine 0.5 to 1.5 mg/day	Frequency of Acute Attacks
Majeed et al, 1990	32	NR, OL	Colchicine 0.5 to 1.5 mg/day	Frequency of Acute Attacks
Majeed et al, 1999	476	NR, OBS	Colchicine 0.5 to 1.5 mg/day	Frequency of Acute Attacks
Ozkaya et al, 2003	62	NR, OL	Colchicine 0.5 to 2 mg/day	Frequency of Acute Attacks
Rawashdeh et al, 1996	192	NR, OL	Colchicine 0.5 to 1.5 mg/day	Frequency of Acute Attacks
Zemer et al., 1991	350	NR, OBS	Colchicine 0.5 to 2 mg/day	Frequency of Acute Attacks

NR: Non-randomized; OL: Open-label; OBS: Observation Study

## 5.2 Review Strategy

Literature reviews can be problematic regarding the analysis of clinic trials when they serve as the primary source of data to support a marketing application. For example, the design of the studies may not be ideal, enrolled patients may not represent the targeted patient population, the primary source data and case report forms are not available for scrutiny, inability to account for patient dropouts if not mentioned by the study authors, and inability to confirm statistical analyses or perform different analyses if necessary.

Indeed, the literature submitted for the current application is less than ideal and presents several shortcomings in support of the proposed clinical indications for colchicine. First, since colchicine was quickly accepted as an effective therapy for the treatment of FMF following the initial case report by Goldfinger in 1972, few randomized, double-blinded, placebo-controlled studies were subsequently performed as it was thought to be unethical to withhold an effective therapy from patients. As a result the Applicant's comprehensive search of the literature was only able to identify three randomized, controlled studies.

These three studies represent the cornerstone of the data submitted to support an indication for the \_\_\_\_\_ related to FMF. As discussed in detail below (Section 6), these three studies enrolled a small number of patients, had a large percentage of patient dropouts, were not ideally designed regarding control and treatment arms, and had some suggestion of patient unblinding due to colchicine-induced side effects. However, despite these deficiencies, the studies appear to provide sufficient data to assess the clinical efficacy of colchicine for \_\_\_\_\_ associated with FMF. Each study had similar clinically meaningful endpoints (frequency of attacks) and adequate diagnostic criteria for the diagnosis of FMF to ensure similar patient populations. Each of the trials used a crossover study design whereby patients served as their own controls. This study design is similar to a randomized-withdrawal study often used in pediatric trials where it would be unethical to withhold a treatment thought to be effective. The results of the efficacy data are further supported by the trial by Zemer et al. (Section 6.1.a.3) who utilized two groups of patients treated with colchicine or placebo for the first two months of the trial before having patients crossover, effectively having a short-term parallel-group, controlled trial whereby an active treatment arm could be compared to a placebo control. As discussed below (Section 6), the data from each trial demonstrates a very large effect size in favor of colchicine making the results easier to interpret. Additionally, analyses of the efficacy data show that patient dropouts were largely due to study discontinuation by the authors (because the interim analyses demonstrated superiority of colchicine compared to placebo treatment) or due to attack symptoms while patients were receiving placebo treatment and not from adverse effects or lack of efficacy of colchicine.

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The three randomized and controlled studies are further supported by the data obtained from the open-label trials in both adult and pediatric populations. Although open-label studies can be subject to patient bias, FMF attacks are definitive and present with objective signs (e.g. fever, rash) in addition to subjective symptoms. Thus, the data may be less biased than that of other studies using patient-reported outcomes alone. Further evidence of the efficacy of colchicine can be inferred by the observation that in both the blinded and open-labeled studies, patients who discontinued their colchicine regimen had a recurrence of attacks within 3 to 7 days. Taken as whole, the three randomized and well-controlled trials in addition to the sixteen open-labeled studies provide adequate data to assess the efficacy of colchicine to \_\_\_\_\_ of FMF.

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The Applicant has also submitted data from the scientific literature to support the indications for the \_\_\_\_\_ in patients with FMF. All of the trials were non-randomized, observation trials or case reports. In each of the trials, the diagnosis of \_\_\_\_\_ was presumed based on the presence of proteinuria in patients diagnosed with FMF. Similarly, evidence of the success or failure of colchicine therapy was based on the development of proteinuria or the improvement/worsening of the proteinuria in colchicine-treated patients. The majority of the trials also used a range of colchicine doses over long periods of time (e.g., 4 to 11 years) without a means to assure patient compliance. Additionally, since these studies were open-labeled and without a placebo treatment arm, the rate of the development or worsening of proteinuria was often compared to historic controls.

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Although colchicine is commonly believed by healthcare providers to \_\_\_\_\_ in patients with FMF, the data submitted in this marketing application have several serious limitations and do not meet the standard of clinical evidence necessary to be used to support the claims. First, because \_\_\_\_\_ occurs as a result of many years of uncontrolled inflammation, studies assessing \_\_\_\_\_ related outcomes would need to be of long duration (multiple years), and use of a placebo-control (since no other treatments are known to be effective and thus no active control could be used) would be considered unethical. Therefore no controlled studies are available. Second, the incidence of \_\_\_\_\_ in patients with FMF has been reported to vary greatly between studies and information on intrinsic risk factors such as MEFV mutation genotype or \_\_\_\_\_ genotype are generally not available in the published studies. Therefore the underlying risk of \_\_\_\_\_ in relation to study outcomes cannot be adequately evaluated and this impedes the ability to discern the treatment effect of colchicine. . The ability to interpret and compare data from a given study compared against historic controls is similarly limited for these reasons.

b(4)

Finally, the use of proteinuria as either a diagnostic criterion or efficacy outcome measure is common in the submitted \_\_\_\_\_ studies but is problematic: many medical conditions can result in proteinuria and therefore it is insufficiently specific to be used as a diagnostic criterion, and the assessment of the progression or regression of

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\_\_\_\_\_ by using proteinuria as a surrogate marker has not been validated and is also subject to other clinical factors, e.g., the use of ACE-inhibitors or diabetes, which can alter the degree of proteinuria independently of \_\_\_\_\_. Therefore, a patient who does not progress may actually have been a patient who did not have \_\_\_\_\_ and a patient who "responds" could have been responding to other agents such as ACE-inhibitors. These factors are not adequately accounted for in the literature articles submitted. Given the small number of patients with FMF that may develop \_\_\_\_\_ during the timeframe of any particular study, misdiagnosis of even a few patients with other medical conditions may distort the data.

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Although colchicine is commonly believed by healthcare providers to \_\_\_\_\_ in patients with FMF, the data submitted in this marketing application is therefore insufficient to provide substantial evidence of the effectiveness of colchicine in the \_\_\_\_\_ to FMF. Consequently, these data will not be addressed in detail in this review and the claims should not be granted.

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### 5.3 Discussion of Individual Studies

The study design, study conduct, and results of the individual studies are discussed in detail in Section 6.

## 6 Review of Efficacy

### Efficacy Summary

The results obtained from the three randomized, controlled trials represent the highest quality data provided for analyzing the efficacy of colchicine to \_\_\_\_\_ patients with FMF. Consequently, the summary of these studies' designs, conduct, and results are presented here as an integrated review of the efficacy of colchicine to \_\_\_\_\_ in patients with FMF.

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The three randomized, double-blinded, placebo-controlled studies enrolled similar demographics of patients and shared common inclusion criteria including a defined set of criteria for the diagnosis of FMF, appropriate ethnicity, and a reliable history of frequent attacks. Exclusion criteria among the three studies were generally similar but varied regarding co-morbidities (e.g., amyloidosis) or concomitant medications (e.g., corticosteroids or narcotics). The differences between the studies' exclusion criteria do not impact the interpretation of the results. The three randomized trials used similar dosing regimens of colchicine using between 1 to 1.8 mg per day.

All three studies utilized a crossover study design whereby each patient received colchicine and placebo during different periods of the same study. This study design is similar to a randomized-withdrawal study often used in pediatric trials where it would be unethical to withhold a treatment thought to be effective. Also, the crossover design is acceptable in this patient population since individual patients have different frequencies of attacks and therefore each patient serves as their own control. The use of a placebo treatment arm in each of the studies was an appropriate choice of control group given that no other known therapies for FMF are available. While each study was susceptible to bias from side effects of colchicine (e.g., diarrhea, nausea, and abdominal pain), analysis of the available data demonstrate that bias appears to be minimal and does not affect the validity of the data.

The primary endpoint for the three randomized trials was predefined as the difference in the number of FMF attacks accompanied by fever between the two treatment periods (i.e., placebo and colchicine). This endpoint has not been validated but does represent a clinically meaningful endpoint. Generally, patient reporting of pain is subjective and potentially prone to bias; however, as a result of the underlying etiology of FMF, patients experience well-defined objective signs and symptoms of an attack, e.g., peritonitis, pleuritis, fever, arthritis, and rash, in addition to their subjective symptoms, making the proper identification of an attack more reliable. Additionally, each study reported treatment periods of at least two months duration which provided an adequate amount of time to discern a meaningful difference between the two treatment arms. Thus, the design of the three clinical studies including the choice of the primary endpoint, duration

of study, limitation of biasing, and choice of the control group are adequate to allow for the assessment of the clinical efficacy of colchicine.

The three studies randomized a total of 48 adult patients who were of various ethnicities commonly affected with FMF. The majority of the patients were male; however, this is not expected to affect the interpretation on the results as males and females share the same genetic mutations and phenotypic expression of the disease. The study by Dinarello et al. was discontinued after six patients had completed the study and a planned interim analysis demonstrated a clear benefit with colchicine treatment. A total of 24 of 37 (65%) patients completed the other two studies with the thirteen patients discontinuing during placebo treatment due to attacks (six patients), noncompliance (six patients), or lost to follow-up (one patient).

As shown in Table 4, the results of the three randomized trials demonstrate that the number of acute attacks were significantly lower with colchicine treatment compared to placebo. Taken together these results demonstrate a clinically meaningful benefit of colchicine therapy for preventing acute attacks in patients with FMF.

**Table 4. Summary of Efficacy Results from the Three Randomized Trials**

Citation	Treatment	Number of Attacks (observation period)
Dinarello et al., 1974	Placebo (N=11)	38 (28 days)*
	Colchicine (N=11)	7 (28 days)*
Goldstein et al., 1974	Placebo (N=15)	59 (90 days)**
	Colchicine (N=15)	5 (90 days)**
Zemer et al., 1974	Placebo (N=13)	68 (60 days)***
	Colchicine (N=13)	18 (60 days)***

\* p<0.001 using Chi-square  
 \*\* p<0.002 using Sign Test  
 \*\*\* 13 of 22 patients completing both treatment phases

As experience with colchicine in patients with FMF expanded, researchers published information from larger open-labeled studies and case series to better characterize the disease and to demonstrate the efficacy and safety of colchicine. Sixteen of these non-randomized studies were selected by the Applicant to further support the results obtained from the three randomized trials demonstrating the ability of colchicine to \_\_\_\_\_ in patients with FMF. Studies were chosen based on the number of patients enrolled and the quality of the data.

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Eight of the non-randomized studies were published between 1973 and 1983 and included a total of 586 patients with FMF. Synopses of the individual studies can be found in Section 6.1. The large majority of patients in these studies were adults treated with doses of oral colchicine similar to what was used in the three randomized trials over periods ranging from six months to fifteen years. Each study used the number of attacks as their primary efficacy variable. As shown in Table 5, the majority of patients

in each trial responded to colchicine treatment in similar proportions as to those observed in the three randomized trials. In fact, of the 508 patients enrolled in the seven studies reporting response rates, 384 (76%) patients reported a complete response, 105 (21%) patients reported a partial response, and only 19 (3%) patients reported no clinical benefit of colchicine therapy. As discussed above, although open-label studies can be subject to patient bias, FMF attacks are definitive and present with objective signs in addition to subjective symptoms. Therefore, patient reporting of attacks in these studies may be less biased than that of other pain-related patient reporting studies and provides acceptable evidence for supporting the randomized data. The results of these eight non-randomized studies conducted in adult patients strongly support the results observed in the three randomized trials which demonstrated the ability of colchicine to prevent or reduce acute attacks in patients with FMF.

