

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-352

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 30, 2008
From	Sarah Okada, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22-352
Supplement#	
Applicant	Mutual Pharmaceuticals
Date of Submission	June 20, 2008
PDUFA Goal Date	December 19, 2008
Proprietary Name / Established (USAN) names	Colstat™ / Colchicine
Dosage forms / Strength	Tablet / 0.6 mg
Proposed Indication(s)	1. _____ Familial Mediterranean Fever (FMF) 2. _____
Recommended:	<i>Approval for _____ of FMF, with revisions to proposed labeling</i>

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1. Introduction

Colchicine, an alkaloid originally derived from the autumn crocus, *Colchicum autumnale*, has a long history of medicinal use, dating back to its first use as a purgative agent in ancient Greece, more than 2000 years ago. Its first use as a selective treatment for gout is attributed to the Byzantine physician Alexander of Tralles in 6 A.D. Historically, the primary clinical uses of colchicine have been along these same lines: as a laxative and for the treatment of "rheumatism;" more specifically, gout.

In the United States, use of colchicine as a purified, single, active ingredient dates back prior to 1938, and is likely to have been prior to 1908 (USP DI Volume III). However, colchicine has thus far only been approved by the FDA as part of combination with probenecid for the chronic treatment of gout (ColBenemid—colchicine 0.5 mg/probenecid 500 mg). ColBenemid was initially approved in 1961 and underwent DESI review (FR Vol.37, No.146, 28 July 1972) which deemed the combination effective for "chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout." Thus, remarkably, although colchicine as a stand-alone product is available from multiple sources and is widely used for Familial Mediterranean Fever (FMF) and gout, it remains an unapproved marketed product.

The subject of this first NDA submission for colchicine as a single ingredient is as a _____ treatment for _____ of FMF. Use of colchicine for FMF dates back to the early 1970's when gastroenterologist Stephen Goldfinger noted that his

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FMF patients who were begun on daily colchicine had a significant reduction in their FMF attacks. Goldfinger's observations were quickly confirmed in 3 small randomized controlled trials which serve as the basis for this 505(b)(2) NDA. Results from these trials and personal/clinical experience with colchicine in the treatment of FMF led to rapid and wide acceptance of colchicine as the standard of care treatment in this disorder, despite the limited controlled trial data. Whether these data and the uncontrolled clinical experience of these 30-plus years are sufficient to provide the substantial evidence necessary for approval is the crux of the issue.

2. Background

Familial Mediterranean Fever (FMF):

FMF is an autosomal recessive condition affecting more than 100,000 people world-wide, with a predominance in non-Ashkenazi Jews, Arabs, Turks, and Armenians; i.e., populations with origins in the Mediterranean region. FMF is the most common of the hereditary periodic fevers, and is clinically characterized by recurrent episodes of fever and polyserositis. Febrile episodes in FMF may begin even in early infancy; 90% of patients have had their first attack by age 20. Typical FMF attacks begin suddenly and generally last 24-72 h, with arthritic attacks tending to last somewhat longer. In some patients the episodes occur with great regularity, but frequency of attacks may vary over time, ranging from as often as once every few days to remissions lasting several years. Attacks are often unpredictable, although some patients may regularly experience prodromal symptoms (primarily constitutional); pregnancy may be associated with remission.

Abdominal pain due to inflammation of the serosa is the most common presenting feature, and eventually affects 95% of patients. Episodes may include acute inflammatory mono- or oligo-arthritis which in rare cases may become protracted but does not typically result in joint destruction. Attacks may include pleuritis (up to 30% of patients) and erysipeloid erythema (up to 40% of patients)—a shiny, erythematous plaque occurring on the dorsum of the foot, ankle, and/or lower leg. Fever up to 40°C commonly accompanies the attacks. Other reported manifestations include pericarditis, myalgia, and splenomegaly. Secondary amyloidosis due to chronic uncontrolled inflammation was not uncommon prior to the advent of colchicine use in the disorder. Historically, up to 60-75% of FMF patients over the age of 40 were affected, and end-organ dysfunction (i.e. renal failure) was the major cause of premature mortality in these individuals. More recent work suggests specific ethnic predisposition toward amyloidosis due to certain mutations (i.e. M694V mutation in North African Jews, Armenians, and Turks).

The genetic mutation and resultant pathophysiology has only been elucidated over the last 16 years, beginning with the identification of the mutation in the MEFV gene (which encodes the protein pyrin) in 1992. The precise function of pyrin has not been well-defined, but data indicate an important role for pyrin in the regulation of caspase-1 and IL-1 activation that may be context dependent. Why the mutation results primarily in serosal inflammation has not been elucidated. The mechanism by which colchicine may exert salutary effects is also not clear; some evidence exists to support its interference with neutrophil migration and localization, and colchicine may also inhibit a postulated pathway by which the N-terminal fragment of pyrin activates NFκ-B [Chae 2008].

Unique considerations for colchicine in FMF:

Prior to the use of colchicine for FMF, no effective treatments for FMF existed. At present, it remains the only widely accepted efficacious treatment, and patients are almost uniformly treated with colchicine from the time of diagnosis. By current estimates, 60% of FMF patients achieve a complete response with colchicine (no attacks) and another 30% achieve significant reductions in attack severity and frequency. Approximately 10% of patients are considered "colchicine-resistant." Colchicine-resistant patients are often tried on TNF inhibitor or IL-1 inhibitor therapies, but thus far response has not been studied systematically, and the high cost/potential risk of these biologic treatments has limited their use. Therefore continued availability of colchicine for the treatment of FMF would be considered extremely important by the medical community treating these patients. Additional randomized controlled studies would be impractical due to patients' reluctance to discontinue, even temporarily, a treatment that they have personally experienced to be effective. Active-control trials are not feasible because there is no proven comparator that could serve as the active-control. These factors were taken into consideration by the Division when the applicant first approached the Agency regarding expectations for additional studies of colchicine in this indication.

Because FMF usually begins in childhood, a significant proportion of patients on colchicine for this disorder are children and adolescents. The only randomized-controlled trials have been adults, necessitating ad hoc dose-finding for clinicians treating pediatric FMF patients early on. Since FMF is an orphan indication, this NDA is not subject to the requirements of the Pediatric Research and Equity Act (PREA). However for the reasons described above, the situation also necessitates continued availability of colchicine for children with FMF and also makes a controlled trial impractical. Fortunately, in the 30-plus years that colchicine has been the standard of care for FMF, the cumulative experience, while not controlled, does allow for well-substantiated conclusions regarding the range of doses for children with an acceptable benefit:risk profile for inclusion into labeling.

