CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-352

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Rigoberto Roca, M.D.
Subject	Deputy Director Summary Review
NDA/Supplement No.	22-352/000
Applicant Name	Mutual Pharmaceutical Co.
Date of Submission	June 20, 2008
PDUFA Goal Date	December 20, 2008
Proprietary Name / Established (USAN) Name	Colcrys / colchicine
Dosage Forms / Strength	0.6 mg tablets
Proposed Indication(s)	——————— in patients with familial Mediterranean fever
Action	Approval

b(4)

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Keith Hull, M.D., Ph.D.
Statistical Review	Dionne Price, Ph.D.
Pharmacology Toxicology Review	Steve Leshin, D.V.M., Ph.D. / Adam Wasserman, Ph.D.
CMC Review	Craig Bertha, Ph.D. / Ali Al-Hakim, Ph.D.
Clinical Pharmacology Review	Srikanth Nallani, Ph.D. / Suresh Doddapaneni, Ph.D.
DDMAC	Michael Sauers / Mathilda Fienkeng Pharm.D.
CDTL Review	Sarah Okada, M.D.
OSE/DMEPA	Loretta Holmes, BSN, Pharm.D. / Lori Cantin, R.Ph. / Kristina Arnwine, Pharm.D. / Denise Toyer, Pharm.D. / Carol Holquist, R.Ph.
OSE/DRISK	LaShawn Griffiths, M.S.H.S.-PH, B.S.N., R.N. / Jodi Duckhorn, M.A. / Claudia Karwoski, Pharm.D.
PMHS	Jeanine Best, M.S.N., R.N. / Karen Feibus, M.D. / Lisa Mathis, M.D.

CDTL = Cross-Discipline Team Leader
CMC = Chemistry, Manufacturing, and Controls
DDMAC = Division of Drug Marketing, Advertising and Communication
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management
PMHS = Pediatric and Maternal Health Staff
OND = Office of New Drugs
OSE = Office of Surveillance and Epidemiology

1. Introduction

Colchicine is an alkaloid derived from the plant *Colchicum autumnale*, also known as the autumn crocus. It has had a role in medicinal applications dating back to the times of ancient Greece, initially as a purgative agent and later as a treatment for gout. In the United States it has been used as a purified, single active ingredient since the early part of the nineteenth century, yet it has only been formally approved by the Food and Drug Administration as part of a combination product with probenecid. The combination, known as ColBenemid, consists of colchicine, 0.5 mg, and probenecid, 500 mg, and was initially approved in 1961. This approval predated the requirement for the demonstration of efficacy, therefore the combination underwent review by the National Academy of Sciences under the Drug Efficacy Study Implementation (DESI) process. The combination was deemed to be effective for the treatment of "chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout" in 1972. As a single-entity product, colchicine, although marketed, remains an unapproved product.

The applicant has submitted an application for the use of colchicine in adults and pediatric patients (≥ 4 years of age) with familial Mediterranean fever (FMF) for the ———————— b(4)

The proposed dosing regimen is based on the patient's age, and is 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

This review will provide an overview of the regulatory and scientific facts of this supplemental application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling modifications requested by the Applicant.

2. Background

Familial Mediterranean fever (FMF) is an autoinflammatory disease caused by mutations in the MEFV (MEditerranean FeVer) gene which encodes for the protein pyrin; FMF is inherited in an autosomal recessive pattern. The disease affects approximately 100,000 people world-wide, with a predominance of in persons with non-Ashkenazi Jews, Arabic, Turkish or Armenian descent. Pyrin is involved in the processes of inflammation and apoptosis and the clinical manifestations of FMF include relatively discrete episodes of fever accompanied by serositis, synovitis, or skin rash. The episodes last around 1 to 3 days and in a majority of patients the first episode occurs by age 10.

It is a disease with significant morbidity, with abdominal pain being the most common presenting feature, due to inflammation of the serosa. The clinical presentation can range from a dull aching pain to full-blown peritonitis, accompanied by board-like rigidity of the abdominal wall, absent bowel sounds, and rebound tenderness. The significance of the latter presentation is that, clinically, it resembles the clinical presentation of an intra-abdominal

process that would require an emergency exploratory laparatomy (volvulus, ischemic bowel, perforated viscus, etc.). Repeated episodes may result in peritoneal adhesions.