**Table 5. Summary of Efficacy Data from the Open-Label Trials in Adults**

Reference	N	Treatment Dose & Duration	Clinical Response to Colchicine Therapy
Barakat & Menon, 1977	43	Dose: Colchicine 0.5 mg BID Duration: 6 months	Mean # of Attacks Colchicine: 1 attack/year Placebo: 12 attacks/year
Barakat et al., 1986	175	Dose: Colchicine 0.5-1.5 mg/d Duration: Over 11 years	WC: 92% (150/163) PR: 6% (9/163) NB: 3% (4/163)
Ben-Chetrit & Levy, 1991	45	Dose: Colchicine 1-3 mg/d Duration: Minimum 15 years	CR: 44% (20/45) PR: 42% (19/45) NB: 13% (6/45)
Levy et al., 1977	47	Dose: Colchicine 0.5-1.5 mg/d Duration: Minimum 1 year	CR: 98% (46/47) PR: 2% (1/47)
Minialawi et al., 1973	22	Dose: Colchicine 0.5 mg BID Duration: Not Reported	CR: 95% (21/22)
Minialawi et al., 1974	85	Dose: Colchicine 0.75-1.5 mg/d Duration: 6 to 12 months	CR: 68% (58/85) PR: 31% (26/85) NB: 1% (1/85)
Peters et al., 1983	85	Dose: Colchicine 1-2.4 mg/d Duration: Minimum 3 years	CR: 63% (39/62) PR 36% (22/62)
Zemer et al., 1976	84	Dose: Colchicine 1-2 mg/d Duration: 1 to 3 years	CR: 60% (50/84) PR: 33% (28/84) NB: 7% (6/84)
CR: Complete Response; WC: Well Controlled; PR: Partial Response; NB: No Benefit			

Soon after the early success of treating adult patients with colchicine was reported, positive experiences in children with FMF began to appear in the literature. Although no randomized, placebo-controlled trials have been conducted, a large amount of evidence has been published from non-randomized, open-label studies. The Applicant has provided eight large case series that were conducted between 1978 and 2003 to support the use of colchicine to \_\_\_\_\_ with FMF. Synopses of these eight cases can be found in Section 6.1.10. The eight studies enrolled a total of 1272 children with similar numbers of males and females aged four months to

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**6.1 Indication: \_\_\_\_\_ of FMF**

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**6.1.a. Study Synopses of the Randomized, Double-Blind, Placebo-Controlled Studies**

**6.1.a.1 "Colchicine Therapy for Familial Mediterranean Fever: A Double-Blind Trial,"  
Dinarello CA, et al, NEJM, 1974**

Eleven adult patients diagnosed with FMF were selected to participate in the double-blind study. All patients were selected based on their frequent attacks and absence of amyloidosis, or hepatic, renal, and hematologic abnormalities. Patients were allowed to receive non-narcotic analgesics, e.g., aspirin or propoxyphene, as needed. Separate courses of colchicine 0.6 mg tablets and placebo were administered in random order. Patients decided whether or not an attack occurred and classified attacks as mild, moderate, or severe.

Each treatment course consisted of one tablet that was to be taken thrice daily for 28 days. If no attacks occurred during the 28 day period then the next course of tablets was initiated. When an attack did occur, the treatment course was discontinued and the patient received no study medication except of non-narcotic analgesics as needed. After recovery from an attack, typically 48 to 72 hours, the patient began the next treatment course. If a patient experienced diarrhea or nausea the study medication was decreased by one tablet per day. Once a dose reduction occurred, patients continued the remainder of the study on the lower dose study drug. Patients continued to take courses every 28 days or after each attack. Colchicine therapy was classified as successful if either no attacks occurred while patients were receiving colchicine therapy and five attacks were recorded during placebo courses, or if patients experienced one attack on colchicine and seven attacks on placebo therapy. Cases where two attacks occurred while on colchicine therapy was considered failure of colchicine therapy.

After completion of the study by the first six patients, an interim analysis of the data was made for all patient attacks and it was decided that the study should be terminated at that point due to a clear therapeutic advantage of colchicine therapy. Thus only six of eleven patients completed the study at the time the study was discontinued. The remaining five patients had not experienced a sufficient number of attacks for therapy to be considered either a success or a failure.

As shown in Table 1, 38 attacks occurred during 60 courses of placebo compared with seven attacks during 60 courses of colchicine ( $p < 0.001$ , chi-square=32).

**Table 1. Number of Attacks During Placebo and Colchicine Treatment**

Drug	No. of Courses	No. of Attacks
Placebo	60	38 (63%)
Colchicine	60	7 (12%)
Totals	120	45

$p < 0.001$   
 $\chi^2 = 32.0$   
 (1 degree of freedom)

\*Table reproduced from manuscript.

Of the six patients who completed the study, three (50%) patients experienced five attacks while on placebo and none while receiving colchicine therapy, one (17%) patient had seven attacks while receiving placebo and one attack while on colchicine, and two (33%) patients did not benefit from colchicine therapy. Attacks appeared to occur during the first seven to ten days of a new treatment course. Attacks while on placebo occurred on average 10 days after beginning placebo when the preceding course was colchicine. These results suggest that discontinuation of colchicine in and of itself precipitated attacks.

Table 2 shows the severity of attacks as classified by the patients. In addition to a greater number of attacks overall, the attacks were also described as more severe while on placebo compared to attacks experienced while on colchicine treatment.

**Table 2. Attack Severity During Placebo and Colchicine Treatment**

Drug	Severity of Attack*			Totals
	Mild	Moderate	Severe	
Placebo	8	9	17	34 <sup>†</sup>
Colchicine	5	1	1	7

\*Information on severity available for only 34 of the 38 attacks with placebo.

<sup>†</sup>No. of attacks.

\*Table reproduced from manuscript.

Comparison of the relative frequency of attacks occurring during therapy with one, two, or three tablets demonstrated that patients experienced fewer attacks with higher doses of colchicine (Table 3). The differences in the number of colchicine tablets taken during the study are explained by the necessary reduction of the colchicine dose(s) due to occurrence of nausea and diarrhea.

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**Table 3. No. of Colchicine Tablets Administered per Treatment Group**

DRUG	NO. OF TABLETS TAKEN / DAY		
	1	2	3
Placebo	4/9*	26/41	8/10
Colchicine	3/11	4/43	0/6

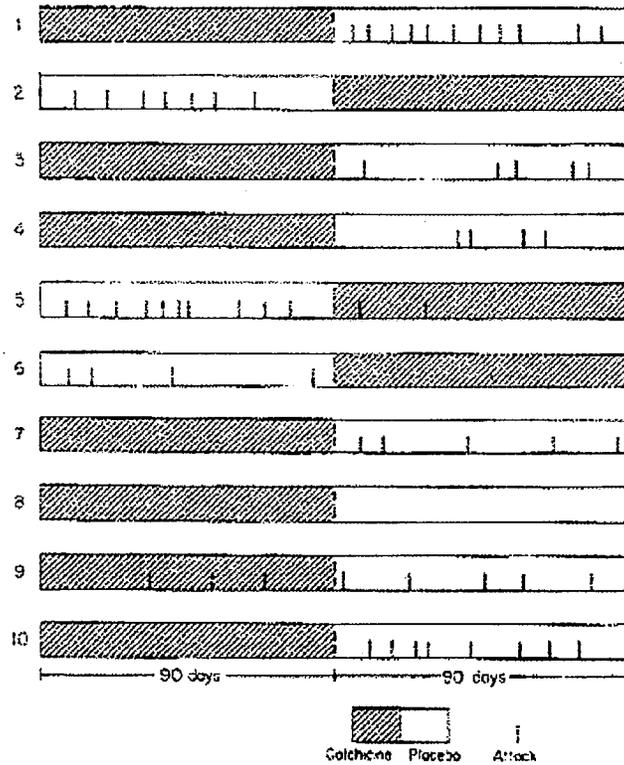
\*No. of attacks/no. of courses.

\*Table reproduced from manuscript.

No major adverse reactions were noted during the study except for diarrhea in patients treated with three tablets of colchicine daily.

Figure 1 shows the attack frequency in ten patients during both treatment phases of the study. Eight patients reported no attacks while receiving colchicine therapy while two patients (numbers 5 and 9) reported a reduction in attack frequency but not attack severity. Patient number 8 experienced no attacks during the 180 day study. Statistical analysis of the nonparametric data using the sign test indicates that the decrease in attacks during colchicine treatment was statistically significant ( $p < 0.002$ ).

**Figure 1. Attack Frequency in Individual Patients**



\*Figure reproduced from manuscript.

6.1.a.3 "*A Controlled Trial of Colchicine in Preventing Attacks of Familial Mediterranean Fever*"; Zemer D et al, NEJM, 1974.

Twenty-two patients (18 males and 4 females) diagnosed with FMF were selected to participate the study. One patient had proteinuria which the authors suggested was evidence of amyloidosis. Patients were randomized to receive either colchicine 0.5 mg or placebo tablets twice daily for two months followed by crossover for a second two month period. No concomitant medications were allowed. Patients and physicians were blinded to study medication. Patients were seen monthly in clinic and provided with one-week postcard calendars that were to be mailed weekly after marking in every attack and related symptoms. Attacks with body temperatures  $\geq 38^{\circ}\text{C}$  were counted as "typical" attacks. Attacks with a lower grade fever or those that were inadequately described were considered equivocal and were considered as "half-attacks".

At the end of the study the code was broken and the data arranged according to treatment groups. Since the order of treatment was randomized, the first two months of the study were considered as two independent samples and the statistical significance of the difference between the two treatment groups was determined by use of the unpaired t-test with a correction for lack of homoscedasticity and also with the Mann-Whitney "U" test. The data from the full four month study were analyzed as a crossover study for both counts of patients using the chi-square test and average number of attacks were analyzed using the paired t-test. Differences yielding p values equal to or less than 0.01 were considered to be statistically significant.

Nine of 22 (41%) patients discontinued the study. One patient was withdrawn when it was learned that he was receiving colchicine from an outside source. One patient was noncompliant with follow-up appointments and was discontinued from the study. Seven patients withdrew while on placebo due to attacks.

Table 1 shows the mean number of attacks in patients during the first two-months of the study were lower in colchicine-treated patients compared to placebo-treated patients. The ten colchicine-treated patients reported a total of 11.5 attacks over the two month treatment period with three patients being free of attacks during the time period. Conversely, the five placebo-treated patients reported a total of 25.5 attacks over the same time period.

**Table 1. Number of Attacks During Placebo and Colchicine Treatment**

Study Month	Mean Number of Attacks	
	Colchicine	Placebo
1	0.7	2.5*
2	0.5	2.8*
Total	1.2	5.3*

\*p<0.01

Table 2 shows the number of attacks according to treatment group over the entire four month study. In general, patients had significantly fewer attacks while receiving colchicine therapy compared to when they were receiving placebo. As a group, patients had a total of 19.5 attacks while receiving colchicine compared to 69.5 attacks when receiving placebo. Of note, Patient 18 experienced 2 flares when her colchicine therapy was interrupted due an unrelated hospitalization.

**Figure 1. Attack Frequency in Individual Patients**

Case No.	COLCHICINE		PLACEBO	
	1st mo	2d mo	1st mo	2d mo
1	A	aA	AAA	AAAA
2			AAA	AAA
3	A		aAA	aA
7	A		AA	AA
12		aA	AAAAA	AAAAAA
18, 19*	AAA'A'	A	AA	AA
21			AA	AA
-----				
4	A	A	AA	/
16				/
	PLACEBO		COLCHICINE	
	1st mo	2d mo	1st mo	2d mo
6	aA	AAA	AAAA	
10	AAAAA	AAAA	aA	
15	AA	AAAA		A
14	AA	AaA	A	a
15	a	AA		
-----				
3	AAAA	AA	/	
8	AAa	/		
11	AAAAA	/		
17	AAA	/		
20		/		

\*Cases 9 & 22 excluded (see text); dropouts below dotted line. A = typical attack; a = equivocal attack; / = approximate time of dropout.

\*Attacks occurred with patient off colchicine (see text)

\*Figure reproduced from manuscript.

The literature submitted in this 505(b)(2) NDA is the result of multiple investigations over a long period time rather than as the result of a cohesive clinical development program. This makes integration of the detailed aspects of these studies difficult. Therefore, Sections 6.1.1 through 6.1.7 of this template are addressed by individual study in Section 6.1.a and 6.1.10.

#### 6.1.1 Methods

#### 6.1.2 Demographics

#### 6.1.3 Patient Disposition

#### 6.1.4 Analysis of Primary Endpoint(s)

#### 6.1.5 Analysis of Secondary Endpoints(s)

#### 6.1.6 Other Endpoints

#### 6.1.7 Subpopulations

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

##### 6.1.8.1 Adult Dosing Recommendations

Initially, dosing regimens of colchicine for the treatment of patients with FMF were based on patients' body weights (e.g., 0.5 mg/25 kg); however, this practice soon evolved to dosing patients based on the nearest whole tablet. Depending on the total dose, oral colchicine therapy is typically divided into one to three daily doses to limit its associated gastrointestinal side effects.

The three randomized, placebo-controlled trials used dosing regimens to the nearest whole tablet ranging from a total dose between 1 mg to 1.8 mg of colchicine daily. All dosing regimens were found to be clinically beneficial in reducing acute attacks. In general, the non-randomized, open-label studies followed similar dosing regimens as those described in the three randomized studies; however, two authors reported using higher daily doses with clinical benefit. Peters et al. (Section 6.1.10.1.7) reported that 2 of the patients from his cohort required 2.4 mg daily of colchicine to control symptoms.