Regulatory history:

1. Pre-IND meeting 31 July 2006: to discuss the requirements for development and approval of colchicine tablets USP, 0.6 mg, for the _____ treatment of acute attacks of gout and Familial Mediterranean Fever. At that time, the Division advised the applicant that the published literature and a single controlled clinical trial in acute gout could be sufficient for filing of NDA's for gout and FMF. Other items of discussion included the applicant's proposed nonclinical program (adequacy of literature, cardiovascular safety study) and biopharmaceutics/clinical pharmacology studies (pharmacokinetic, QT evaluations, and drug-drug interaction studies).
2. IND submitted on 9 February 2007 and allowed to proceed on 14 March 2007 (FMF was not its focus although the pharmacokinetics studies performed under the IND serve to support the FMF indication).
3. Based on the rarity of FMF in the U.S. (estimated to be less than 5000 patients), the applicant requested and received orphan designation for this indication, which was granted on September 25, 2007 (ODD 07-2458).
4. A second meeting with the Division (pre-NDA) was requested on 3 October 2007 and a briefing package in support of the meeting was submitted on 21 December 2007.

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The Division responded to all questions posed in the briefing package *via* email on 1 February 2008. As the Division's responses did not require extensive clarifications, the pre-NDA meeting, originally scheduled for 4 February 2008, was deemed unnecessary by the applicant and was, therefore, canceled. The applicant sought confirmation that a thorough review of the publicly available information would be sufficient for NDA submission for colchicine in FMF; the Division concurred.

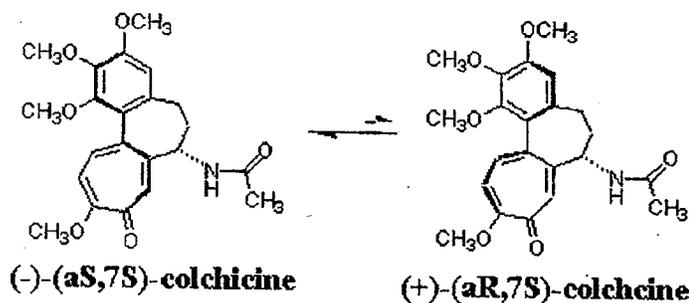
3. CMC/Device

This section is excerpted from the primary CMC Review by Dr. Craig Bertha, and the CMC TL review by Dr. Ali Al-Hakim

- **General product quality considerations**

Colchicine is Acetamide, N-[5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy 9-oxobenzo[*z*]heptalen-7-yl], (S)-, with a molecular formula of C₂₂H₂₅NO₆ and a molecular weight of 399.44 g/mole.

Figure 1: Conformers of colchicine



Because of the unique structure of colchicine, it exists as a mixture of conformers that can interconvert relatively quickly when the compound is in solution and at ambient temperatures. The ratio of these conformers is approximately 99:1.

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The drug substance is supplied by _____ The drug product is Colchicine Tablets and each immediate release tablet contains 0.6 mg of colchicine. It is packaged in high density polyethylene (HDPE) bottles and _____, the _____ . There is a Colchicine Tablets monograph in the official edition of the USP. The drug product is formulated as a tablet with the following excipients: lactose monohydrate, pre-gelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and is coated with a proprietary coating from _____. The primary stability/registration batch BB 374 0215 of the drug product was used in the clinical pharmacology studies supporting the application. This batch has the same formulation and is manufactured by the same process proposed for the commercial tablets. Thus, no formulation comparability studies were necessary.

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The recommended daily dose for the colchicine product for FMF is proposed as _____ mg with a maximum daily dose of 2.4 mg (i.e., four tablets). Doses are given once a day or can be

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divided. The marketed drug product will be packaged in HDPE bottles with internal desiccants and with the following tablet counts: 30, 60, 100, 250, 500, 1000. The current proposed expiration dating period for the bottled product of 24 months is supported by the data provided. Whereas the applicant proposes that the _____ expiration dating period, the data provided _____

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The application is recommended for **approval** from a CMC perspective (pending Office of Compliance determination for the facilities inspections). No CMC-related Phase 4 commitments are deemed necessary.

- **Facilities review/inspection**

Several sites have pending inspections, including two sites associated with the manufacture of the drug substance. All facilities _____

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- **Other notable issues (resolved or outstanding)**

1) The following comment should be included in the action letter regarding the expiration dating period supported by the data provided in the application:

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2) Pending facilities inspection by Office of Compliance.

4. Nonclinical Pharmacology/Toxicology

Refer to the primary pharmacology/toxicology review by Dr. Lawrence Leshin and the supervisory pharmacology/toxicology memorandum by Dr. Adam Wasserman. This section is largely excerpted from Dr. Wasserman's memorandum.

- **General nonclinical pharmacology/toxicology considerations**

Drs. Leshin and Wasserman have identified the following primary issues with regard to the nonclinical literature submitted to support this NDA:

1. Nonclinical studies are almost exclusively old, pre-date GLP regulations instituted to ensure quality and integrity, and in most cases do not use current and preferred evaluation methodologies; they were designed with dose levels to determine the effects of colchicine rather than the safety of colchicine.

2. Nonclinical studies available are almost exclusively of short duration (i.e. ≤ 5 weeks) and do not support chronic dosing;
3. Genetic toxicology studies and knowledge of the mechanism of action indicate colchicine may reasonably be expected to promote or induce neoplasia;
4. Reproductive toxicology studies conducted in nonclinical models indicate a significant risk for embryofetal harm and reduced parental fertility;
5. The colchicine product used in the published studies is frequently of unknown quality and comparability when compared with the Applicant's drug product;
6. Nonclinical data provided do not provide full ability to address all standard nonclinical label sections (e.g. carcinogenicity); and,
7. There is a potential drug product photo-degradant impurity which possesses a structural alert for mutagenicity and is not adequately controlled by specifications or qualified through nonclinical studies.

However, Dr. Wasserman goes on to note: "...the mechanism of action of colchicine (as a microtubule inhibitor/mitotic spindle poison) is certainly operative in all eukaryotic organisms. This is the reason that the manifestations of toxicity are so similar across species, including human, as mentioned by Dr. Leshin. This, when combined with the well-understood clinical toxicity of long-term colchicine administration, precludes the need to provide modern, GLP-compliant chronic toxicology studies in animals for support of the application."

Thus, despite the aforementioned limitations of the submitted nonclinical literature, and given the extensive clinical experience with colchicine, the pharmacology/toxicology (P/T) team has determined that sufficient information is available to support labeling and recommends **approval** of the NDA with revisions to the proposed label. However, there remain issues of concern for which the nonclinical team is recommending post-marketing obligations:

1. Mutagenicity/reproductive toxicology of colchicine

Colchicine is not directly genotoxic, but is a known mitotic spindle poison which can result in aneuploidy, where mitotic dysfunction results in chromosome loss or gain. Teratogenic effects have been noted in multiple species with maternal exposure to colchicine. The P/T team believes there is sufficient literature available to adequately address the mutagenicity and reproductive toxicology of the colchicine label. However they also recommend the establishment of a pregnancy registry for FMF patients taking colchicine. This idea of a pregnancy registry will be addressed further in clinical section 8, below.