As many as a third of the patients will also present with pleuritis, which is usually unilateral, with sharp stabbing chest pain which results in splinting and atelectasis. If a pleural effusion is present, it is most likely a neutrophilic exudate, and as with the abdominal episodes, pleural thickening may develop after multiple attacks. Other examples of serosal inflammation include arthralgias and acute mono- and poly-articular arthritis, and, more rarely, pericarditis.

Systemic amyloidosis develops in a subset of FMF patients, secondary to the deposition of a fragment of serum amyloid A (SAA), an acute phase reactant produced by the liver and found at high levels in the serum during FMF attacks. As noted in Dr. Okada's review, there appears to be a certain ethnic predisposition toward amyloidosis due to certain mutations (i.e., M694V mutation in North African Jews, Armenians, and Turks). Deposition in the kidneys may result in the nephrotic syndrome, which may progress from albuminuria to the full syndrome over the course of 3 to 5 years, while deposition in the gastrointestinal tract may cause malabsorption, and deposition in the testis may cause azoospermia and infertility. Cardiac involvement, neuropathy, and arthropathy are very uncommon with the amyloidosis of FMF.

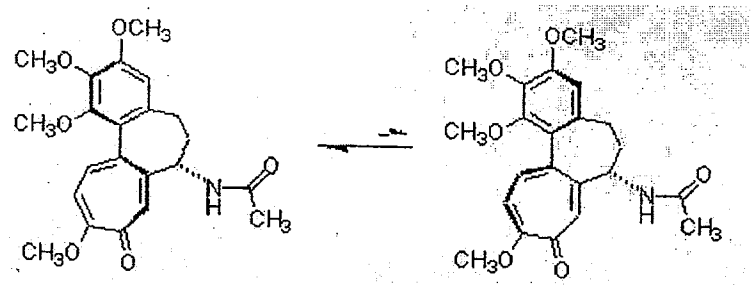
Colchicine was first used to treat FMF in the early 1970's and has established itself as the standard of care for patients with this disorder, despite the limited controlled trial data. There are anecdotal reports regarding the use of interleukin-1 antagonists or interferon; however, these therapies are still experimental and have not been shown to be effective in well-controlled, double-blinded studies. Narcotics and non-steroidal anti-inflammatory agents are used for the symptomatic relief of the acute attacks, but do not appear to alter the frequency, duration, or severity of the attacks.

Due to low incidence of FMF in the United States (which is estimated to be less than 5000 patients), the applicant sought, and was granted, orphan drug designation for this indication. Although the applicant intended to conduct pharmacokinetic studies, the applicant sought to submit an application where the efficacy and safety of colchicine for this indication would be supported by the available clinical literature and publicly available safety databases. At the Pre-NDA meeting, the Division was open to this possibility.

3. CMC/Device

General Product Considerations

The chemical name of Colchicine is N-[5,6,7,9-tetrahydro-1,2,3,10-tetratmethoxy 9-oxobenzo[*a*]heptalen-7-yl], (S)-acetamide. The molecular formula is $C_{22}H_{25}NO_6$ and the molecular weight is 399.44 g/mole. In nature, colchicine exists in two forms, (-)-(*a*S,7S)-colchicine and (+)-(*a*R,7S)-colchicine. The two conformers interconvert relatively quickly when the compound is in solution and at ambient temperatures. The ratio of the two conformers is 99:1.



(-)-(aS,7S)-colchicine (+)-(aR,7S)-colchicine

The drug substance is provided by ——————————. The Drug Master File (DMF——— for the drug substance was initially found to be deficient and comments were sent to the applicant in a Discipline Review letter. The applicant responded to Dr. Bertha's concerns and the DMF has now been found to be adequate for approval. b(4)

The drug product is formulated as a tablet with the following excipients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and a proprietary coating from ———. The drug product will be packaged in HDPE bottles with internal desiccants, in the following tablet counts: 30, 60, 100, 250, 500, and 1000. The applicant also intended to ——————————. The expiration period proposed by the applicant for the ——————— was —months, and was supported by data in the application. b(4)

Facilities Review/Inspections

The originally scheduled inspection visits to —— by the Office of Compliance were cancelled due to the ——————————. In the absence of the inspection, the Division was not able to take an action by the PDUFA date of December 20, 2008. The inspections were postponed until January of this year, have been conducted, and the sites have been found to be acceptable. b(4)