Similarly, Ben-Chetrit et al. (Section 6.1.10.1.3) reported that several of their patients required between 2 and 3 mg/day of colchicine to control symptoms, although details were not included in the publication.

The Applicant has proposed a dosing range of colchicine between — mg to 2.4 mg per day for adults and children  $\geq 12$  years of age with FMF. However, the data from both the randomized and non-randomized studies clearly demonstrate the efficacy of colchicine as low as 1 mg/day and that some patients reliably benefited from doses as high as 2.4 mg daily. Consequently, in keeping with dosing to the nearest whole tablet, the Division proposes a dosing range for adults and children  $\geq 12$  years of age (see Section 6.1.8.2) from 1.2 mg to 2.4 mg daily with adjustments in dosing as necessary based on clinical response and adverse effects.

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#### 6.1.8.2 Pediatric Dosing Recommendations

In the non-randomized pediatric trials, colchicine dosing consistently ranged between 0.5 mg to 2 mg per day. There was no single study that provided an ideal analysis demonstrating safe and effective colchicine doses by age group or weight in children. Gedalia et al (Section 6.1.10.2.1) dosed children with colchicine 0.5 mg/15 kg of body weight up to a maximum of 2 mg and reported a clinical benefit. In 1990, Majeed et al. (Section 6.1.10.2.4) initially dosed children with colchicine based on age; children  $\leq 5$  years of age received 0.5 mg/day and children older than 5 years of age received 1 mg/day. The doses were adjusted based on clinical response but the final effective/toxic doses were not reported. However, in 1999, Majeed et al. (Section 6.1.10.2.5) suggested that clinical efficacy was achieved using a similar dosing regimen; children  $\leq 5$  years of age received 0.5 mg/day, children 6 to 10 years of age received 1 mg/day, and children older than 10 received 1.5 mg/day. Ozkaya and Yalcunkaya (Section 6.1.10.2.6) performed an open-label study in an attempt to identify an "ideal" colchicine dosing regimen in children with FMF using either mg/kg of body weight or surface body area calculation. The mean doses were 0.05 mg/kg/day or 1.46 mg/m<sup>2</sup>/day with children younger than 5 years of age requiring higher dosing based on body weight and body surface area compared to older children. However, the authors did not include a comparison group that used the nearest whole (or half) tablet dosing regimen and a true comparison is not possible and somewhat impractical given the difficulty of accurately dispensing fractions of 0.6 mg tablets.

The Applicant has proposed dosing colchicine in children  $\geq 4$  to 6 years of age 0.3 mg to —mg daily and children 6 to 12 years of age — mg/day. Children 12 years of age are to be dosed as an adult. Based on the available data from non-randomized pediatric studies, it appears appropriate to have children  $\leq 6$  years of age initiate therapy at a conservative starting dose of 0.3 mg, which would represent one half of the scored COLSTAT tablet. Several studies started dosing children aged approximately 6 to 12 with colchicine 1 mg daily and demonstrated excellent efficacy. Therefore, a conservative starting dose in this age group would be 0.9 mg daily, which represents one and one-half scored COLSTAT tablets daily. Initial dosing of colchicine at 1.2 mg

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per day for children older than 12 years of age is supported by the results from several of the open-label trials which demonstrated clinically effective doses of colchicine between 1 mg and 1.5 mg per day for this age group (Section 6.1.10.2). Additionally, the study by Ozkaya and Yalcunkaya (Section 6.1.10.2.6) reported clinically effective doses of colchicine for children between 11 and 15 years of age as 0.03 mg/kg  $\pm$  0.01 mg/kg. Based on data from the CDC, the 50 percentile weight for this age group is approximately 45 kg, therefore an effective dose is calculated between 0.9 mg to 1.8 mg daily. Only several pediatric patients required dosing above 1.8 mg daily and none of the trials dosed children above 2 mg daily. Thus, given the lack of evidence that doses above 2 mg/day are effective in young children, I recommend that an upper limit dose of 1.8 mg/day be reflected in the product label. Overall, I recommend the following revision of the proposed dosing regimen to the following dosing regimen for children: children  $\geq$ 4 to 6 years of age 0.3 mg to 1.8 mg daily; children >6 to 12 years of age 0.9 mg to 1.8 mg daily; and children >12 years of age dosed as an adult.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Since patients with FMF experience life-long symptoms, it is important that colchicine maintains its clinical benefit over a long period of time. Indeed, the data from the non-randomized studies demonstrate that patients continue to receive a clinical benefit from daily colchicine greater than 15 years of therapy (Section 6.1.10.1.3). Further evidence of the long-term efficacy of colchicine can be inferred from the publications reporting patients experiencing attacks within days of discontinuing colchicine therapy, even after years of continued compliance, and resolution of attacks following restarting of colchicine therapy (Sections 6.1.a and 6.1.10). Overall, the data suggest that the clinical benefit of colchicine is durable and that tolerance does not develop to the drug.

#### 6.1.10 Additional Efficacy Issues/Analyses: Non-randomized open-label supportive studies

##### 6.1.10.1. Study Synopses of the Non-Randomized, Open-Labeled Studies in Adults

6.1.10.1.1 "*The Treatment of Familial Mediterranean Fever with Colchicine. The Results of Short and Long Term Therapy*"; Barakat MH and Menon NK, J. Kuwait Med Assoc, 1977.

A total of 43 patients (41 males and 2 females) diagnosed with FMF were enrolled to receive open-label colchicine 0.5 mg orally BID for six months. Following the active treatment period, patients were asked to discontinue the colchicine for an additional six months or until the patient experienced three consecutive attacks. The diagnostic criteria for FMF included a history of recurrent fevers lasting 6-72 hours associated with evidence of concurrent serositis. All patients were of Mediterranean/Arab ancestry. Concomitant medications were prohibited. Table 1 shows the baseline demographics of enrolled patients.

**Table 1. Baseline Patient Demographics of Enrolled Patients**

	<b>Range (n=43)</b>	<b>Mean (n=43)</b>
<b>Age (years)</b>	15-49	29
<b>Duration of FMF Diagnosis (years)</b>	5-23	10
<b>Frequency of Attacks (attacks/year)</b>	4-50	16
<b>Duration of Attacks (hours)</b>	6-72	32

All patients completed the initial 12 month study and 32 of the 43 (74%) patients completed a long-term, open-label, follow-up extension study of at least two years.

During the six month active treatment period with colchicine, patients experienced an average of 1 attack/year with each attack lasting an average of 18 hours in duration as compared to an average of 12 attacks/year each lasting 28 hours in duration during the subsequent six month observation period (Table 2).

**Table 2. Number of Attacks During Trial**

	<b>First 6 Months</b> (Colchicine 0.5 mg BID) (n=43)	<b>Second 6 Months</b> (No Active Drug) (n=43)
<b>Total Number of Attacks</b> (attacks/person/year)	1	12
<b>Mean Number of Attacks</b> (attacks/year)	12	97
<b>Length of Attacks</b> (Hours; Range)	6-24	6-48
<b>Length of Attacks</b> (Hours; Mean)	18	28

The clinical efficacy of colchicine was further supported by data from the two-year, open-label extension period which demonstrated that on average patients receiving colchicine experienced approximately 1 attack/year each lasting approximately 22 hours (Table 3).

**Table 3. Number of Attacks During Long-Term Extension Trial**

	<b>Range</b> (n=32)	<b>Mean</b> (n=32)
<b>Follow-up Period</b> (months)	24-42	33
<b>Total Number of Attacks</b> (attacks/year)	0-5	1
<b>Length of Attacks</b> (Hours)	6-48	22

No serious adverse effects were reported.

6.1.10.1.2 *"Familial Mediterranean Fever (Recurrent Hereditary Polyserositis) in Arabs- A Study of 175 Patients and Review of the Literature"*; Barakat, MH, et al., Quarterly Journal of Medicine, 1986.

A total of 175 patients (110 males and 65 females) diagnosed with FMF were enrolled and followed clinically by the authors between May 1974 and October 1985. Diagnosis of FMF was made based on the diagnostic criteria of Heller et al and included a history of recurrent fevers lasting 6-72 hours associated with evidence of concurrent serositis. Each patient was seen at least once during an acute attack and at least twice per year. All patients were of Arab/Jewish/Mediterranean ancestry. Table 1 shows the baseline demographics of the enrolled patients.

**Table 1. Baseline Patient Demographics of Enrolled Patients**

	<b>Range (n=175)</b>	<b>Mean (n=175)</b>
<b>Age (years)</b>	1-70	25
<b>Duration of FMF Diagnosis (years)</b>	0.5-38	12
<b>Frequency of Attacks (attacks/year)</b>	4-50	16
<b>Duration of Attacks (hours)</b>	6-72	32

<b>All Patients' Symptoms (n=175)</b>	<b>Number of Patients with Symptoms (n;%)</b>
<b>Fever</b>	175 (100)
<b>Abdominal Pain</b>	164 (94)
<b>Arthritis</b>	59 (34)
<b>Pleuritic Pain</b>	56 (32)
<b>Skin Lesions</b>	5 (3)
<b>Splenomegaly</b>	5 (3)
<b>Pleural Effusion</b>	3 (2)
<b>Meningitis</b>	1 (1)

A total of 163 of the 175 (93%) patients were treated with open-label colchicine ranging from 0.5 mg to 1.5 mg orally per day. In 150/163 (92%) patients the attacks were described as "well-controlled". In 9/163 (6%) of the patients, the attacks were recurrent but were less frequent and milder in severity. The remaining 4 patients had no appreciable change in symptoms. Adverse effects were not reported.

6.1.10.1.3 *"Colchicine Prophylaxis in Familial Mediterranean Fever: Reappraisal After 15 Years"*; Ben-Chetrit E and Levy M, Semin in Arthritis Rheumatism, 1991.

A total of 53 patients diagnosed with FMF were enrolled in a long-term, open-label colchicine observation study beginning in 1972. Diagnosis of FMF was made on preset clinical criteria that included medical history, ethnic origin, family history, clinical observation, and laboratory workup during at least one acute attack. Following the initiation of colchicine therapy patients were scheduled for visits every 6 months. Eight of the 53 patients were lost to follow-up after five to eight years of treatment and were not included in the analysis although they had similar baseline and disease demographics as the remaining patients in the study. Consequently, the analysis included a total of 45 patients (23 males and 22 females) who were observed for a minimum of 15 years by the authors. Table 1 shows the baseline demographics of the enrolled patients. The frequency and/or duration of acute attacks prior to colchicine therapy were not reported.

**Table 1. Baseline Patient Demographics of Enrolled Patients**

	<b>Range (n=45)</b>	<b>Mean (n=45)</b>
<b>Age (years)</b>	2-67	39
<b>Duration of FMF Diagnosis (years)</b>	16-52	29

All patients were treated with oral colchicine for a minimum of 15 years: 17 patients received 1 mg/day; 17 patients received 1.5 mg/day; and 11 patients received 2 to 3 mg/day. A total of 32 out of 45 (72%) of patients were characterized as "responded well", which was defined as patients experiencing less than one attack every 6 months. Of the 32 patients who responded well, 20 (63%) patients were completely attack-free. Of the remaining 13 patients, 7 (16%)-patients reported experiencing less than one attack every 3 months and 6 (13%) patients responded poorly and experienced one or more acute attacks per month. In most cases, discontinuation of colchicine resulted in relapse of attacks.

Colchicine was reported as well tolerated over the 15 years of the study with adverse effects from colchicine being reported as relatively mild and infrequent. Four patients had nausea and three patients had diarrhea which improved following a dose reduction. One patient had transient leukopenia and one patient had azoospermia, although baseline status of the patient was unknown. Seven children included in the analysis demonstrated normal patterns of growth and development. Three females experienced spontaneous abortions during the trial. Two of the women experienced at least one spontaneous abortion prior to colchicine therapy. At total of 11 women taking colchicine delivered 15 normal babies at term. No malignancies were reported.

6.1.10.1.4 "Long-term Colchicine Prophylaxis in Familial Mediterranean Fever"; Levy M and Eliakim M, Br Med J, 1977.

A total of 47 patients (26 males and 21 females) diagnosed with FMF were enrolled to receive oral colchicine 0.5 mg/25 kg of body weight. Patients ranged in age between 9 and 60 years-old. Prior to colchicine therapy, 21 (45%) patients reported experiencing an acute attack at intervals of less than one month, 20 (43%) patients reported attacks every two to three months, and six (13%) patients reported an attack at intervals longer than three months.