2. Potential mutagenicity of colchicine photodegradants

Drs. Leshin and Wasserman have also identified a concern regarding the potential presence of photo-degradants bearing a structural alert for mutagenicity (identified as β - and γ -lumicolchicine) which they have determined has not yet been adequately addressed by the applicant. While the applicant has not observed these degradants in the drug product, they have not developed detection methods which are sensitive enough to preclude such impurities being above 1.5 $\mu\text{g/day}$ total daily intake (TDI), the current standard which the Agency follows for approval of an NDA and which is also recognized by the European Medicines

Agency (EMEA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). As per CMC review, the packaging of the drug product in HDPE bottles or _____ packages should be sufficiently protective from light such that photo-degradant development should not occur. Furthermore, these photo-degradants would be a concern for the marketed and unapproved colchicine products currently available as well as the approved colchicine combination products and the levels for these products are also not known at this time. Given the known mutagenic effects of colchicine, the issue of the structural alerts for mutagenicity of the photo-degradants is therefore, overall, not enough of a concern to be an approval issue. However, Drs. Leshin and Wasserman recommend that the applicant be required to develop an improved assay to provide for a lower limit of detection as a post-marketing requirement such that the total levels of these photo-degradants will not exceed 1.5 µg/TDI.

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3. Carcinogenicity of colchicine

Colchicine is not directly genotoxic, but exposure in eukaryotes can result in aneuploidy, which in itself may be a risk factor for tumorigenesis, and colchicine has not been studied in standard rodent carcinogenicity bioassays. Although the P/T team has determined that sufficient information exists in the literature for labeling, the literature also raises important questions that have not been addressed; specifically, whether colchicine at human therapeutic doses may promote de novo tumorigenesis via aneuploidy or whether colchicine may inhibit progression of malignancy by impairing the ability of mutant and transformed cells to divide, or both (if exposure-dependent). Evaluation of colchicine in a standard 2-year rat bioassay along with a 6-month transgenic mouse study may provide information to address both possibilities. Dr. Leshin noted a long-term nonclinical study in which rodents developed respiratory difficulties over time with continual low-dose exposure to colchicine in drinking water and was not certain that such studies would be feasible and instead recommended a human malignancy registry. Dr. Wasserman was concerned that a human malignancy registry in FMF, which is a rare condition in the U.S., would be too small to provide useful information and that carefully designed and conducted rodent carcinogenicity studies, which incorporate appropriate dose-finding, would be feasible and would provide important information given the life-long clinical use of colchicine. However, in keeping with the extensive existing clinical experience with colchicine, Dr. Wasserman felt that rodent carcinogenicity studies could reasonably be conducted post-marketing and their lack was not an approvability issue.

- **Other notable issues (resolved or outstanding)**

From Dr. Wasserman's supervisory memo:

- 1) The applicant must evaluate the potential carcinogenicity of colchicine in two rodent species. Studies may consist of a 2-year bioassay in rat and a 6-month transgenic study in an appropriate mouse model. The applicant is strongly encouraged to submit protocols for Agency concurrence on study design prior to initiation of studies.
- 2) The applicant must improve detection assays to allow reduction of the specifications for the photo-degradant impurities β- and γ-lumicolchicine to ensure a limit of NMT 1.5 µg TDI for

the combined degradants. Alternatively, the applicant may conduct genetic toxicology studies which, if negative, would support the current proposed specifications.

5. Clinical Pharmacology/Biopharmaceutics

Refer to the review by primary clinical pharmacology/biopharmaceutics reviewer, Dr. Srikanth Nallani, and team leader Dr. Suresh Dodappaneni for further details.

To supplement the published literature, the applicant conducted and submitted 6 clinical pharmacology/biopharmaceutics studies:

1. MPC-004-07-1001, a single-dose crossover study in 28 healthy subjects to assess the bioavailability of colchicine 0.6 mg tablets administered under standard fasting conditions and compared to Col-Probenecid;
2. MPC-004-07-1002, a single-dose, double-blind, double-dummy study in 18 healthy subjects to evaluate the pharmacokinetic (PK) profile of colchicine and its metabolites (2-, 3-, and 10- demethylcolchicine); 15 subjects were given 4.8 mg colchicine administered as two 0.6 mg over-encapsulated tablets followed by one 0.6 mg over-encapsulated tablet every hour for six additional doses. Three subjects were given a single 400 mg over-encapsulated moxifloxacin tablet. In addition to PK, the effect of these doses on subjects' electrocardiograms (ECGs) was assessed.
3. MPC-004-07-1003, a single-dose (1.2 mg), open-label study in 13 healthy subjects to further assess the pharmacokinetic profile of colchicine and its metabolites;
4. MPC-004-07-1004, a single- and multiple- dose open-label study in 13 healthy subjects to determine the single- and multiple- dose pharmacokinetics of colchicine;
5. MPC-004-07-1005, a multiple-dose, randomized, double-blind, two-sequence study in 30 healthy subjects designed to determine whether the steady-state dosing of colchicine influences the steady-state pharmacokinetic profile of ethinyl estradiol or norethindrone;
6. MPC-004-07-1006, a single-dose, open-label study in 24 healthy subjects designed to confirm the extent to which multiple oral doses of clarithromycin influence the single-dose pharmacokinetic profile of colchicine and its metabolites.

• General clinical pharmacology/biopharmaceutics characteristics

Colchicine is predominantly eliminated by biliary excretion and through the stool, with gastrointestinal tract lining cell turnover playing a variable role in colchicine elimination. Colchicine is extruded from cells (including enteric lining cells) into the gastrointestinal tract, mediated by the multidrug resistance transporter molecule ABCB1 (full name: ATP-binding cassette subfamily B member 1, MDR1, P-gp, P-glycoprotein [P-gp] or CD243). Normally, a lesser but significant role in colchicine metabolism (~5 to 20%) is played by enteric and hepatic cytochrome P450 3A4 (CYP3A4), which catalyzes demethylation of colchicine to inactive metabolites. Hepatic demethylation of colchicine dependent on CYP3A4 occurs before hepatobiliary excretion of colchicine. Renal elimination has been estimated to be responsible for 10 to 20% of drug disposition in normal subjects.

However, CYP3A4 and renal disposition of colchicine become more critical with certain drug–drug interactions that affect ABCB1, with hepatobiliary dysfunction and with aging.