A domestic site responsible for packaging the drug product in ——— for distribution of ———————, which was also an alternate site used for stability testing for the drug product, was inspected and found to be unacceptable by the Office of Compliance. The site, ——————————, was removed from the application by the Applicant, and they noted in an amendment on May 5, 2009, that they did not intend to distribute any ——————————— until they obtain FDA approval of the site. b(4)

With the withdrawal of the ——— site by the Applicant, the inspection request was removed from the Establishment Evaluation System and the Office of Compliance was requested to re-evaluate their overall recommendation. On May 7, 2009, the Office of Compliance made an Acceptable recommendation for the NDA. b(4)

Outstanding or Unresolved Issues
I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months———————— b(4)

4. Nonclinical Pharmacology/Toxicology

General Considerations
The applicant has relied almost entirely on the published literature to support the nonclinical aspects of the application. As such, the pharmacology/toxicology review team has noted several important aspects of the application:

- The nonclinical studies submitted in support of the application are almost exclusively old, pre-dating the Good Laboratory Practices (GLP; in most cases they do not use current and preferred evaluation methodologies.
- The dose levels used in the nonclinical studies were intended to determine the effects, rather than the safety, of colchicine.
- The nonclinical studies available are almost exclusively of short duration (i.e. $\leq$ 5 weeks) and, therefore, do not support chronic dosing.
- The colchicine product used in the published studies is frequently of unknown quality and comparability when compared with the Applicant's drug product.
- The nonclinical data in the submission do not address all the nonclinical sections of the label (e.g. carcinogenicity).
- Genetic toxicology studies and the mechanism of action indicate colchicine may reasonably be expected to promote or induce neoplasia.
- Reproductive toxicology studies conducted in nonclinical models indicate a significant risk for embryofetal harm and reduced parental fertility.
- 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.

Nevertheless, while cognizant of the limitations identified above, Dr. Wasserman has noted that "...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." Drs. Wasserman and Leshin proceed to note that given the extensive clinical experience with colchicine, there is sufficient information available to support labeling of the product.

Genotoxicity and Reproductive Toxicology
Colchicine is not directly genotoxic, but as a mitotic spindle poison, promotes the development of aneuploidy (a deviation from the normal complement of chromosomes) in the affected cells.

The severity of the developmental outcome is dependent on when, and to which cells, the aneuploidy occurs. Dr. Wasseman noted that embryonic or germ line aneuploidy causes developmental abnormalities in many species, and that colchicine administration in reproductively aged animals induces significant reductions in fertility through direct effects on germ cells as well as hormonal alterations supporting the embryonic environment. Teratogenic effects have been noted in multiple species after maternal exposure to colchicine. The degree and nature of the defects are dependent on the developmental stage of embryo exposure.

Carcinogenicity

Colchicine has not been studied in the standard rodent carcinogenicity bioassays; however, aneuploidy, which is in itself a risk for tumorigenesis, has been known to occur in eukaryotes that have been exposed to colchicine. Drs. Wasserman and Leshin have noted that there is sufficient information to label the product; however, they note that the literature raises the question whether colchicine, at clinically therapeutic doses, may promote de novo tumorigenesis via aneuploidy, may inhibit progression of malignancy by impairing the ability of mutant and transformed cells to divide, or both (in an exposure-dependent fashion). Their recommendation is that colchicine should be evaluated in a standard 2-year rat bioassay, as well as in a 6-month transgenic mouse study, but, that in view of the existing clinical experience, they do not need to be conducted prior to approval.

Outstanding or Unresolved Issues

There is the potential for the presence of photo-degradants which contain a structural alert for mutagenicity (identified as β- and γ-lumicolchicine), which has not been adequately addressed in the submission. The Applicant has indicated that they have not observed these degradants in the drug product; however, they have not developed detection methods which are sensitive enough to preclude such impurities being above the current standard of 1.5 µg/day total daily intake (TDI). Dr. Bertha has noted that the proposed packaging of the drug product in HDPE bottles or ——————— packages (the latter form for ———————) should protect the product sufficiently from light such that significant photo-degradant development should not occur. The final recommendation from Dr. Wasserman is that the Applicant must improve their detection assays to allow reduction of the specifications for the photo-degradant impurities β- and γ-lumicolchicine to a limit of not more than 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.