Thirty-five patients received oral colchicine 1 mg/day, seven patients received 0.5 to 0.75 mg/day, and five patients received 1.5 mg/day. Over half of the patients received treatment for at least one year. Forty-six of the 47 (98%) patients experienced complete remission of symptoms. The remaining patient continued to experience acute attacks but described them as milder in intensity. Lack of compliance (eight cases) or an inadequate dosage of colchicine (four patients) resulted in relapse of symptoms. Patients who voluntarily discontinued colchicine after prolonged absence of symptoms had recurrence of attacks within 48 to 72 hours after discontinuation of colchicine.

In general, colchicine was well tolerated and the only adverse reactions reported were mild diarrhea and abdominal pain, which resolved following reduction of the colchicine dose. Five children included in the analysis demonstrated normal patterns of growth and development. The wives of three men treated with colchicine and one woman treated with colchicine delivered normal babies at term.

6.1.10.1.5 "Colchicine for Familial Mediterranean Fever"; Minialawi M, N Engl J Med, 1973.

A total of 22 patients diagnosed with FMF were enrolled in the trial to receive oral colchicine 1 mg/day. All patients experienced at least one attack every three weeks at baseline. A total of 21 out of the 22 (95%) patients had a complete remission of symptoms. Two patients who were non-compliant with their medication experienced an acute attack prior to restarting colchicine.

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6.1.10.1.6 "*Colchicine Therapy for Familial Mediterranean Fever: Experience with 85 Patients*"; Minialawi MS, Hassan A, Hamed MA, J Egypt Med Assoc, 1974.

A total of 85 patients (54 males and 31 females) diagnosed with FMF and treated with colchicine were reported. Diagnosis of FMF was made based on the diagnostic criteria of Heller et al and included a history of symptoms for at least several years, have had at least one witnessed acute attack, and to have had relatively short intervals between acute attacks at the time of entry into the trial.

The study was originally designed as a double-blind, randomized trial; however, during an interim analysis of the initial 22 patients, the data demonstrated an overwhelming clinical benefit in favor of colchicine in reducing FMF attacks. Consequently, the study was converted to an open-labeled trial and an additional 63 patients were enrolled. Twelve pediatric patients received oral colchicine 0.75 mg/day, while patients older than twelve years of age received 1 mg/day. All patients were followed for at least six months.

A total of 84 of the 85 (99%) patients reported a clinical benefit with colchicine therapy as measured by a decrease in attack frequency. One patient reported no reduction in attacks and withdrew from the study after two months of colchicine treatment. Fifty-eight of the 85 patients (68%) reported complete resolution of attacks while on colchicine. Twenty patients in this group who were noncompliant with medication experienced a recurrence of their attacks three to twelve days after discontinuing colchicine. Of the remaining 26 patients who reported a decreased frequency of attacks, twelve patients reported a single attack, four patients reported two attacks, and 8 patients reported three attacks. Two patients reported between eight and ten attacks but noted that the attacks were less frequent than before receiving colchicine. No adverse reactions were reported.

6.1.10.1.7 "Colchicine Use for Familial Mediterranean Fever: Observations Associated with Long-term Treatment", Peters RS, et al., The West J Med, 1983.

A total of 99 patients (56 males and 43 females) diagnosed with FMF and followed at two California hospitals between 1967 and 1978 were enrolled in an open-labeled trial of oral colchicine. Patients ranged in age between four and sixty-four years and were of Arab/Mediterranean ancestry. Indications for receiving colchicine were based on frequent and/or severe attacks that interfered with normal daily living, failure of alternative therapy, and family history of FMF amyloidosis. Oral colchicine 0.5 mg or 0.6 mg BID was initially recommended but subsequently increased to TID for patients older than 16 years of age in 1974. All patients were observed at regular intervals and questioned regarding regimen, symptoms, frequency of attacks, and side effects.

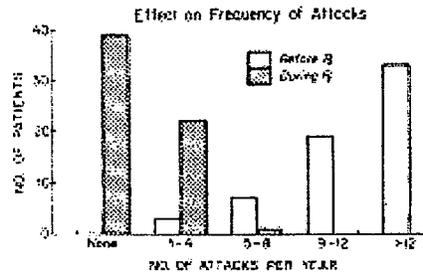
Patient disposition is shown in Table 1. Fourteen of the original 99 patients were not available for analysis due to two FMF-unrelated deaths and twelve patients lost to follow-up. Of the remaining 85 patients, 62 (73%) patients have continued to take colchicine for at least three years and 42 patients have completed at least five years of therapy. At the time of the report, the mean duration of treatment was 76 months (range 36 to 169 months). Of 23 patients who discontinued the study, eight were reported to be apprehensive about the potential side effects of colchicine.

**Table 1. Patient Disposition**

	<b>Number of Patients</b>
<b>Entered Study</b>	99
<b>Study Discontinuation</b>	14
Died	2
Lost to Follow-up	12
<b>Followed Regularly</b>	85
<b>Study Discontinuation</b>	23 (27%)
Noncompliant	8
Therapy withdrawn due to AE	3
No clinical response	12

Of the 62 patients responding to colchicine therapy, maintenance doses were 1.2 mg/day (n=29), 1.8 mg/day (n=31), and 2.4 mg/day (n=2). Sixty-two of the 85 (73%) patients reported a marked clinical improvement as evidenced by a decrease in the frequency and severity of attacks. Thirty-nine of 85 (46%) patients reported no acute attacks over a three year period. Additionally, 22 of the 85 (26%) patients reported experiencing only one to four attacks per year. The decrease in number of attacks is markedly reduced compared to the frequency of attacks prior to colchicine treatment (Figure 1).

**Figure 1. Number of Attacks**



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Overall, colchicine appeared to be well tolerated although almost all patients reported mild, transient diarrhea and abdominal discomfort for one to three days after initiating treatment. One of the three patients who discontinued colchicine treatment due to adverse effects resulted from chronic diarrhea. The other two patients had reported a marked clinical benefit from colchicine but decided to discontinue due to a decreased libido, and voluntary discontinuation due to trying to conceive and fears of potential colchicine-related birth defects.

6.1.10.1.8 "Colchicine in Familial Mediterranean Fever"; Zemer D, et al., N Engl J Med, 1976.

A total of 84 patients diagnosed with FMF were treated with oral colchicine ranging in dose of 1 mg to 2 mg daily for one to three years. Fifty of the 84 (59%) patients reported having no attacks while receiving colchicine. Children included in the analysis demonstrated normal patterns of growth and development. Three male patients fathered normal children while on colchicine. Eight female patients conceived while on colchicine; one female continued colchicine treatment and delivered a healthy baby at term. Of the seven females who discontinued colchicine after pregnancy was detected, three delivered healthy babies to term, three were still continuing a normal pregnancy at the time of the report, and one patient with amyloidosis had a spontaneous abortion during the first trimester.

#### 6.1.10.2 Study Synopses of the Non-Randomized, Open-Labeled Pediatric Studies

##### 6.1.10.2.1 "Familial Mediterranean Fever in Children"; Gedalia A et al., J Rheum, 1992.

A total of 101 pediatric patients (46 males and 56 females) diagnosed with FMF were treated with open-labeled oral colchicine 0.5 mg/15 kg up to a maximum of 2 mg/day. Diagnosis of FMF was made based on the diagnostic criteria of Heller et al and included clinical presentation and ancestry. Ninety-one of the 101 patients (91%) had complete resolution of attacks with colchicine therapy. Seven (7%) patients were noncompliant with therapy but reportedly experienced a partial response. One patient did not respond to colchicine therapy. Treatment duration was not defined.

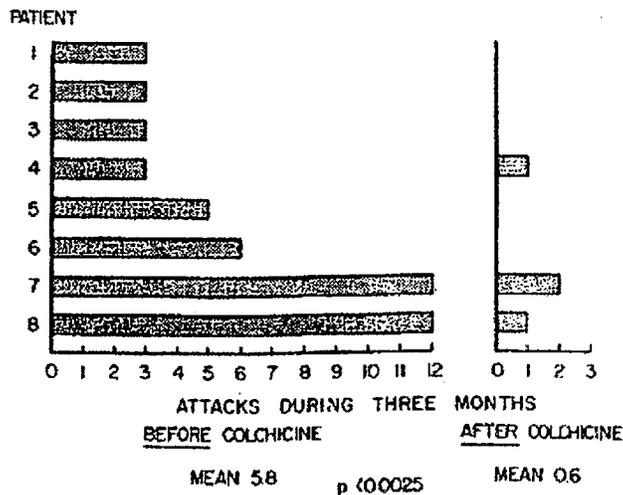
##### 6.1.10.2.2 "Long-term Colchicine Therapy of Familial Mediterranean Fever"; Lehman TJA, et al., J Pediatr, 1978.

A total of 14 pediatric patients (8 males and 6 females) diagnosed with FMF were selected to receive open-labeled oral colchicine. Diagnosis of FMF was made based on the diagnostic criteria of Heller et al and included medical history, ethnic origin, family history, and clinical observation. Patients had a mean age of 12 years (range 3 to 18 years of age) and were selected in part because they experienced frequent severe attacks. The initial dosage of oral colchicine was based on the nearest whole tablet (0.6 mg) equivalent of 1 mg/m<sup>2</sup>; consequently, five patients received 0.6 mg colchicine daily, seven patients received 1.2 mg daily, and two patients received 1.8 mg daily. Colchicine dosage was subsequently increased as necessary to suppress attacks.

The authors reported that five patients receiving 1.2 mg of colchicine daily and three patients receiving 1.8 mg daily experienced suppression of attacks while no attacks were suppressed in patients receiving 0.6 mg of colchicine daily. Nine of the fourteen patients who either reduced their dose of colchicine or discontinued it all together during the observation period experienced a recurrence of attacks but responded clinically following reintroduction or an increased dosage of colchicine.

The authors reported that eight of the patients were maintained on continuous prophylactic colchicine therapy. Figure 1 shows that these patients experienced an average of six attacks (range 3 to 12) over the three months prior to the initiation of colchicine therapy compared to an average of less than one (range 0 to 2) attack over the same time period while on colchicine therapy. Children demonstrated normal patterns of growth and development.

**Figure 1. Number of Attacks Before and After Colchicine**



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6.1.10.2.3 "Familial Mediterranean Fever (recurrent hereditary polyserositis) in Children: analysis of 88 cases"; Majeed HA and Barakat M, Eur J Pediatr, 1989.

A total of 88 pediatric patients (39 males and 49 females) diagnosed with FMF were enrolled and followed clinically by the authors between June 1976 and June 1987. Diagnosis of FMF was made based on the diagnostic criteria of Heller et al and all patients were of Arab ancestry. Patients were seen once every one to six months and more frequently during acute attacks. The mean age of onset of FMF symptoms was 5 years of age (range 4 months to 14 years) and the frequency of attacks ranged between one and forty per year.

A total of 45 children were treated with oral colchicine in a daily dose ranging between 0.5 mg to 1.5 mg over a period of one to three years. Patients reported between twelve and forty attacks per year prior to receiving colchicine therapy. Following initiation of colchicine therapy, 24 (53%) patients reported complete cessation of attacks, thirteen patients reported less than four attacks per year, and five children reported five to eight attacks per year that were milder and of shorter duration compared to attacks prior to colchicine therapy. Three children had no response to colchicine therapy. A proportion of children discontinued colchicine after several months of therapy and had a return of attacks within seven days; however, resolution of attacks occurred following re-initiation of colchicine therapy.

Colchicine was generally well tolerated with mild hair loss in being reported in one child. Children were reported to have normal growth and development over the duration of the study.

6.1.10.2.4 "Long-term Colchicine Prophylaxis in Children with Familial Mediterranean Fever (recurrent hereditary polyserositis)"; Majeed HA and Khuffash FA, J Pediatr, 1990.

A total of 32 pediatric patients (12 males and 20 females) diagnosed with FMF were chosen to receive colchicine with patients younger than five years old receiving 0.5 mg daily and patients older than 5 years of age receiving 1 mg daily. Doses of colchicine were adjusted as needed. Diagnosis of FMF was made based on the diagnostic criteria of Heller et al and all patients were of Arab ancestry. Patients were seen at least once every two months and more frequently during acute attacks. The frequency, duration, and severity of attacks were recorded before and during colchicine treatment.

Table 1 shows that the average number of attacks decreased from approximately 20 attacks per year prior to colchicine therapy to 3 attacks per year while on colchicine therapy. In general, daily doses of colchicine 0.5 mg, 1 mg, and 1.5 mg were effective in preventing acute attacks in children of ages less than seven years, seven to twelve years, and older than twelve years of age, respectively. A number of children discontinued colchicine after several months of therapy and had a return of attacks within seven days; however, resolution of attacks occurred following re-initiation of colchicine therapy.

**Table 1. Number of Attacks Before and After Colchicine**

	<b>Before Colchicine (n=32)</b>	<b>During Colchicine (n=32)</b>
<b>Mean Observation Period (patient years)</b>	3.4	2.4
<b>Total Observation Period (patient years)</b>	109	78
<b>Total Number of Attacks (patient years)</b>	628	104
<b>Mean Frequency of Attacks (patient years)</b>	20	3
<b>Mean Duration of Attacks (hours)</b>	52	4

In general, colchicine therapy was well tolerated. Three patients developed mild diarrhea which resolved with reduction of the colchicine dose.