Absorption: In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean C_{max} of 2.5 ng/mL (range 1.1 to 4.4 ng/mL) in 1.0 to 2 hours (range 0.5 to 3 hours) after a single 0.6-mg dose administered under fasting conditions. [PK studies MPC-004-07-1001, -1004, and -1006] Following repeated dosing, colchicine appears to achieve steady state concentrations within 14 days. Mean C_{max} after multiple dosing was 3.1 to 3.6 ng/mL [MPC-004-07-1004, -1005]. Absolute bioavailability was reported to be approximately 45%.

Distribution: Colchicine is a lipid-soluble molecule that is rapidly and widely distributed throughout the body. It binds to tubulin on a single high-affinity site, contributing to the large apparent volume of distribution. The mean apparent volume of distribution in healthy young volunteers was approximately 5 to 8 L/kg. Colchicine binding to serum protein is low, 39 ± 5%, primarily to albumin regardless of concentration. Colchicine crosses the placenta (plasma levels in the fetus are reported to be approximately 15% of the maternal concentration) and distributes into breast milk.

Metabolism: Colchicine is demethylated to two primary metabolites, 2-DMC and 3-DMC, and one minor metabolite, 10-DMC (also known as colchiceine). *In vitro* studies using human liver microsomes have shown that CYP3A4 is involved in the metabolism of colchicine to 2- and 3-DMC; however, the overall extent of hepatic metabolism is minimal. *In vivo*, exposure to 2-DMC and 3-DMC metabolites is minimal (< 5% of parent drug).

Elimination/Excretion: Enterohepatic recirculation and biliary excretion, mediated by P-gp, are postulated to be a major route of elimination. Following multiple oral doses (0.6 mg twice daily), the mean elimination half-life in young healthy volunteers (mean age 25 to 28 years of age) is 26.6 to 31.2 hours. Colchicine is excreted in the urine by both glomerular filtration and tubular secretion, reportedly as glucuronides. Renal clearance has been reported to account for about 10-20% of total body clearance. Extracorporeal Elimination: Colchicine is not removed by hemodialysis.

- **Drug-drug interactions**

Consistent with current understanding of colchicine metabolism, certain drugs increase the potential for colchicine toxicity via dual modulation of ABCB1 and CYP3A4. These include the macrolide antibiotics erythromycin and clarithromycin, and the statins, e.g., lovastatin, simvastatin, atorvastatin. Case reports suggest use of these agents, particularly clarithromycin, may result in fatal colchicine toxicity, even when the concomitant doses of colchicine are in the therapeutic range. Case studies have reported acute myopathy after concurrent use of colchicine with a statin that was either not metabolized or minimally metabolized by the CYP3A4 isoenzyme (fluvastatin). The working hypothesis on this interaction is the disruption of the integrity of the cytoskeleton and the capacity of colchicine to promote vacuolization in muscle by disruption of the microtubule network. [Terkeltaub 2008].

To supplement the published literature, the applicant conducted a colchicine - clarithromycin drug interaction study (Study # 1006). In this study, a three-fold increase in colchicine C_{max} and AUC was noted when Colstat was coadministered with clarithromycin. Based on the current information, this drug interaction appears mainly due to P-gp inhibition rather than CYP3A4 inhibition. The applicant is conducting additional studies that could clarify the role of CYP3A4, to include studies with ritonavir, ketoconazole, grapefruit juice, and cyclosporine. The available data suggest dosage adjustment is necessary with strong CYP3A4 and P-gp inhibitors. The clinical pharmacology team recommends that the Colstat dose be reduced 2/3rd to 0.3 mg twice daily when patients with FMF are also on strong CYP3A4 and P-gp inhibitors such as macrolides (e.g. clarithromycin), azole antifungal agents (e.g. ketoconazole), protease inhibitors (e.g. ritonavir, atazanavir, saquinavir), and the serotonin/norepinephrine reuptake inhibitor nefazodone. The applicant also conducted a drug-drug interaction study to assess the effects of colchicine on oral contraceptives (Study # 1005). This study demonstrated that multiple dose administration of colchicine does not affect plasma levels of ethinyl estradiol and norethindrone.

- **Intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment**

Pharmacokinetic studies were not conducted by the sponsor to address the influence of age, race, bodyweight, pregnancy and organ dysfunction. However, several publications addressing these intrinsic factors have been discussed in the NDA.

Colchicine PK in elderly: Pharmacokinetics of colchicine was not evaluated in elderly. However, because decreases in renal and hepatic function are common in the elderly, caution is warranted when using colchicine in this population.

Colchicine PK in pediatric patients: The applicant did not conduct any PK studies in pediatric patients and no information on the PK of colchicine in pediatric patients was found in the published literature, although there is a fairly extensive published literature on the use of colchicine in pediatric patients otherwise.

Colchicine PK in renal impairment patients: As noted above, renal elimination accounts for approximately 10-20% of colchicine clearance. A four-fold decrease in colchicine clearance is noted in severe renally-impaired subjects undergoing hemodialysis compared to healthy volunteers. The biopharmaceutics team recommends consideration of dosage reduction in patients with mild and moderate renal impairment, and definite dose reduction in patients with severe renal impairment and undergoing dialysis—for whom the total daily dosage should be reduced to 0.3 to 0.6 mg colchicine per day.

Colchicine PK in patients with hepatic impairment: PK studies of Colstat were not conducted in patients with hepatic impairment. However, published studies with IV colchicine and oral colchicine in patients with severe hepatic impairment are available. These studies suggest that colchicine clearance is decreased in these patients, with reports ranging from 2.5-fold lower clearance up to 10-fold lower clearance reported in cirrhotic patients when compared to healthy subjects. Therefore the biopharmaceutics team recommends caution when Colstat is

considered for patients with mild hepatic impairment and consideration of dose reduction in patients with moderate and severe hepatic impairment.

- **Demographic interactions/special populations**

At present, no information is available regarding whether other demographic or special population interactions affect colchicine metabolism or elimination.

- **Other relevant clinical pharmacology issues arising from investigations by gender, age, including pediatrics and geriatrics, and other demographic-based investigations**

No additional issues noted.

- **Thorough QT study or other QT assessment**

The applicant was not required to pursue formal QT prolongation studies based on the known toxicity profile of colchicine and the results of their pre-clinical studies (see Pharm/Tox review). However, the collective data from their PK studies included an informal QT study which used moxifloxacin-treated patients as a positive control for QTc prolongation (Study #1002). In this study, subjects were randomized to receive colchicine (n=15) or moxifloxacin (n=3). As noted by the clinical pharmacology team, this study was insufficiently powered to detect a difference between colchicine and moxifloxacin, which was intended to serve as a positive control. Nonetheless, there was little change in QT interval regardless of correction methodology [Fridericia (QTcF) or Bazett's (QTcB)]. Moxifloxacin response was lower than expected and the time course was not consistent with the typical findings; however the QTcB and QTcF values in colchicine-treated subjects were lower at all time points compared to moxifloxacin-treated subjects. Overall, in this study and in the other PK studies, no effect on QTc or any other ECG parameter was noted with colchicine in therapeutic doses.