b(4)

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

General Considerations

The Applicant submitted the results from six clinical pharmacology/biopharmaceutics studies:

MPC-004-07-1001	A single-dose crossover study in 28 healthy subjects to assess the bioavailability of colchicine 0.6 mg tablets compared to Col-Probenecid, administered under standard fasting conditions.
MPC-004-07-1002	A single-dose, double-blind, double-dummy study in 18 healthy subjects to

	evaluate the pharmacokinetic profile of colchicine and its metabolites (2-, 3-, and 10- demethylocolchicine). In addition to the pharmacokinetic evaluation, the effect of these doses on subjects' electrocardiograms (ECGs) was assessed
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.
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.
MPC-004-07-1005	A multiple-dose, randomized, double-blind, two-sequence study in 30 healthy subjects to determine whether the steady-state dosing of colchicine influences the steady-state pharmacokinetic profile of ethinyl estradiol or norethindrone
MPC-004-07-1006	A single-dose, open-label study in 24 healthy subjects to confirm the extent to which multiple oral doses of clarithromycin influence the single-dose pharmacokinetic profile of colchicine and its metabolites.

Colchicine is predominantly eliminated by biliary excretion and through the stool; gastrointestinal tract lining cell turnover has a variable role in colchicine elimination. As noted in Dr. Okada's review, colchicine is extruded from cells, including the 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, PGY1; also known as 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 3E4 (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. 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 orally administered, reaching a mean C_{max} of 2.5 ng/mL (range 1.1 to 4.4 ng/mL) in 1 to 2 hours (range 0.5 to 3 hours) after a single 0.6-mg dose administered under fasting conditions. Following repeated dosing, colchicine appears to achieve steady state concentrations within 14 days. The mean C_{max} after multiple dosing was 3.1 to 3.6 ng/mL. Absolute bioavailability was reported to be approximately 45%.

Distribution:
Colchicine is lipid-soluble and has a mean apparent volume of distribution in healthy young volunteers of approximately 5 to 8 L/kg. Colchicine binding to serum protein is 39 ± 5%, and binds primarily to albumin; it crosses the placenta and distributes into breast milk.

Metabolism:
There are two primary metabolites, 2-O-demethylcolchicine and 3-O-demethylcolchicine (known as 2- and 3-DMC, respectively), and one minor metabolite, 10-O-demethylcolchicine (also known as 10-DMC or colchiceine). Human liver microsomes studies have shown that

CYP3A4 is involved in the metabolism of colchicine to 2- and 3-DMC. In vivo, exposure to 2-DMC and 3-DMC metabolites is less than 5% of parent drug.

Elimination/Excretion:
A major route of elimination is thought to be enterohepatic recirculation and biliary excretion, mediated by P-gp. The mean elimination half-life in young healthy volunteers after multiple oral doses (0.6 mg twice daily) was 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; colchicine is not removed by hemodialysis.

Critical Intrinsic Factors
The Applicant did not conduct any studies to evaluate the effects of age, race, body weight, organ dysfunction, or pregnancy on the pharmacokinetics of colchicine. The submission addressed the following intrinsic factors.

Age:
Pharmacokinetics of colchicine was not evaluated in elderly; however, since decreases in renal and hepatic function are common in the elderly, caution is warranted when using colchicine in this population. There is no information on the pharmacokinetics of colchicine in pediatric patients in the published literature; however, there is a fairly extensive literature on the use of colchicine in pediatric patients.

Renal impairment:
Renal elimination accounts for approximately 10-20% of colchicine clearance. A four-fold decrease in colchicine clearance is noted in severe renally-impaired patients with FMF compared to patients with normal renal function. Drs. Nallani and Doddapaneni recommended that consideration should be given to the reduction of the dosage in patients with mild and moderate renal impairment, and definite dose reduction in patients with severe renal impairment and undergoing dialysis (total daily dosage should be reduced to 0.3 to 0.6 mg colchicine per day).

Hepatic impairment:
Published studies with intravenous and oral colchicine in patients with severe hepatic impairment 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. Drs. Nallani and Doddapaneni recommended caution when colchicine is considered for patients with mild hepatic impairment and consideration should be given to the reduction of the dosage in patients with moderate and severe hepatic impairment.