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6.1.10.2.5 "*Familial Mediterranean Fever in Children: The Expanded Clinical Profile*":  
Majeed HA et al., Q J Med, 1999.

The authors describe their clinical experience from a large cohort of 476 pediatric patients (221 males and 255 females) diagnosed with FMF who were followed at three sites in Jordan from January 1991 through December 1998. Diagnosis of FMF was based on the criteria of Heller et al including short attacks of fever recurring at varying intervals and absence of any causative factor or pathological finding capable of explaining the clinical picture. Colchicine was prescribed to all patients with children younger than 5 years of age receiving 0.5 mg daily, children between 5 and 10 years of age 1 mg daily, and children older than 10 years of age received 1.5 mg daily.

Overall, 96% of patients reported "a favorable response to colchicine". Very few patients required 2 mg of colchicine daily to control attacks. Colchicine was generally well tolerated with several patients reporting diarrhea as an adverse reaction. Two girls developed alopecia that resolved in one patient 4 weeks after discontinuing colchicine therapy. The second child was lost to follow-up.

6.1.10.2.6 "Colchicine Treatment in Children with Familial Mediterranean Fever":  
Ozkaya N and Yalcinkaya F, Clin Rheumat, 2003.

A total of 62 pediatric patients (34 males and 28 females) diagnosed with FMF were enrolled to receive open-label colchicine with the goal of finding an "optimal effective dose". The diagnostic criteria for FMF was based on criteria described by Livneh et al and confirmed with mutation analysis in 49 patients. All patients were seen at least once every two months at which time a medical history was taken and physical exam performed. Table 1 shows the demographics of enrolled patients.

**Table 1. Patient Demographics**

	<b>N=62</b>
<b>Age (mean years <math>\pm</math> SD)</b>	12 $\pm$ 9
<b>Age at Onset of FMF (mean years <math>\pm</math> SD)</b>	4 $\pm$ 3
<b>Age at Initiation of Colchicine Treatment (mean years <math>\pm</math> SD)</b>	8 $\pm$ 4
<b>Mean Duration of Colchicine Treatment (mean years <math>\pm</math> SD)</b>	46 $\pm$ 36

Oral colchicine was initiated at 0.5 mg to 1 mg daily. Two patients under one year of age were started on lesser doses. Sixteen patients had an increase in their dosage of colchicine during the course of the study to a maximum of 2 mg per day. When an "optimal effective dose" was achieved, the dose of colchicine was calculated according to body weight (mg/kg/day) and surface area (mg/m<sup>2</sup>/day) for each patient. The patients were grouped according to their different "optimal effective colchicine dosages". Groups 1, 2, and 3 include patients who received different colchicine doses according to body weight (0.01-0.03, 0.04-0.05, and 0.06-0.08 mg/kg/day, respectively). Groups A, B, and C include patients who received different colchicine doses according to body surface area (0.7-0.9, 1-1.5, and 1.6-2 mg/m<sup>2</sup>/day, respectively).

Table 2 shows the “optimal effective dose” of colchicine for patients based on body weight. All groups demonstrated a reduction of attacks while receiving colchicine therapy as well as decreased acute phase reactants as evidenced by lower serum CRP levels. Similar responses were observed when the data was analyzed based on body surface area (data not shown).

**Table 2. Number of Attacks Before and After Colchicine**

	<b>Group 1</b> 0.01-0.03 mg/kg/day		<b>Group 2</b> 0.04-0.05 mg/kg/day		<b>Group 3</b> ≥0.06 mg/kg/day	
<b>Patients, n (%)</b>	31 (50%)		16 (26%)		15 (24%)	
	<b>Before Rx</b>	<b>After Rx</b>	<b>Before Rx</b>	<b>After Rx</b>	<b>Before Rx</b>	<b>After Rx</b>
<b>Number Attacks/Year</b>	6	1	15	3	24	4
<b>CRP (mg/dL)</b>	2±2	0.1±0.2	9±25	0.4±0.8	6±9	3±7

The authors calculated “mean colchicine dosage” based on age groups (Table 3).

**Table 3. Mean Colchicine Dosage**

<b>Age Groups (years)</b>	<b>Body Weight mg/kg/day</b>	<b>Body Surface Area mg/m<sup>2</sup>/day</b>
<b>&lt;5</b>	0.05±0.02	1.5±0.4
<b>6-11</b>	0.03±0.01	1.2±0.3
<b>11-15</b>	0.03±0.01	0.8±0.2
<b>16-20</b>	0.02±0.01	0.8±0.1

Colchicine was well tolerated by the majority of patients. There were no major side effects except for six (10%) patients with mild diarrhea, five (8%) patients with nausea, and one (2%) patients with transient leukopenia, which improved with reduction of colchicine dose.

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6.1.10.2.7 "Familial Mediterranean Fever in Arab Children: The High Prevalence and Gene Frequency"; Rawashdeh MO and Majeed HA, Eur J Pediatr, 1996.

The authors describe their clinical experience from a large cohort of 192 pediatric patients (86 males and 106 females) diagnosed with FMF who were followed at a hospital in Jordan from April 1991 through March 1994. Diagnosis of FMF was based on the criteria of Heller et al including short attacks of fever recurring at varying intervals; painful sensations in the abdomen, chest, joints or skin accompanying the fever; and absence of any causative factor or pathological finding capable of explaining the clinical picture. Colchicine was prescribed to all patients with children younger than 7 years of age receiving 0.5 mg daily, children between 7 and 13 years of age 1 mg daily, and children older than 13 years of age received 1.5 mg daily.

Colchicine prophylaxis induced a complete cessation of attacks in 129 (67%) patients while 60 (31%) patients reported less frequent, milder, and shorter duration of attacks. Three patients reported no change in symptoms while on colchicine therapy.

Colchicine was well tolerated with the exception of six patients who experienced mild diarrhea which resolved after reduction in the dose of colchicine.

6.1.10.2.8 "Long-term Colchicine Treatment in Children with Familial Mediterranean Fever"; Zemer D, et al, Arthritis and Rheumatism, 1991.

A total of 350 pediatric patients (177 males and 173 females) diagnosed with FMF were enrolled to receive open-label colchicine before reaching 16 years of age. Diagnosis of FMF was made based on clinical symptoms and patient ethnicity. Table 1 shows the age of the children at disease onset and the age at which colchicine therapy was initiated.

**Table 1. Age of Onset of FMF Symptoms and Initiation of Colchicine**

<b>Age Groups (years)</b>	<b>Age at Onset of FMF Symptoms (n; %)</b>	<b>Age of Initiation of Colchicine Therapy (n; %)</b>
<b>≤5</b>	269 (82)	67 (19)
<b>6-10</b>	51 (16)	111(32)
<b>11-15</b>	9 (3)	172 (49)

Oral colchicine was originally initiated at 0.5 mg daily but was observed to be inadequate to control symptoms. Consequently, the dose of colchicine was increased to 1 mg/day and could be increased to 2 mg/day as needed to optimize dosing to control symptoms. At the time of the report, 40% of patients were receiving colchicine 1 mg/day, 25% of patients 1.5 mg/day, and 35% of patients 2 mg/day.

Two hundred and twenty-four (64%) patients had complete remission of attacks and 109 (31%) of patients reported a partial remission of symptoms defined as either a significant decrease in the frequency and severity of all forms of attacks or a remission of one symptom but not all symptoms. Seventeen (5%) patients did not have a noticeable change in their symptoms despite colchicine therapy.

In general, colchicine was well tolerated with the most common adverse reactions being diarrhea and nausea, which were transient and reversible with symptomatic treatment. The authors describe the successful desensitization of patients using increasing doses of colchicine to allow for the continued treatment of four patients with severe diarrhea and three patients who presented with angioneurotic edema, epistaxis, and leukopenia. Children were reported to have normal growth and development over the duration of the study.

Nineteen males from the cohort have fathered healthy children. Thirty-one females from the cohort have experienced 48 pregnancies while continuing to receive colchicine during the pregnancy. Forty-four of the pregnancies have produced healthy full-term infants. Four pregnancies terminated in first trimester spontaneous abortions. No fetal abnormalities were observed.

## 7 Review of Safety

### Safety Summary

Given the nature of this primarily literature-based 505(b)(2) application, there are a number of limitations in the safety data in this submission:

- Since colchicine has been, and is, most commonly prescribed for the treatment of gout the majority of the safety data submitted from the sponsor was obtained from patients with gout and not FMF. However, since the patient population with FMF is generally healthier than patients with gout, the use of safety data from the gout population is acceptable as it is more likely to overestimate the frequency and severity of the adverse effects related to colchicine as they relate to FMF patients.
- The safety data provided by the Applicant are not reported using a standardized coding dictionary such as COSTART or MedDRA. Additionally, since the safety data was not collected from Applicant-initiated clinical trials, the data is not presented in a manner that directly compares the types or incidences of adverse events between an active treatment arm and a placebo treatment arm from a randomized trial.
- One limitation of using the publicly available data is that only the more serious and life-threatening AEs or those resulting in death are likely to be reported to the FDA and WHO databases or published in the literature. Thus, this safety review is likely to be skewed toward the more serious AEs and less so toward common and less severe AEs.

However, on balance, the Applicant has included numerous sources of reliable safety data and categorized these data in a manner that facilitated adequate assessment of the safety of orally administered colchicine. The data submitted for safety analysis in this review are compiled from a thorough review of the scientific literature for oral colchicine, regardless of indication, FDA and WHO postmarketing safety databases, labeling from the US and foreign colchicine products, and six, Applicant-initiated, Phase 1 PK studies.

These data are consistent in supporting the conclusion that orally administered colchicine is generally well tolerated when used in therapeutic doses and adjusted for patients with renal and/or hepatic insufficiency. Gastrointestinal AEs are typically the most common toxicity and when severe can be viewed as the harbinger of more serious colchicine toxicity and allows for discontinuation/dose adjustment to prevent serious toxicity from occurring. Even with long-term treatment, AEs other than gastrointestinal toxicities are uncommon (<15%). The majority of significant AEs that do occur are most often related to inappropriate dosing in patients with renal or hepatic insufficiency, concomitant drug-interactions, or intentional/unintentional overdosing. Serious and life-threatening AEs associated with colchicine include myelosuppression, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, neuromuscular toxicity, and

rhabdomyolysis. An informal study performed by the sponsor did not indicate prolongation of QTc intervals in healthy volunteers administered colchicine.

## 7.1 Methods

### 7.1.1 Clinical Studies Used to Evaluate Safety

Colchicine has been used clinically as a single drug entity for over 70 years and its safety profile has been well-documented over this period of time. Although this is the first NDA for colchicine, it did receive approval as part of the DESI reviews in 1972 as the combination product Col-Benemid (colchicine 0.5 mg and probenecid 500 mg) for use in patients with chronic gouty arthritis. Over 1200 publications were identified during a thorough review of the scientific literature for oral colchicine of which 127 publications were submitted for safety analysis in this review is based on a regardless of indication, FDA and WHO postmarketing safety databases, labeling from the US and foreign colchicine products, and six, Applicant-initiated, Phase 1 PK studies (Table 7). Colchicine has been, and is, most commonly prescribed for the treatment of gout; consequently, the majority of the safety data presented here was obtained from patients with gout and not FMF. However, since the patient population with FMF is generally healthier than patients with gout, the use of safety data from the gout population is acceptable as it is more likely to overestimate the frequency and severity of the adverse effects related to colchicine as they relate to FMF. This review focuses solely on the safety for the oral administration of colchicine since the Applicant is seeking an indication to use oral colchicine for the treatment of patients with FMF

\_\_\_\_\_ Additionally, it is important to note that common and less severe AEs are less likely to be reported to the FDA and WHO databases or published in the literature, rather AEs that are serious and life-threatening or those resulting in death are most likely to be reported. Thus, this safety review is likely to be skewed toward the more serious AEs and less so toward common and less severe AEs.

b(4)

**Table 7, Sources of Safety Data**

Source	Population	N	Data Source / Study Design
Applicant's Pharmacokinetic Studies	Healthy Adults	119	Single- and multiple-dose pharmacokinetic and drug-drug interaction studies (83 subjects single dose/1-day regimen and 43 subjects 10- to 14-day steady state regimen)
<b>Medical Literature</b>			
Efficacy studies in FMF	Adults and children	3545	3 randomized and 21 non-randomized studies contributing efficacy data
Meta-analyses of studies in other indications (Cochrane Reviews)	Randomized, controlled trials	443	11 studies in patients with alcoholic and non-alcoholic cirrhosis (Rambaldi et al., 2005)
		228	11 studies in patients with primary biliary cirrhosis (Gong et al., 2004)
Case reports	--	--	Additional case reports of adverse effects
<b>Postmarketing Safety Data</b>			
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
<b>Labeling</b>			
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

\*adapted from Applicant's submission

7.1.1.1 Applicant-Initiated Studies

A total of 119 healthy volunteers were exposed to at least one dose of colchicine in the Applicant-initiated PK studies. Seventy-nine of the subjects received a single 0.6 mg dose or single day acute regimen of 1.8 mg or 4.8 mg. Forty subjects received 0.6 mg BID for ten to fourteen days. Laboratory evaluations were obtained at screening, study check-in, and at discharge. Vital sign measurements were performed at screening, prior to dosing, and at multiple post-dose intervals. Adverse events were monitored throughout all six studies.