- **Other notable issues (resolved or outstanding)**

The application is recommended for approval by the Clinical Pharmacology/Biopharmaceutics Team.

1) Intrinsic and extrinsic factors (detailed above) can result in changes in colchicine metabolism and elimination to a potentially dangerous degree. Drug-drug interaction information and dose-reduction recommendations to address these factors will be included in labeling.

2) No Phase 4 commitments or requirements were recommended by Agency clinical pharmacologists.

6. Clinical Microbiology-N/A

7. Clinical/Statistical- Efficacy

- **Indication:** _____ of FMF

The foundational claim sought by the applicant for this colchicine product is to _____ of FMF. The evidentiary basis for this claim consists of the only 3 randomized, controlled studies available for colchicine in this disorder, but colchicine's story in FMF began with a seminal letter to the editor of the New England Journal of Medicine (NEJM) by Dr. Stephen Goldfinger in 1972. Dr. Goldfinger documented the frequency of 5 patients' attacks before colchicine treatment and after beginning colchicine at 1 to 3 tablets daily:

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Table 1: First Documented Results of Colchicine in FMF [Goldfinger 1972]

FEATURE	CASE NO.				
	1	2	3	4	5
Age (yr)	42	26	47	43	27
Sex	M	F	F	M	M
Ancestry	Hebrew	Hebrew	Syrian	Hebrew	Hebrew
Duration of illness (yr)	27	20	41	20	4
Serum uric acid (mg/dl)	6.1-7.1	4.0	3.1	8.2	6.4
Attack frequency before colchicine	3-4 wk	4 wk	4 wk	6-10 days	6 wk
Duration of colchicine therapy (mo)	54	27	20	16	10
No. of attacks after colchicine instituted	1*	2	0	0	1*

*Attack occurred shortly after patient discontinued colchicine.

This dramatic treatment effect, where 9 to 37 attacks per year were reduced to almost none, revolutionized the treatment and further study of FMF.

The three randomized, double-blind, placebo-controlled studies of colchicine in FMF are discussed individually in the clinical review by Dr. Keith Hull, to which the reader is referred for additional details. Overall, the three studies were similar in patient population, design and treatment: patients had to meet accepted clinical criteria for the diagnosis of FMF and have a reliable history of attacks; studies utilized a cross-over design where each patient received colchicine and placebo during different periods of the same study; the primary endpoint for each study was the difference in the number of FMF attacks accompanied by fever between the two treatment periods; and similar dosing regimens of colchicine were used, with doses ranging between 1 to 1.8 mg per day.

The three studies randomized a total of 48 adult patients who were of various ethnicities commonly affected with FMF. 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 2, the results of the three randomized trials demonstrate that the number of acute attacks were significantly lower with colchicine treatment compared to placebo.

Table 2: 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		

Excerpted from the clinical review (Table 4) of Dr. Keith Hull

Why are these three small studies sufficient to provide substantial evidence of the effectiveness of colchicine for this indication?

1. The nature of the disorder. FMF is a hereditary disorder with a distinct phenotype that includes objective signs of inflammation (e.g. fever, rash, synovitis, serositis, and elevated inflammatory markers). While there is inter-individual variability in attack characteristics, any given individual's attack characteristics are generally consistent. Thus the disorder lends itself well to a cross-over design, and the primary endpoint of number of attacks is one that is not easily misconstrued because attacks are unmistakable.
2. The consistently large treatment effect size. FMF is a rare disorder, and the numbers of patients in these studies are accordingly small. These small numbers could make interpretation problematic if it were not for the fact that the treatment effect size is very large. While results were not quite as dramatic as in Goldfinger's initial case series, they were also unequivocal, with a 4- to 10-fold reduction in attacks during the colchicine treatment period.
3. Independent substantiation. The three studies, while small, were independently designed, conducted, and analyzed, and were consistent.
4. Consistent and supportive experience over time in uncontrolled trials. Sixteen articles describing uncontrolled trials were submitted by applicant in support of the randomized trials. Dr. Hull described 8 of the largest studies in his review, and these results are summarized in Table 3, below. These studies, published between 1973 and 1983, included 586 patients with FMF. The doses and regimens of colchicine used were similar to those used in the three randomized trials, and the duration of treatment ranged from 6 months to 15 years. As shown in Table 3, response rates were high and

the proportion of patients experiencing no benefit was very low. 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.

Table 3: 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			

Excerpted from the clinical review (Table 5) of Dr. Keith Hull

Evidence in children with FMF

Since FMF begins in childhood, when reports of colchicine's effectiveness in treating adults were published, the treatment began to be used in children as well. Dosing in children was apparently ad hoc and extrapolated from adults. 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 _____ in children with FMF. The eight studies enrolled a total of 1272 children, with similar numbers of males and females aged four months to eighteen years of age, although patients less than four years of age were too few in number to be able to draw definitive conclusions about efficacy or safety. Details of these case series may be found in the Dr. Hull's review.

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Three of the studies collected data at baseline and were able to compare the frequency of attacks before and after starting colchicine therapy using patients as their own control. Lehman et al. (1978) reported an average of 5.8 attacks in 8 children over the three month baseline period compared to a mean of 0.6 attacks over the following three months while the same patients were receiving colchicine therapy. Five of the eight children experienced a complete resolution of symptoms. Majeed and Khuffash (1990) reported on 32 patients who experienced an average of 20 attacks per year at baseline compared to 3 attacks per year while receiving colchicine therapy. Similarly, Ozkaya and Yalcinkaya (2003) collected data at baseline on 62 children before assigning them to receive different doses of colchicine based on body weight. As shown below in Table 4, all three colchicine treatment arms demonstrated a marked reduction in the number of attacks compared to baseline.