Thorough QT study
Study MPC-004-07-1002 included an informal assessment of QT prolongation. Subjects were randomized to receive colchicine (n=15) or moxifloxacin (n=3); however, as noted by Drs. Nallani and Doddapaneni, this study was insufficiently powered to detect a difference between colchicine and moxifloxacin, which was intended to serve as a positive control. 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. There was little change in QT interval regardless of correction methodology [Fridericia (QTcF) or Bazett's (QTcB)]. Overall, in this study and in the other pharmacokinetic studies conducted by the Applicant, no effect on QTc or any other ECG parameter was noted with therapeutic doses of colchicine.

Drug-Drug Interactions

The macrolide antibiotics erythromycin and clarithromycin, and the statins, e.g., lovastatin, simvastatin, atorvastatin, have the potential to increase colchicine toxicity via dual modulation of ABCB1 and CYP3A4. There are case reports suggesting that 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, which could be attributed to either drug.

The Applicant conducted Study MPC-004-07-1006 to evaluate the potential interaction between colchicine and clarithromycin, since in vitro studies had demonstrated colchicine to be a substrate of CYP3A4 and P-gp and clarithromycin, a strong inhibitor of P-gp and CYP3A4. A three-fold increase in colchicine C_{max} and AUC was noted when colchicine was coadministered with clarithromycin and, 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 roles of CYP3A4 and P-gp, including studies with ritonavir, ketoconazole, grapefruit juice, and cyclosporine.

The available data suggest dosage adjustment is necessary with strong CYP3A4 and P-gp inhibitors. Drs. Nallani and Doddapaneni recommended that the colchicine dose should be reduced to 0.3 mg twice daily when patients with FMF are concomitantly being treated with 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 MPC-004-07-1005). This study demonstrated that multiple dose administration of colchicine does not affect plasma levels of ethinyl estradiol and norethindrone.

Outstanding or Unresolved Issues

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Colchicine is not a therapeutic antimicrobial, therefore clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical-Efficacy

The Division had indicated to the Applicant that, in principle, the application for FMF could potentially rely solely on publicly available information, specifically, published articles in the scientific and medical literature. Subsequently, the Applicant performed a comprehensive search of the following databases, as noted in Dr. Hull's review:

- 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.

The applicant included 74 of the more than 1200 published articles identified in the above searches; of these 74, only 19 were deemed to be of adequate quality to be of use in the determination of the efficacy and dosing information of colchicine to prevent attacks of FMF in adults and children. These are summarized in the tables below, adapted from Dr. Hull's review.

Studies Used to Support the Efficacy of Colchicine

Reference	N	Study Design	Treatment Regimen	Primary Efficacy Outcome
Randomized, controlled Trials				
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
Non-randomized, Open-label Trials, Adults				
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	Frequency of Acute Attacks

Reference	N	Study Design	Treatment Regimen	Primary Efficacy Outcome
			1.5 mg/day	
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 to 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
Non-Randomized, Open-Label Trials, Children				
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
R: Randomized; DB: Double-blind; PC: Placebo-controlled; C/O: cross-over; NR: Non-randomized; OL: Open-label; OBS: Observation Study				

The three, randomized, controlled trials were the focus of the review team's assessment for evidence of efficacy. As noted in Dr. Hull's and Okada's review, pertinent aspects of the three studies were as follows:

- The three randomized, double-blinded, placebo-controlled studies enrolled patients with similar demographics 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.
- Although the exclusion criteria among the three studies were generally similar, they did differ regarding the co-morbidities (e.g., amyloidosis) and concomitant mediations (e.g., corticosteroids or narcotics). However, the differences between the studies' exclusion criteria were not believed to impact the interpretation of the results.
- The three randomized trials used similar dosing regimens of colchicine, between 1 to 1.8 mg per day.
- The three studies utilized a crossover study design, whereby each patient received colchicine and placebo during different periods of the same study. Since the individual patients have different frequencies of attacks, the crossover design allows each patient

serves as their own control. This design also required fewer patients than a parallel group design study, which is helpful when evaluating a rare disorder.

- 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), Dr. Hull's 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). Well-defined objective signs and symptoms of an attack, e.g., peritonitis, pleuritis, fever, arthritis, and rash, in addition to their subjective symptoms, were utilized in the studies, making the proper identification of an attack more reliable.
- Each study reported treatment periods of at least two months duration, which was felt to be an adequate amount of time to discern a meaningful difference between the two treatment arms.