#### 7.1.1.2 Published Scientific Literature

Four comprehensive database searches (Biosis Previews, EMBASE, JICST-Eplus, and MEDLINE) were performed between 2006 and 2008 to identify publications relating to the clinical safety of colchicine. Search terms included colchicine and terms related to adverse event (e.g., safety, adverse effect, adverse reaction, toxic, drug reaction) as well as specific organ system classes (e.g., kidney, renal, bladder, urinary, urethra). For all searches, all titles and abstracts were reviewed for safety information and references or the retrieved publications were examined for information and selected primary sources were obtained as needed. The Applicant included 127 publications out of the more than 1200 publications obtained through the database searches in their analysis of the safety data.

#### 7.1.1.3 Postmarketing Safety Data

The Applicant obtained a complete summary of the marketing experience with colchicine using the Spontaneous Reporting System (ADR Database; 1969 to 1997) and the FDA's Adverse Event Reporting System (AERS Database; 1977 to 2008). Approximately 751 MedWatch reports were obtained in which colchicine was a primary or secondary suspected drug. Additionally, the Applicant obtained reports of AEs for colchicine that were submitted to the WHO, which include both regulatory as well as voluntary reports. A total of 1380 reports were obtained from 79 countries between 1968 and 2006.

#### 7.1.1.4 Labeling

The Applicant has included safety information from the US package insert for the generic combination product, colchicine-probenecid. Additional safety information is provided from 6 foreign labels involving colchicine: Argentina (Xuric), Australia (Colgout; Lengout), France (Colchimax, Colchicine-Opocalcium), Germany (Colchysat), Mexico (Cochiquim), Singapore (Colchicine tablets), Uganda (Goutrnil), and the UK (Colchicine tablets).

#### 7.1.2 Adequacy of Data

The bulk of the safety data in this submission are derived from the published literature and therefore have inherent limitations as discussed above in the safety summary. **However, the literature is a rich source of safety data with regard to colchicine's toxicities and these toxicities have been well described in the long history of its clinical use.** Thus controlled data are not necessary to explore for potential safety signals, as would be important for a new molecular entity, and sufficient information exists to adequately inform the colchicine label. In this submission, the Applicant has provided a comprehensive and well-organized safety section that facilitates the assessment of safety.

### 7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The data presented for the analysis of safety was acquired largely from publications, product labels, and postmarketing safety reports and is not amenable to pooling.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As noted above, the majority of safety data comes from the use of colchicine in patients with gout, a patient population that tends to have a higher incidence of co-morbidities than patients with FMF. Consequently, adverse event reporting in this patient population may overestimate the risk of colchicine compared to use in patients with FMF and thus provides a more conservative analysis.

A total of 119 healthy volunteers were exposed to at least one dose of colchicine in the Applicant-initiated PK studies. Seventy-nine of the subjects received a single 0.6 mg doses or single day acute regimens of 1.8 mg or 4.8 mg. Forty subjects received 0.6 mg BID for ten to fourteen days. Subjects ranged in age between 18 and 50 years, were largely Caucasian (88%), and mostly female (60%). The majority of the data from the published literature comes from the use of colchicine in the treatment of gout but also other less common inflammatory diseases (e.g., FMF, Beçhet's disease) and for the treatment of cirrhosis. The literature encompasses both sexes of all ages (under 1 year to elderly) and a variety of ethnicities.

Although the Applicant was not required to pursue formal QT prolongation studies based on the results of their pre-clinical studies, they did submit data collected from their PK studies that informally studied effect of colchicine on QT prolongation. The results are discussed in Section 7.4.4.

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

### 7.2.2 Explorations for Dose Response

Not applicable to this application.

### 7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this application.

#### 7.2.4 Routine Clinical Testing

Not applicable to this application.

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4, Clinical Pharmacology

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable as colchicine is the only member of its drug class.

### 7.3 Major Safety Results

Orally administered colchicine is generally well tolerated when used in therapeutic doses and adjusted for patients with renal and/or hepatic insufficiency. Therapeutic concentrations of colchicine range from 0.015 to 0.03 mg/kg. Toxicity is noted when given in concentrations greater than 0.1 mg/kg and lethal at doses exceeding 0.8 mg/kg. Gastrointestinal AEs are typically the most common toxicity and when severe can be viewed as a harbinger of more serious colchicine toxicity. Even with long-term treatment, AEs other than gastrointestinal toxicities are uncommon. The majority of significant AEs that do occur are most often related to inappropriate dosing in patients with renal or hepatic insufficiency, concomitant drug-interactions, or intentional/unintentional overdosing.

#### 7.3.1 Deaths

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  $\leq 2$  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 clarithromycin, 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

For purposes of this review, serious adverse events and significant adverse events will be discussed together. Given the different sources used to analyze safety data, discussion of colchicines' adverse events will be organized based on the originating source of data as follows: Applicant-initiated PK studies, Published scientific literature, Postmarketing safety data, and Labeling.

#### 7.3.2.1 Adverse Events from Applicant-Initiated PK Studies

Table 8 shows the AEs reported in at least 2 subjects from the Applicant-initiated PK studies. The most commonly reported AEs among the 119 healthy volunteers exposed to at least one oral dose of colchicine 0.6 mg were diarrhea (18/119 patients; 14%) and nausea and vomiting (10/119 patients; 8%), the majority of which occurred at the high-dose regimen (4.8 mg over 6 hours). None of the AEs required discontinuation from the study or dose reduction. Other AEs reported in 1 subject were abdominal pain, cold sweat, decreased appetite, dry mouth, dyspepsia, epistaxis, flatulence, flushing, muscle spasm, nasal congestion, pharyngeal pain, rash, rhinorrhea, sinus congestion, sinus headache, skin laceration, vessel puncture site hematoma, and vessel puncture site pain.

**Table 8. Adverse Events from Applicant's PK Studies**

MedDRA System Organ Class / Preferred Term	Single Dose		Low Dose	High Dose	Multiple Dose	All Exposure
	Fasted	Fed				
	N=63	N=27	N=13	N=15	37	N=119
<b>General Disorders and Administration Site Conditions</b>						
Cold sweats	0	0	0	0	2 (5%)	2 (< 1%)
Pallor	2 (3%)	0	0	0	0	2 (< 1%)
<b>Gastrointestinal Disorders</b>						
Diarrhoea	0	0	2 (15%)	15 (100%)	6 (16%)	23 (19%)
Hypoaacusis	2 (3%)	0	0	0	0	2 (< 1%)
Nausea	2 (3%)	0	1 (8%)	7 (47%)	3 (8%)	13 (11%)
Stomach discomfort	0	1 (4%)	0	0	4 (11%)	5 (4%)
Vomiting	0	1 (4%)	0	9 (60%)	0	10 (8%)
<b>Musculoskeletal and Connective Tissue Disorders</b>						
Pain in extremity	3 (5%)	0	0	0	0	3 (< 1%)
<b>Nervous System Disorders</b>						
Dizziness	2 (3%)	1 (4%)	0	1 (7%)	1 (3%)	5 (4%)
Headache	5 (8%)	1 (4%)	2 (15%)	1 (7%)	0	9 (8%)
Syncope	2 (3%)	0	0	0	0	2 (< 1%)
<b>Respiratory, thoracic and mediastinal disorders</b>						
Nasopharyngitis	1 (2%)	0 (0%)	0	1 (7%)	0	2 (< 1%)
<b>Eye disorders</b>						
Vision blurred	2 (3%)	0 (0%)	0	0	0	2 (< 1%)

### 7.3.2.2 Adverse Events from Published Scientific Literature

This section will review the AEs by organ system from the published scientific literature obtained through the Applicant's database searches. Many of these reports are the serious toxic manifestations associated with colchicine, e.g., bone marrow suppression, disseminated intravascular coagulation, and cellular injury. Many of these effects have occurred after attempted suicide with very large amounts of colchicine. Overdosing of colchicine is discussed separately in Section 7.6.4.

#### 7.3.2.2.1 Cardiovascular System

No cardiovascular AEs with therapeutic doses of colchicine were identified in the literature search; however, AEs were identified with colchicine overdosing (Section 7.6.4).

### 7.3.2.2.2 Gastrointestinal System

Gastrointestinal effects are the most common side effect in patients receiving colchicine and include abdominal pain, cramping, diarrhea, and vomiting. Generally, these symptoms are mild, transient, and reversible upon discontinuation of the drug or reduction of the dose; however, if the symptoms are severe they may be an indication of more significant toxicity. Table 9 shows the incidence of AEs from two randomized, placebo-controlled, double-blinded studies in patients treated for prevention of acute gout. The incidence of the AEs is similar to that reported in various review articles.

**Table 9. Adverse Events in Two Randomized, Placebo-Controlled Trials for Acute Gout**

	Colchicine	Placebo
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 (5%)
Paulus et al., 1974	0.5 mg t.i.d. × 6 months	
N	20	18
Any AE	15 (75%)	8 (44%)
Gastrointestinal AEs	15 (75%)	8 (44%)
Diarrhea	9 (45%) <sup>4</sup>	6 (33%)
Nausea, vomiting, or anorexia	11 (55%)	5 (28%)
Steadily increasing SGOT / SGPT	1 (5%)	0

Two of the three randomized, placebo-controlled trials of colchicine reviewed in Section 6.1.a for the treatment of FMF did not report AEs. Dinarello et al. (Section 6.1.a.3) only reported that loose stools and frequent bowel movements occurred in several patients which resulted in unblinding of the patients. Severe gastrointestinal AEs associated with overdosing of colchicine are described in Section 7.6.4.

### 7.3.2.2.3 Hepatotoxicity

No serious hepatotoxic AEs with therapeutic doses of colchicine were identified in the literature search. Even with severe colchicine toxicity, hepatotoxicity is an uncommon manifestation and may present as hepatomegaly with liver tenderness and increased transaminases (discussed in Section 7.6.4). One review from the literature search reported elevations in serum transaminases are frequently seen in FMF patients treated with colchicine. It was unclear whether the elevation was caused by liver or muscle toxicity.

### 7.3.2.2.4 Hematologic and Lymphatic System

Myelosuppression is a known dose-related AE associated with colchicine and life-threatening granulocytopenia and/or thrombocytopenia generally occur 24 to 48 hours after an acute overdose. Several published reports of leukopenia 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, although the doses were not adjusted appropriately for the patient's renal and/or liver function.

One publication studied the epidemiology of aplastic anemia in France based on a national registry over an approximate 10-year period in 83 medical centers. Associations between medical conditions, drug use, and aplastic anemia were approximated by using a case-control series for a 3-year period. A significant association was found with any use of colchicine. There was an odds ratio of 13 (95% CI: 1.5-115) compared to controls when the association was limited to use within the year prior to onset of aplastic anemia.

#### 7.3.2.2.4.1 Leukopenia

Three cases of leukopenia were identified and brief narratives appear below. The first case occurred in an otherwise healthy young female being treated with colchicine 1.5 mg/day for two years for FMF with a positive dechallenge and rechallenge. The other two cases involved doses of colchicine that were likely inappropriate given their medical status.

- A 19-year-old female patient with FMF was being treated with colchicine 1.5 gm/day over a two year period when a routine blood count demonstrated a WBC of 2650/mm<sup>3</sup>. The patient discontinued colchicine and had an increase in her WBC; however, after restarting colchicine, her WBC decreased. Further diagnostic evaluation suggested a recent CMV infection and following a recovery period she was rechallenged with colchicine and did not experience any further episodes of leukopenia. Despite treatment with colchicine.
- A 76-year-old female with primary biliary cirrhosis and "adult polycystic liver disease" developed granulocytopenia while being treated with colchicine 1.2 mg/day for 2 months. The patient was also receiving concomitant hydrochlorothiazide/amiloride. During an evaluation she was found to be leukopenic with a WBC of 1500/mm<sup>3</sup> and both medications were discontinued. Four days later her WBC had risen to 5100/mm<sup>3</sup> and her hydrochlorothiazide/amiloride was restarted without a recurrence of the granulocytopenia.
- A 68-year-old male treated with colchicine 0.6 mg BID for 3 years was hospitalized for an attack of acute gout. Upon admission his dose of colchicine was increased to 0.6 mg every four hours and subsequently decreased to 0.6 mg TID on hospital day 2 and further reduced to 0.6 mg QD on hospital day 4 due to diarrhea. Colchicine was discontinued on hospital day 9. The patient also had a medical history significant for diabetes mellitus, COPD, SVT, and cardiomyopathy (EF 38%). Concomitant medications included metformin, glyburide, verapamil (a moderate P-gp inhibitor), warfarin, theophylline, KCl, lisinopril, digoxin (P-gp substrate/inhibitor), metolazone, ASA, lansoprazole (P-

gp inhibitor), various inhalers and a nasal spray. During the four day period his WBC decreased from  $11.2 \times 10^3/\text{mm}^3$  to  $2 \times 10^3/\text{mm}^3$ . He was administered G-CSF on hospital days 9 and 12 with a resulting increase in his WBC to  $18 \times 10^3/\text{mm}^3$ .