Table 4: Summary of Efficacy Results from Ozkaya and Yalcinkaya

	Group 1 0.01-0.03 mg/kg/day		Group 2 0.04-0.05 mg/kg/day		Group 3 ≥0.06 mg/kg/day	
Patients, n (%)	31 (50%)		16 (26%)		15 (24%)	
	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx
Number Attacks/Year	6	1	15	3	24	4

Excerpted from the clinical review (Table 6) of Dr. Keith Hull

In the pediatric trials, colchicine dosing ranged between 0.5 mg to 2 mg per day and no single study provided definitive information regarding the best dose regimen. Gedalia et al dosed children with colchicine 0.5 mg/15 kg of body weight up to a maximum of 2 mg and reported a clinical benefit. Majeed et al. suggested that clinical efficacy was achieved using a regimen where children ≤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’s study attempted to identify an “ideal” colchicine dosing regimen in children 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/m²/day, with children younger than 5 years of age requiring higher dosing based on body weight and body surface area compared to older children. In some pediatric texts (e.g., Rudolph’s Pediatrics 2003), initial dosing is recommended to be started at 1 mg daily regardless of age, weight, severity, or frequency of attacks, because this dose is considered to be the minimum effective dose to prevent amyloidosis and prevents attacks in 65% of patients.

Efficacy conclusion

I concur with the primary clinical reviewer, Dr. Keith Hull, that sufficient evidence exists to support the conclusion that daily colchicine is effective in _____ of FMF in adults and children.

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1 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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- Notable efficacy issues both resolved and outstanding: None.

8. Safety

- Discuss the adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing as discussed in the Pre-Approval Safety Conference (if NME will be approved)

The safety data sources include the following:

1. The applicant's PK studies include 126 healthy volunteers, 83 exposed to single-dose/1-day regimens, and 43 subjects exposed to 10- to 14-day steady state regimens;
2. The medical literature includes 3545 FMF patients, both adults and children, in the 3 randomized, controlled studies and 21 uncontrolled studies, and meta-analyses of studies in other indications which included 671 patients with hepatic and biliary cirrhosis;
3. The FDA postmarketing adverse event report database included 751 adverse event reports from 1969 through 30 June 2007;
4. The WHO postmarketing adverse event report database included 1380 adverse event reports from 79 countries, including the US, from 1968 through March 2006;
5. Currently approved labeling for Col-Probenecid (US), and oral colchicine labels from Argentina, Australia, Britain, Germany, Mexico, France, Singapore, and Uganda.

These data have a number of obvious limitations: much of it is uncontrolled, the controlled data have been primarily obtained from the literature in which safety data are typically not reported extensively or systematically, postmarketing adverse event reporting is biased toward the most severe events and also is limited by lack of a reliable denominator from which to derive incidence and relative risk, and safety information in labeling is, by necessity, abbreviated. Nonetheless, these limitations are not as crucial in the case of single-entity colchicine because of its long history of clinical use and well-described toxicity profile.

The most frequent adverse effects of oral colchicine in therapeutic doses are those involving the gastrointestinal tract. Diarrhea, nausea, vomiting, and abdominal pain are often the first signs of toxicity and are the first indication that colchicine therapy may need to be stopped or the dose reduced. Larger doses may cause profuse diarrhea, gastrointestinal hemorrhage, skin rashes, and renal and hepatic damage. Rarely, bone marrow suppression with agranulocytosis, thrombocytopenia, and aplastic anemia has occurred on prolonged treatment, as have peripheral neuropathy, myopathy, rashes, and alopecia.

Overdose with colchicine is uncommon, despite its narrow therapeutic index and despite wide variation in the dose required for significant morbidity and mortality. _____

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_____ colchicine tablets were sold in the U.S. in 2007 (IMS data), compared to approximately 20 adverse event reports and 5 deaths reported on average per year (the caveat being an unknown degree of underreporting to the postmarketing adverse event databases). Above the standard therapeutic doses (which range from the 2.4 mg typical maximum daily chronic dose to the 4.8 mg maximal acute dose) there does not seem to be any clear-cut separation between non-toxic, toxic or lethal doses of colchicine. Generally, therapeutic concentrations of colchicine range from 0.015 to 0.03 mg/kg. Doses less than 0.5 mg/kg are usually not fatal; but fatalities have been reported with as little as 0.5 to 0.8 mg/kg, with more consistent lethality at doses exceeding 0.8 mg/kg. However, patients have survived ingestion of more than 60 mg and conversely others have died after ingesting only 7 mg. In children, fatalities have been reported with doses as low as 0.37 mg/kg, which would equate to 4.8 mg in a 4 year old in the 5th percentile for weight (13 kg).

Overdose with colchicine constitutes a toxicological emergency and rapid intervention is required. Other than gastric lavage and oral charcoal, treatment is primarily supportive and tailored to organ manifestations. The symptoms of toxicity are well described in the literature and can be separated into three characteristic phases: Phase 1 (0-24 hours)—nausea, vomiting, diarrhea, abdominal pain, anorexia, electrolyte imbalance and hypovolemia, and peripheral leukocytosis; phase 2 (2-7 days)—bone marrow hypoplasia with profound leukopenia and thrombocytopenia, cardiac arrhythmias and cardiovascular collapse, respiratory distress/hypoxia/pulmonary edema, oliguric renal failure, rhabdomyolysis, continued electrolyte derangements and metabolic acidosis, mental status changes, seizures, peripheral neuropathy and ascending paralysis; and phase 3 (day 7 on)—rebound leukocytosis and transient alopecia. Death typically occurs within the first 48 hours due to dysrhythmias, cardiovascular collapse and respiratory failure, with a second peak 3-7 days after exposure due to sepsis.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests**

In the applicant's PK studies, no deaths or SAEs were reported. Adverse events (AEs) were consistent with the known toxicity profile of colchicine (see Table 8 in the clinical review by Dr. Keith Hull). 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.

Deaths in the published literature related to colchicine were in focused articles on the toxicity of colchicine and/or case reports on acute or chronic overdose, whether accidental or intentional, or due to drug-drug interactions. Deaths due to colchicine toxicity were not noted in the literature documenting its efficacy in the treatment of FMF and related amyloidosis. By contrast, deaths were commonly reported to the postmarketing adverse event databases. In the FDA postmarketing adverse event databases from 1969 to 30 June 2007, 234 deaths were

reported in 751 reports total (31%). This may include duplicates, as the applicant had line listings but did not have full narratives for all cases. Of these death reports, 169 (72%) were associated with oral colchicine, consistent with the far greater use of oral as compared to IV colchicine. Thirty-one percent of reports were overdoses. Of the non-overdose fatalities, 60/117 (51%) reported clarithromycin as a co-suspect / concomitant / interacting drug. In the WHO postmarketing database, 48/1380 (3%) reports were regarding deaths.

Adverse events by organ system are detailed in section 7.3.2 of the clinical review by Dr. Keith Hull. The gastrointestinal system is by far the most commonly affected system, with the most common AEs being diarrhea, nausea and vomiting, abdominal pain and cramping. In the FDA postmarketing databases from 1969 to 30 June 2007, 340 of 751 (45%) reports were for GI adverse events, with diarrhea again topping the list. In the WHO postmarketing database from 1968 to March 2006, 46% (633/1380) of reports were related to gastrointestinal events.