I concur with Drs. Hull and Okada that the designs of the three clinical studies, specifically the choice of the control group, the primary endpoint, the duration of study, and the definitions used to identify an attack, are adequate to allow for the assessment of the clinical efficacy of colchicine. The number of patients enrolled in the studies was small: a total of 48 patients were enrolled in the three studies. The patients were of various ethnicities commonly affected by FMF, and although the majority of the patients were male, it was felt that this would not affect the ability to extrapolate the results of the studies, as males and females share the same genetic mutations and the phenotypic expression of the disease is similar in both genders.

The study by Dinarello, et al., was discontinued after six patients had completed the study, when a planned interim analysis was interpreted to indicate a clear benefit with the colchicine treatment. In the other two studies, a total of 24 of 37 (65%) patients completed the studies. Thirteen patients discontinued during the placebo treatment due to attacks (six patients), noncompliance (six patients), or lost to follow-up (one patient).

Although the number of patients enrolled in the studies was small, the treatment effect observed was sufficient to allow the three trials to demonstrate evidence of efficacy in the reduction in the number of febrile acute attacks experienced by the patients, as summarized in the following table, adapted from Drs. Okada's and Hull's review:

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

Dr. Price noted the potential for unblinding, given the gastrointestinal side effects known to be associated with colchicine therapy. However, since the outcome of interest was the number of attacks, it was felt that this was an entity that was could be objectively evaluated, minimizing the concerns for an awareness of the treatment assignment.

As noted in Dr. Price's review, the statistical methods reported to be used in the articles by Goldstein and Schwabe, and Zemer, et. al., were reasonable. Specifically, Goldstein and Schwabe used a nonparametric alternative to a paired t-test, the sign test, and Zemer et. al., used several analysis methods including an unpaired t-test, a Mann-Whitney test (a nonparametric alternative to an unpaired t-test), and a paired t-test. The data were provided in both published studies, permitting Dr. Price to replicate the authors' results. In addition, Dr. Price conducted a nonparametric analysis on the Month 4 data from Zemer's study. For both articles, Dr. Price found that there was a statistically significant difference in the number of attacks experienced by patients while on colchicine compared to the period when they received placebo, and her final conclusion was in agreement with that of the authors.

The results from these three studies, in conjunction with the additional clinical experience reported in the literature, are supportive of the efficacy of colchicine in the treatment of febrile episodes of familial Mediterranean fever.

It is worth noting that the application did not contain enough data to support the Applicant's contention that colchicine was also effective in the treatment of ——————————

b(4)

8. Safety

General Considerations

The Applicant did not conduct any clinical trials evaluating the efficacy of colchicine in FMF, therefore the only safety data from clinical exposure to their product originated from the pharmacokinetic studies conducted by the applicant. Of the 126 healthy volunteers, 83 were exposed to a single-dose, 1-day regimen, and 43 were exposed to 10- to 14-day multi-dose regimens intended to evaluate colchicine's steady state pharmacokinetics. The remainder of the safety information in the application, as noted by Dr. Okada, included the following:

1. Information from the medical literature, including 3,545 patients with FMF, both adults and children, in the 3 randomized, controlled studies and 21 uncontrolled studies. There were also meta-analyses of studies of colchicine in other indications, which included 671 patients with hepatic and biliary cirrhosis;

2. The FDA post marketing adverse event report database, which included 751 adverse event reports from 1969 through 30 June 2007;
3. The World Health Organization (WHO) post marketing adverse event report database, which included 1380 adverse event reports from 79 countries, including the United States, from 1968 through March 2006;
4. Currently approved labeling for Col-Probenecid (US), and oral colchicine labels from Argentina, Australia, Britain, Germany, Mexico, France, Singapore, and Uganda.

It is clear that the data from these sources have a number of limitations. Much of the data are uncontrolled, and any controlled data have been primarily obtained from the literature, which typically does not report safety data in an extensive or systematic manner. Further, post marketing adverse event reporting is biased toward the most severe events and is limited by the lack of a reliable denominator from which one can derive incidence and relative risk.