#### 7.3.2.2.4.2 Agranulocytosis

A single report was identified of an 86-year-old female with end-stage renal disease who was started on colchicine 0.5 mg/day for gouty arthritis and subsequently developed agranulocytosis. Seven days after starting colchicine the drug was discontinued due to diarrhea. At the start of therapy her WBC was 8700 cells/mm<sup>3</sup> (67% neutrophils) but decreased to 3500 cells/mm<sup>3</sup> by day 7. On day 9 her neutrophil count was <500 cells/mm<sup>3</sup>. A serum colchicine level was found to be 6 µ/L, which is two-times the upper limit of normal. The patient's neutrophil count subsequently returned to normal.

#### 7.3.2.2.4.3 Thrombocytopenia and Leukopenia

A 69-year-old male on no medications was administered intravenous colchicine 4 mg/day for 2 days to treat an attack of acute gout, followed by oral colchicine 2 mg/d for 3 months. After 2 months of therapy the patient was found to have an elevated GGT level and thrombocytopenia ( $<10 \times 10^3/\text{mm}^3$ ). Colchicine was discontinued and his platelet count increased to  $70 \times 10^3/\text{mm}^3$  over the following 2 months. One month later he developed thrombocytopenia again as well as leukopenia. He was treated with corticosteroids and improved; however, a bone marrow biopsy revealed a hypocellular marrow. The patient remained in stable condition.

#### 7.3.2.2.4.4 Pancytopenia

A single report was identified of pancytopenia in a young female patient receiving no other medications but with hepatic and renal insufficiency. The patient was a 46-year-old female treated with colchicine 0.5 mg TID for polyarticular gouty arthritis. Three days after starting colchicine she presented with common signs of colchicine toxicity (abdominal pain, jaundice, moderate sensorimotor polyneuropathy, and alopecia) and was found to have developed pancytopenia with a nadir WBC of  $0.24 \times 10^9/\text{L}$ , Hgb of 8.4 g/dL, and platelet count of  $54 \times 10^3/\text{mm}^3$ . Bone marrow aspirate was consistent with drug-induced marrow suppression. Colchicine was discontinued and the patient received G-CSF and made a full recovery after 7 months.

#### 7.3.2.2.5 Metabolic and Nutritional Disorders

No metabolic or nutritional disorder AEs with therapeutic doses of colchicine was identified in the literature search; however, AEs were identified with colchicine overdosing (Section 7.6.4).

### 7.3.2.2.6 Musculoskeletal System

#### 7.3.2.2.6.1 Neuromuscular Toxicity

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.

Patients with renal impairment and elderly patients, even with normal renal and hepatic function, are at increased risk to develop colchicine-induced neuromuscular toxicity. Concomitant use of statins, fenofibrate, or cyclosporine may potentiate the development of myopathy.

Two reviews were identified that described case series of colchicine-related myopathies.

- Wilbur et al (2004) reviewed 75 published cases of colchicine-induced myopathy (mean age 58 years) and found the mean daily dose of colchicine was 1.4 mg with the duration of therapy ranging from 4 days to 11 years (mean 40 months). The majority of patients with myopathy also had either renal failure or had undergone renal transplant and had been taking standard doses of colchicine. In numerous cases, colchicine toxicity presented after short-term use of increased doses or after a recent change in the underlying disease state (e.g., organ transplant, decreased renal function).
- Wallace et al (1991) reported 17 consecutive patients with gout who had neuromyotoxicity. The patients averaged 66-years of age and all had at least a moderate degree of renal impairment. Serum creatinine was significantly higher in these 17 patients compared to 15 matched colchicine-treated patients from the same practice without myotoxicity.

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.

#### 7.3.2.2.6.2 Rhabdomyolysis

The literature search identified several cases of colchicine-associated rhabdomyolysis. One publication reported on 475 patients hospitalized for rhabdomyolysis. Of these, 8 cases attributed to colchicine therapy, although details of the cases were not reported.

A second publication was a case report describing rhabdomyolysis in a 24-year-old female with FMF and severe renal impairment due to secondary amyloidosis. She had been taking colchicine 1 mg QD for 1 year and prior to her hospital admission had developed gastrointestinal symptoms and proximal muscle weakness in both legs. She was found to have an elevated CK (100 U/L) and marked myoglobinuria (1600 µg/L) as well as renal failure. Following supportive treatment and reduction of the colchicine dose to 0.5 mg QD she recovered to her baseline health status.

#### 7.3.2.2.7 Nervous System

A proportion of patients who develop colchicine-induced myopathy also experience a mild sensory polyneuropathy with distal areflexia and a minor distal sensory loss. The neuropathy typically improves following discontinuation of colchicine.

#### 7.3.2.2.8 Respiratory System

No respiratory AEs with therapeutic doses of colchicine were identified in the literature search; however, AEs were identified with colchicine overdosing (Section 7.6.4).

#### 7.3.2.2.9 Skin and Appendages

The literature search identified several reports of rash associated with colchicine. These included a maculopapular rash occurring on the lower extremities, a single reported case of colchicine-induced toxic-epidermal-necrosis-like syndrome complicated by concomitant administration of allopurinol, and a single case of vascular purpura in a 33-year-old male. Alopecia is clearly associated with colchicine overdose but has also been described with chronic colchicine use in children with FMF. Two publications reported a total of 3 children with FMF who developed alopecia.

#### 7.3.2.2.10 Urologic System

The literature search identified one publication that reported two cases of Peyronie's disease while receiving chronic colchicine therapy for FMF; however, the clinical significance of these cases are unclear.

#### 7.3.2.3 Postmarketing Safety Data

The most common AEs associated with colchicine as reported to the FDA's ADR and AERS data bases are shown in Table 10. Data from the ADR database demonstrates

that diarrhea, myopathy, and pancytopenia were the most commonly reported AEs prior to 1997, and using the AERS database showed that diarrhea, drug interactions, vomiting, acute renal failure, and nausea have been the most common events since 1997. Individual cases were not reviewed further.

**Table 10. Adverse Events reported from the FDA's ADR and AERS 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		

The most common AEs associated with colchicine treatment were obtained from the WHO database and included diarrhea, vomiting and nausea (Table 11). Individual cases were not reviewed further.

**Table 11. 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

#### 7.3.2.4 Labeling

The FDA approved label for Col-probenecid (Watson Labs; ANDA 84-279) lists nausea, vomiting, abdominal pain, diarrhea, aplastic, anemia, agranulocytosis, peripheral neuritis, muscular weakness dermatitis, purpura, and alopecia as AEs of the product and notes that the adverse effects due to colchicine appear to be a function of the dose.

Review of the labels for colchicine from foreign countries included the following AEs: gastrointestinal disturbances (nausea, diarrhea, vomiting, abdominal pain) and skin disturbances (skin irritation, morbilliform rash, purpura, alopecia, urticaria), dizziness, kidney disturbances, low blood pressure, hypersensitivity reaction, and azoospermia.

### 7.3.3 Dropouts and/or Discontinuations

Not applicable to this application.

### 7.3.4 Significant Adverse Events

Refer to Section 7.3.2

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Refer to Section 7.3.2

### 7.4.2 Laboratory Findings

Given the different sources used to analyze safety data, discussion of changes of laboratory findings associated with colchicine will be organized based on the origination source as follows: Applicant-initiated PK studies, Published scientific literature, Postmarketing safety data, and Labeling.

#### 7.4.2.1 Laboratory Findings from Applicant-Initiated PK Studies

Post-dose laboratory results were obtained from 108 healthy volunteers from the Applicant-initiated PK studies. Eighty-two of the subjects had received a single dose of colchicine 0.6 mg or a single-day regimen of colchicine 1.8 mg or 4.8 mg and 26 subjects had received a 10 to 14 day course of colchicine 0.6 mg BID. Overall, there were no clinically significant changes in blood chemistry or hematologic laboratory values; however, 25 of 108 (23%) subjects demonstrated neutrophil values below the normal laboratory range (50% neutrophils or  $2.3 \times 10^3$  cells/ $\mu$ L). There were no trends with respect to red blood cells or platelets. A total of 6 out of 108 (6%) patients with post-dose laboratories demonstrated abnormal liver function studies which were reported as elevated ALT (n=1), elevated AST (n=2), or elevated bilirubin (n=3). None of the increases exceed two-fold the upper limit of normal. These abnormalities were not reported to have resulted in clinical adverse events.

#### 7.4.2.2 Published Scientific Literature

Myelosuppression is a known dose-related AE associated with colchicine and life-threatening granulocytopenia and/or thrombocytopenia generally occur 24 to 48 hours after an acute overdose. As discussed above, published reports were identified that described cases of leukopenia and granulocytopenia, and one case each of

thrombocytopenia, pancytopenia, and aplastic anemia for therapeutic doses of colchicine. Although abnormal serum chemistry values during AEs or toxic exposures have been reported, in general clinically significant serum chemistry values have not been reported with therapeutic doses of colchicine.

#### 7.4.2.3 Postmarketing Safety Data

The most common abnormal laboratory tests reported in at least 10 patients obtained from the ARD database were pancytopenia, increased CK concentrations, and abnormal liver function tests while data from the AERS database were reported as elevated blood creatinine, increased blood CK concentrations, and pancytopenia. Individual cases were not reviewed.

The most common abnormal laboratory tests reported from the WHO database were thrombocytopenia, leukopenia, and increased blood CK concentrations. Individual cases were not reviewed.

#### 7.4.2.4 Labeling

The FDA approved label for Col-probenecid (Watson Labs; ANDA 84-279) does not list any AEs related to the effects of colchicine on laboratory test parameters other than reporting agranulocytosis and aplastic anemia.

Review of the labels for colchicine from foreign countries included the following reported laboratory abnormalities: thrombocytopenia, leukopenia, neutropenia, agranulocytosis, aplastic anemia, rare disturbances in hematopoiesis, hemolytic anemia, increased ALT and AST.

#### 7.4.3 Vital Signs

There were no clinically meaningful changes in vital signs observed in the Applicant-initiated PK studies. Similarly, no publications were identified from the scientific literature search regarding colchicine-related changes to patient vital signs. Only fever, hypotension, and tachycardia were reported as abnormal vital signs in greater than 5 patients using the ARD, AERS, and WHO databases. There was no information regarding abnormal vital signs contained in the US or foreign drug labels.

#### 7.4.4 Electrocardiograms (ECGs)

Although the Applicant was not required to pursue formal QT prolongation studies based on the the known toxicity profile of colchicine and the results of their pre-clinical studies (see Pharm/Tox review), they did submit data collected from their PK studies including an informal QT study which used moxifloxacin-treated patients as a positive control for QTc prolongation. Due to the narrow therapeutic index of colchicine, it was decided as unethical to administer supra-therapeutic doses of colchicine to healthy

volunteers. Therefore, the study was conducted in patients who had received the highest single-day dosing regimen of colchicine. The study was a randomized, double-blind, double-dummy PK study and exploratory ECG safety study using a standard acute gout colchicine regimen (total dose 4.8 mg over 6 hours). Subjects were randomized to receive colchicine (n=15) or moxifloxacin (n=3). A 12-lead ECG was obtained at screening and subjects were subsequently monitored for 24 hours using a continuous Holter monitor with triplicate ECG recordings obtained from a 5-minute observation period 30 minutes prior to the first dose and at post-dose study hours 1, 3, 6, 7, 8, 10, 12 and 23. There was little change in QT interval regardless of correction by use of Fridericia (QTcF) or Bazett's (ATcB) correction factors. For colchicine treated subjects, the upper bounds of the CI did not reach the 10 msec level for QTcF and at hour 23, the bounds for QTcB minimally exceeded the referenced level with a mean of 4.29 msec and an upper bound of 10.19 msec. Moxifloxacin response was lower than expected and the time course was not consistent with the typical findings. The dQTcB and dQTcF values were lower at all time points compared to the moxifloxacin treatment arm. Overall there appeared to be no effect on QTc or any other ECG parameter.