Other organ systems which are uncommonly affected by therapeutic doses of colchicine but for which good evidence exists to implicate colchicine causality include:

1. Hematologic/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. In the FDA postmarketing databases (1969 to June 30, 2007), 87 of 751 (~12%) total reports pertained to marrow or lineage specific suppression.
2. Musculoskeletal/Neuromuscular. Although rare, colchicine-induced neuromuscular toxicity has been well documented and has occurred in both the short-term and long-term use setting, and with standard therapeutic doses (however these doses may not have been appropriately reduced for the given patient population of elderly or renally impaired patients). Patients typically present with proximal muscle weakness and pain that may also include mild sensory polyneuropathy. The effects are typically reversible within weeks to months following the discontinuation of colchicine. Based on literature reviews [Wilbur 2004 and Wallace 1991], 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. Rhabdomyolysis associated with colchicine treatment has also uncommonly been reported. In the FDA postmarketing databases (1969 to June 30, 2007), 177 of 751 (~24%) total reports pertained to neuromuscular manifestations or creatine phosphokinase (CPK) elevations, including 40 reports of rhabdomyolysis.
3. Skin and appendages. Alopecia is clearly associated with colchicine overdose but has also been described with chronic colchicine use in children with FMF (two publications detailing 3 children). Several reports of maculopapular drug eruptions have been reported with colchicine treatment. A single reported case of toxic epidermal necrolysis with colchicine was confounded by concomitant allopurinol use. None of these types of adverse events were reported in the FDA postmarketing

databases. However in the WHO database from 1968 to March 2006, 217 of 1380 (16%) reports were for rash or pruritis.

- **Immunogenicity:** There are no significant immunogenicity concerns with colchicine.
- **Special safety concerns**
 1. Drug-drug interactions. There is a wealth of evidence supporting a potentially lethal interaction between strong P-gp inhibitors, such as clarithromycin, and colchicine. However, there are many other interactions that could be cause for concern and are detailed more extensively in the clinical pharmacology and primary clinical reviews. The applicant has created a comprehensive list of potential drug interactions in tabular format for the warning section of the label.
 2. Susceptibility to toxicity in special populations. Based on the published literature, a 4-fold decrease in colchicine clearance is noted in severe renally-impaired subjects undergoing hemodialysis compared to healthy volunteers. A 2.5- to 10-fold lower clearance as been reported in cirrhotic patients when compared to healthy subjects. No PK studies have been performed in the elderly or in pediatric patients. However since the elderly are more likely to have significant renal or hepatic impairment, as a whole, they are more at risk.
 3. Fertility, reproductive/developmental toxicity, and lactation. Because FMF starts early in childhood and is life-long, it affects patients throughout their reproductive years and there has been a longstanding concern and interest regarding the effects of the disease and its treatment on fertility and reproductive/developmental toxicity. Colchicine crosses the placenta (plasma levels in the fetus are reported to be approximately 15% of the maternal concentration). It also distributes into breast milk, but ingestion *via* breast feeding results in doses that are estimated to be 1/10th to 1/20th therapeutic doses. Studies submitted by the applicant and reviewed by Pharm/Tox indicate colchicine administration in animals induces significant reductions in fertility through direct effects on germ cells as well as hormonal alterations supporting the embryonic environment. Also, teratogenic effects have been noted in multiple species with maternal exposure to colchicine, and the degree and nature of the defects are dependent on the developmental stage of embryo exposure. 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.

Keeping in mind the limitations of the available human data, overall there does not appear to be a major negative impact of colchicine in therapeutic doses on fertility or development. The effect of FMF or colchicine on male fertility has not been systematically studied, however the bulk of the literature support no significant effect and only sporadic case reports of azoospermia have been published, some of which were the result of amyloidosis of the testes. Similarly, there are no reports of diminished female fertility [Ben Chetrit and Levy, 1998]. Based on their FMF cohort's

experience, these same authors later (2003) concluded that colchicine treatment actually improved fertility in patients with FMF.

Rabinovitch and colleagues (1992) reported on 116 women with FMF who had 225 pregnancies. Ninety-one women took colchicine throughout the pregnancy, 40 women were taking colchicine at the time of conception but discontinued during the first trimester, and 94 women had FMF but had not yet and therefore did not take colchicine during the pregnancy. There was an increased rate of spontaneous abortions (20% compared to 12%) in women who were not taking colchicine, postulated to be due to uncontrolled inflammation. Two children out of 131 children born to women taking colchicine were born with trisomy 21, but this was considered to be within expected rates for the population. These 131 children otherwise had no growth disturbances or developmental abnormalities for a 10-year follow up period. In another paper by Berkenstadt et al (2005), chromosomal abnormalities and birth defects in 901 babies born to 326 couples in which one partner was being treated with colchicine for FMF were compared to what would be expected from published rates. Seven chromosomal abnormalities (5 expected based on maternal age), 6 structural abnormalities (3 expected) and 7 birth defects (“considerably lower rate”) were reported in this cohort. These differences were not statistically significant.

As previously mentioned, low levels of colchicine are passed into breast milk. However, there are no published reports of adverse effects of colchicine in breast-feeding infants of mothers taking colchicine. In a 1998 article, Ben-Chetrit and Levy described their experience with more than 50 children of mothers with FMF who continued to nurse while taking colchicine, without adverse effects.

- **Discussion of primary reviewer’s comments and conclusions**

I concur with the primary clinical reviewer, Dr. Keith Hull, that overall, when colchicine is taken in therapeutic doses, and when appropriate attention is paid to reducing doses in susceptible populations or with potentially interacting drugs, colchicine is generally safe and well-tolerated.

- **Highlight differences between CDTL and review team with explanation for CDTL’s conclusion and ways that the disagreements were addressed**

Not applicable.

- **Discussion of notable safety issues (resolved or outstanding)**

1) Colchicine taken during pregnancy. Although colchicine would be an expected teratogen based on its mechanism of action, and animal studies have confirmed this potential, based on limited data, in therapeutic doses it does not appear to be detrimental in humans. Thus current clinical recommendations are for women with FMF to continue colchicine treatment during pregnancy in order to minimize inflammatory attacks, which are considered to be more detrimental. Drs. Leshin and Wasserman have suggested a pregnancy registry to obtain

additional information. Dr. Hull believes that the currently available information and long history of use of colchicine minimizes the utility of clinical postmarketing studies. I agree that a pregnancy registry, which is unlikely to have very many enrollees who will not be taking colchicine to serve as a control, is not likely to provide information that has not already been published from the carefully followed patient cohorts at major FMF academic centers, e.g. in Israel and Turkey.

2) The narrow therapeutic index of colchicine and potentially lethal drug-drug and drug-disease interactions. Again, these issues are long- and well-known. However, in addition to FDA-approved labeling (which is not currently available for marketed unapproved single-entity colchicine products), a medication guide should be considered to standardize patient information and mandate distribution of that information. Since colchicine is widely available and used currently, I do not believe that the medication guide is necessary for the approval of this application, but should be required of the applicant as a post-marketing commitment.

9. Advisory Committee Meeting

An advisory committee meeting was deemed unnecessary for this product and indication, despite the fact that this would be the first approval for colchicine as a stand-alone entity. Colchicine is not a new molecular entity, having been approved as part of a combination with probenecid as chronic treatment for gout in 1961 (DESI, 1972). Given colchicine's extremely long history of medicinal use and associated clinical experience, and the long history of use of colchicine for the indication of FMF (30+ years), no new issues were identified in this submission.

10. Pediatrics

Since FMF is an orphan indication, PREA does not apply. However, FMF does occur in children, and the efficacy and safety of colchicine treatment in children is interwoven in the discussions in the efficacy and safety sections above.

The Agency's Maternal Health Team (MHT) was consulted by the Division on September 25, 2008, regarding the proposed pregnancy category designation and pregnancy/nursing mothers language in the proposed label. MHT agreed with the applicant's proposed Pregnancy Category C designation and has provided revisions to the proposed Pregnancy and Nursing Mothers sections of the colchicine labeling to include required regulatory language and clinically relevant human data in order to provide guidance for healthcare providers and patients in their risk/benefit decision making regarding colchicine use during pregnancy and lactation. In addition, MHT is requiring additional regulatory language regarding colchicine use during pregnancy and lactation to the Highlights of Prescribing Information, Use in Specific Populations section of the labeling.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues.
- **Exclusivity or patent issues of concern**

Colchicine is not a new molecular entity, having been approved in combination with probenecid for the chronic treatment of gout. However it has not yet been approved for the FMF indication, which is an orphan indication and conveys orphan exclusivity, which the applicant will receive for this indication, if approved.

- **Financial disclosures, other GCP issues, DSI audits**

Since the applicant only conducted clinical pharmacology studies in support of the application, and none of these were essential for the efficacy and safety evaluation, which were based primarily on the published literature, financial disclosure or GCP concerns or DSI audits were deemed not to apply in this case.

- **Other discipline consults**

Finalized consults from the Division of Drug Marketing, Advertising, and Communications and Office of Surveillance and Epidemiology were pending at the time of this review. The proposed tradename "Colstat" was submitted relatively late in the review cycle and is still being reviewed for appropriateness. OSE was also consulted and has informally raised some concerns regarding the possibility of a 0.3 mg starting dose, since the 0.6 mg tablets are scored but do not always split completely evenly. This issue was discussed with the clinical team, who felt that this was unlikely to be clinically relevant, since even young children with FMF are typically maintained on higher doses of colchicine (between 1 and 1.8 mg).

- **Any other outstanding regulatory issues**

Inspection of manufacturing facilities ————by Office of Compliance is still pending at the time of this review.

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12. Labeling

Other aspects of the review will address labeling in more detail. Only highlights of labeling discussions and areas of concern are to be addressed in this review.

- **Proprietary name:** Colstat, submitted late in the review cycle, is still being reviewed.
- **Physician labeling**
 1. Indications will need to be amended to only include _____ of FMF.
 2. Dose modifications for renal and hepatic impairment and for serious drug-drug interactions should be included in section 2.4 and in Table 1.
 3. Pregnancy/nursing mothers sections will need to be amended as per MHT consult.

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4. Nonclinical sections will need to be amended as per Pharm/Tox recommendations.
5. Clinical studies section will need to be amended to remove the uncontrolled study information, including studies in _____

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- **Carton and immediate container labels (if problems are noted):** Consult pending.
- **Patient labeling/Medication guide (if considered or required):** Consult pending.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of the NDA for the indication of _____ of FMF, pending favorable site inspections by the Office of Compliance.

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- **Risk Benefit Assessment**

Attacks of FMF are debilitating and have been shown to result in premature morbidity and mortality due to secondary amyloidosis if chronically uncontrolled. While colchicine is a narrow therapeutic index drug with severe and potentially lethal toxicities, when taken in therapeutic doses and dose-modified accordingly in patients with renal impairment, hepatic impairment, or who are taking drugs with high interaction potential, it appears to be safe and well tolerated. Although the controlled trial data are limited, the totality of the evidence that has accumulated over the last 35 years confirms that the risk benefit profile of colchicine in FMF is favorable.

- **Recommendation for Postmarketing Risk Management Activities**

I recommend a medication guide for colchicine in order to standardize patient information and mandate distribution. This may positively impact safety by improving patient awareness of potentially dangerous drug-drug interactions. However, colchicine is widely used and available as a marketed unapproved product currently, making approval of a medication guide pre-marketing a moot point.

- **Recommendation for other Postmarketing Study Commitments**

Pharmacology/Toxicology recommends that the potential carcinogenicity of colchicine be assessed in two rodent species. Although not an approval issue, improved detection assays to allow reduction of the specifications for photo-degradant impurities is also recommended as a postmarketing commitment (see both pharmacology/toxicology comments below).

- **Recommended Comments to Applicant**

CMC Comment:

“Our evaluation of your submitted stability data as per ICH Q1E, in conjunction with your updated drug product specifications leads to the conclusion that a _____ expiration dating period is not appropriate at this time for the _____ drug product. An _____ expiration dating period is granted for this presentation of the product. You may extend the expiration dating period after approval as per 21 CFR 314.70(d)(2)(vi).”

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Pharmacology/Toxicology Comments

“You must evaluate the potential carcinogenicity of colchicine in two rodent species. Studies may consist of a 2-year bioassay in rat and a 6-month transgenic study in an appropriate mouse model. You are strongly encouraged to submit protocols for Agency concurrence on study design prior to initiation of studies.”

“You must improve detection assays to allow reduction of the specifications for the photo-degradant impurities β - and γ -lumicolchicine to ensure a limit of NMT 1.5 μg TDI for the combined degradants. Alternatively, you may conduct genetic toxicology studies which, if negative, would support the current proposed specifications.”

Clinical comments

I recommend utilizing standard Medication Guide request language as per the Safety Requirements Team (SRT) and Office of Chief Counsel (OCC) templates. The Medication Guide for colchicine should highlight the risk of fatal overdose, that colchicine does not work like other pain medicines and should not be taken by anyone except for whom it is prescribed, and that patients should contact their health care provider for dose adjustment instructions if prescribed drugs with known drug-drug interaction potential, or if they have kidney or liver problems.

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