#### 7.4.5 Special Safety Studies

Not applicable for this application.

#### 7.4.6 Immunogenicity

Not applicable for this application.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

Not applicable for this application.

#### 7.5.2 Time Dependency for Adverse Events

Not applicable for this application.

### 7.5.3 Drug-Demographic Interactions

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.

### 7.5.4 Drug-Disease Interactions

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 colchicine in patients with creatinine clearance <10 mL/min. As discussed in Section 7.3.2, 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

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 12 shows established and other potentially significant drug interactions based on drug class and mechanism of actions. Specific cases found from the literature are discussed below.

**Table 12. 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	Simvastatin 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

7.5.5.1 Grapefruit Juice

A case of near fatal acute colchicine toxicity was reported in an 8-year-old female with FMF who had been receiving treatment with colchicine 2 mg/d. Two-months prior to hospitalization she began drinking a liter of grapefruit juice daily. Although conflicting results have been published regarding the effect of grapefruit juice on P-gp, it has been shown to selectively inhibit the organic anion transporter polypeptide (OATP) which is expressed in many of the same tissues as P-gp.

#### 7.5.5.2 Cyclosporine

Cyclosporine has been demonstrated to inhibit both P-gp and CYP3A4 in humans. The Applicant identified a case report describing 4 men with FMF treated who had undergone renal transplantation and were receiving chronic colchicine therapy. After years of stable renal graft function the patients were being converted from azathioprine to cyclosporine. Cyclosporine was slowly added to the stable azathioprine/prednisone regimen and colchicine; however, before reaching therapeutic levels of cyclosporine the patients developed diarrhea (n=4), elevated LDH levels (n=4), increases in ALT (n=3), hyperbilirubinemia (n=3), and elevated serum creatinine (n=2). One patient was hospitalized for muscle weakness and severe myalgia. Signs and symptoms quickly resolved following discontinuation of colchicine. This case most likely represents a combination of cyclosporine and colchicine toxicity as a result of their interaction with CYP3A4 and P-gp.

Eleven cases of patients treated with colchicine who received concomitant cyclosporine and developed neuromyopathy (n=10) or hepatitis (n=1). All but one of the patients were transplant recipients with significant co-morbidities and were receiving colchicine for gout.

#### 7.5.5.3 Macrolide Antibiotics

The Applicant's literature search identified several published reports of fatal and non-fatal drug interactions between colchicine and clarithromycin. There was one non-fatal case involving erythromycin and no reports with azithromycin. Clarithromycin and erythromycin are recognized inhibitors of CYP3A4 and P-gp, an effect which is potentiated when administered to patients with impaired renal function. Further details describing the parameters of the interaction between clarithromycin and colchicine were investigated in an Applicant-initiated PK study and discussed in Dr. Nallani's Clinical Pharmacology Review (Section 4.4).

#### 7.5.5.4 Lipid Lowering Agents

Published reports of patients developing myopathy or rhabdomyolysis while on concomitant lipid-lowering drugs were identified in the Applicant's search of the literature. Nine cases of myotoxicity that were associated with the concomitant use of

HMG Co A reductase inhibitors and colchicine were identified. Three of the cases, one which was fatal, involved patients who were on stable doses of colchicine and developed rhabdomyolysis within 1 month of starting atorvastatin or simvastatin. Five of the nine patients had been on stable doses of HMG Co A reductase inhibitors (simvastatin (n=3), pravastatin (n=1), and fluvastatin (n=1)) and developed myotoxicity (n=3) or rhabdomyolysis (n=2) within one month of starting therapeutic doses of colchicine (1.3 to 3 mg/day). The Applicant's literature search also identified one case each of myalgia, neuromyopathy, and rhabdomyolysis after short-term concomitant use with gemfibrozil, fenofibrate, and bezafibrate, respectively.

#### 7.5.5.5 Calcium Channel Antagonists (Verapamil and Diltiazem)

Verapamil and diltiazem are well-known of CYP3A4 and P-gp inhibitors. A case of flaccid tetraparesis was reported in an elderly patient on stable long-term treatment with verapamil who was administered short term colchicine therapy. Two cases of rhabdomyolysis were reported in two patients taking concomitant verapamil (n=1) or diltiazem (n=1) who were administered colchicine. Given that verapamil and diltiazem are known inhibitors of CYP3A4 and P-gp the AE are likely related to a drug interaction between the calcium channel blockers and colchicine.

#### 7.5.5.6 Digoxin

Although not attributed directly to a drug interaction, three publications were identified that involved cases of rhabdomyolysis in association with colchicine. Since digoxin is a P-gp substrate, it is possible that the concomitant administration of digoxin could interfere with the metabolism of colchicine.

#### 7.5.5.7 Other Drugs

Several publications were identified that did not directly implicate a drug interaction with colchicine but were listed as concomitant medications. These drugs include fluindione and digoxin or furosemide, tolbutamide and vinblastine/vincristine, and proton-pump inhibitors. Given these drugs interaction with CYP3A4 or P-gp suggest a drug interaction is at the least possible.

### 7.6 Additional Safety Explorations

#### 7.6.1 Human Carcinogenicity

No reports of malignancies were identified in the data submitted by the Applicant.

## 7.6.2 Human Reproduction and Pregnancy Data

The Applicant is proposing colchicine be labeled as an FDA Category C based on animal reproduction studies demonstrating adverse effects on the fetus but in the absence of adequate and well-controlled studies in humans.

In 1968, a report of trisomy 21 in 2 children born to patients on chronic colchicine therapy was published. One year later the findings of this study were disputed because the cases of trisomy 21 could have occurred due to chance alone. Regardless, in the early 1970's women with FMF were counseled to discontinue colchicine 3 months prior to conception and during pregnancy. Subsequent reports in the literature have suggested that colchicine is safe during pregnancy or at least less harmful than attacks of FMF. One study followed 116 women with FMF who had 225 pregnancies (Rabinovitch O, et al, Am J Repro Immunol, 1992). The women were divided into three groups: colchicine taken throughout pregnancy (n=91), colchicine taken at time of conception and discontinued during the first trimester (n=40), and pregnancy occurred before colchicine therapy was introduced (n=94), which served as the control arm. Spontaneous abortions occurred in 12% of women treated with colchicine compared to 20% of untreated patients. The increased rate of spontaneous abortions in the untreated patients was believed to be due to increased attacks of FMF. Trisomy 21 was observed in 2 children of 131 pregnancies in the colchicine group and thought to be due to chance. Overall the authors concluded there was no increase in fetal abnormalities, growth disturbances or other developmental abnormalities in 130 children of mothers treated with colchicine.

An additional publication was identified that retrospectively reviewed patients of childbearing age with gout who conceived children while taking colchicine for 5 to 20 years (Yu TF, Semin Arthritis Rheum, 1982). No cases of teratogenicity were reported. Additionally, no increases in chromosomal abnormalities were reported in 326 couples with FMF in which one partner was receiving colchicine.

### 7.6.2.2 Lactation

No publications, postmarketing reports, or inclusion of data from US or foreign labels of AEs were identified in breast-feeding infants of mothers treated with colchicine.

### 7.6.2.3 Fertility

No well controlled trials have been conducted to assess the effect of colchicine on male and female fertility. However, in several case series reported in the literature, colchicine dose not appear to adversely affect either male or female fertility.

### 7.6.3 Pediatrics and Effect on Growth

Two retrospective studies were identified that reviewed the long-term safety and efficacy of colchicine in children with FMF and concluded that growth of these children were normal. Study synopses of these studies, Zemer et al (1991) and Ben Chetrit et al (1991) are reviewed in Section 6.1.10.2.

A prospective study performed in 2001 compared the growth and insulin-like growth factor-1 (IGF-1) levels of prepubertal children with FMF treated with colchicine compared to healthy controls. Forty-two healthy children and 51 children with FMF were enrolled in the study and the variable included standing height, height velocity over 6 months, height standard deviation scores, and target height. Skeletal ages were determined according to the Greulich-Pyle Atlas and compared with sex- and age-matched standard deviation tables. Overall, there was no statistical difference between age, BMI, height standard deviation scores, target height standard deviation scores, or bone age in children with FMF versus healthy controls.

Overall, colchicine does not appear to affect the growth or development of children with FMF.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Colchicine is generally well-tolerated at normal therapeutic doses with the most common side effects being related to gastrointestinal symptoms, e.g., diarrhea, nausea and vomiting. Although colchicine has a narrow therapeutic index, oral administration generally limits the majority of patients from achieving toxic serum levels since the gastrointestinal adverse effects become rather severe. Severe toxicities were common with intravenously administered colchicine as therapeutic doses could be exceeded without the patient experiencing the typical side effects seen with orally administered colchicine; however, the intravenous formulation of colchicine has been recently pulled from the market. Currently, when toxic levels of colchicine are reached it generally occurs as a result of a drug interaction or an accidental/intentional overdosing, often with life-threatening.

The specific dose of colchicine that produces significant toxicity is unknown as fatalities have occurred after ingestion of a dose as small as 7 mg over a four day period while other patients have survived after ingestion more than 60 mg. A retrospective study of 150 patients who overdosed on colchicine reported that patients who ingested <0.5 mg/kg survived and tended to have mild gastrointestinal symptoms, those patients who ingested between 0.5 to 0.8 mg/kg experience more severe AEs, and those patients ingesting >0.8 mg/kg had a one-hundred percent mortality.

Ben-Chetrit and Levy (1998) proposed dividing the manifestations of colchicine toxicity into three sequential overlapping stages as outlined in Table 13. Stage 1 starts within 24 hours of ingestion and includes gastrointestinal symptoms. Stage 2 begins 24 to 72

hours after drug ingestion and is accompanied by life-threatening complications due to multi-organ failure and death. Survival through Stage 2 is followed by recovery which is manifested by alopecia, rebound leukocytosis, and recovery from multi-organ failure.

**Table 13. Clinical Stages of Colchicine Overdose**

Stage 1	Stage 2	Recovery
Abdominal pain	Renal failure	Leukocytosis
Nausea	Respiratory failure	Alopecia
Vomiting	Cardiac failure	
Diarrhea	Pancytopenia	
Dehydration	Metabolic Acidosis	
	Electrolyte disturbances	
	DIC	
	Convulsions	
	Coma	

Putterman et al (1991) published a summary of the toxic effects of colchicine on the different body systems in which the authors concluded that the most common cause of death from colchicine overdose is cardiovascular collapse, which is manifested by cardiogenic shock. Respiratory involvement occurs in approximately 33% of colchicine overdoses with increasing respiratory distress leading to hypoxemic respiratory failure. Hematologic manifestations occur in all three stages of colchicine overdosing. In Stage 1, patients may have leukocytosis but during the second stage bone marrow hypoplasia and coagulation abnormalities including diffuse intravascular coagulation are evident. Marrow recovery typically begins around day 8 post-ingestion and is manifested by a rebound leukocytosis. Neurologic involvement includes mental status changes, transverse myelitis, ascending paralysis, and seizures. Renal complications associated with colchicine overdose include azotemia, proteinuria, and hematuria, all of which may progress to acute renal failure. Rhabdomyolysis may occur with colchicine overdoses and this may also contribute to renal failure. Liver damage is an uncommon manifestation of colchicine toxicity but hepatomegaly with liver tenderness and elevated transaminases may be evident. Fever has also been reported and may occur due as a direct drug effect or perhaps as a sign of infection following the onset of leukopenia. Alopecia is well-documented in colchicine overdoses and most cases are reversible after drug discontinuation. Dermatological manifestations are rare but may include toxic epidermal necrosis.

Treatment of acute colchicine overdose includes aggressive bowel decontamination with gastric lavage and administration of activated charcoal as soon as possible. Hemodialysis is ineffective due to the extensive volume of distribution of colchicine.

## 8 Postmarketing Experience

Postmarketing data is discussed in the Safety Review (Section 7).

## 9 Appendices

### 9.1 Literature Review/References

No references were appended in this review.

### 9.2 Labeling Recommendations

1. Amend the clinical indication of colchicine to only the \_\_\_\_\_ in adults and children  $\geq 4$  years of age with FMF.
2. Amend the recommended dosing as follows:
  - Adults & Children  $>12$  yo: 1.2 -2.4 mg QD
  - Children 6-12 yo: 0.9-1.8 mg QD
  - Children  $\geq 4$  yo-6: 0.3-1.8 mg QD
3. Emphasis on drug-interactions and dosing in patients with renal and/or hepatic impairment.

**b(4)**

### 9.3 Advisory Committee Meeting

No Advisory Committee Meeting was conducted for this application.

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this page is the manifestation of the electronic signature.**

/s/

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Keith Hull  
11/30/2008 10:13:51 AM  
MEDICAL OFFICER

Sarah Okada  
12/1/2008 09:39:05 AM  
MEDICAL OFFICER  
I concur. Refer to my separate secondary review memo  
for details.