The review team felt that these limitations are not as critical in the case of single-entity colchicine, predominantly because of its long history of clinical use and previously well-described toxicity profile. The most frequent adverse effects of oral colchicine in therapeutic doses are those involving the gastrointestinal tract with diarrhea, nausea, vomiting, and abdominal pain often being the first signs of toxicity and the first indication that the colchicine dose may need to be reduced or the therapy stopped. Larger doses may cause profuse diarrhea, gastrointestinal hemorrhage, skin rashes, and renal and hepatic damage. Bone marrow suppression with agranulocytosis, thrombocytopenia, and aplastic anemia has rarely occurred with prolonged treatment, as have peripheral neuropathy, myopathy, rashes, and alopecia.

Overdose with colchicine is uncommon, but when it does occur, it constitutes a toxicological emergency and rapid intervention is required. Treatment is primarily supportive, and in addition to gastric lavage and orally administered activated charcoal, is dependent on the target organ manifestations. As noted by Dr. Okada, the signs and symptoms 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.

If the overdose is significant enough to result in the death of the individual, expiration typically occurs within the first 48 hours after ingestion and is due to cardiac dysrhythmias, cardiovascular collapse and respiratory failure, with a second peak 3 to 7 days after exposure, usually due to sepsis.

Adverse events in the Clinical Pharmacology Trials

The adverse events (AEs) seen in the clinical pharmacology trials were consistent with the known toxicity profile of colchicine, and are summarized in the table below (reproduced from Dr. Hull's review).

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
General Disorders and Administration Site Conditions						
Cold sweats	0	0	0	0	2 (5%)	2 (< 1%)
Pallor	2 (3%)	0	0	0	0	2 (< 1%)
Gastrointestinal Disorders						
Diarrhea	0	0	2 (15%)	15 (100%)	6 (16%)	23 (19%)
Hypoacusis	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%)
Musculoskeletal and Connective Tissue Disorders						
Pain in extremity	3 (5%)	0	0	0	0	3 (< 1%)
Nervous System Disorders						
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%)
Respiratory, Thoracic and Mediastinal Disorders						
Nasopharyngitis	1 (2%)	0 (0%)	0	1 (7%)	0	2 (< 1%)
Eye disorders						
Vision blurred	2 (3%)	0 (0%)	0	0	0	2 (< 1%)

* MedDRA = Medical Dictionary for Regulatory Activities

The most commonly reported adverse events among the 119 healthy volunteers exposed to at least one oral dose of colchicine 0.6 mg were diarrhea and nausea and vomiting, the majority of which occurred at the high-dose regimen (4.8 mg over 6 hours). None of the adverse events required discontinuation from the study or dose reduction and there were no deaths or serious adverse events (SAEs).

Deaths

Deaths due to colchicine toxicity were not noted in the literature reporting colchicine's efficacy in the treatment of FMF and FMF-related amyloidosis. Report of deaths related to colchicine therapy in the published literature were primarily found in articles discussing the toxicity of colchicine, and in case reports of acute or chronic overdose.

The post marketing adverse event databases, however, did have several reports of fatalities associated with colchicine therapy. In the WHO post marketing database, 48/1380 (3%) reports were regarding deaths. In the FDA post marketing adverse event databases from 1969 to 30 June 2007, 234 deaths were reported in the total 751 adverse events reports identified (31%). Since the applicant did not have full narratives for all cases, this total may contain duplicates. 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 the reports

were associated with overdoses. Of the fatalities not associate with an overdose, 60/117 (51%) reported clarithromycin as a co-suspect/concomitant/interacting drug.

Other Adverse Events

The most commonly affected organ system reported in the post marketing adverse events database was the gastrointestinal system. As noted by Drs. Hull and Okada, the most commonly reported adverse events were diarrhea, nausea and vomiting, abdominal pain and cramping. In the FDA post marketing databases, 340 of 751 (45%) reports were for gastrointestinal adverse events, with diarrhea being the most common, for the period from 1969 to 30 June 2007. For the period from 1968 to March 2006, 46% (633/1380) of reports in the WHO post marketing database were related to gastrointestinal events.

Drs. Hull and Okada also noted that there is evidence for implication of colchicine therapy in the adverse events reported in the following organ systems, event though, at therapeutic doses, the incidence is low. The following summary is reproduced from Dr. Okada's review.

Hematologic/Lymphatic System

Myelosuppression is a known dose-related adverse event associated with colchicine. 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 post marketing databases (1969 to June 30, 2007), 87 of 751 (~12%) total reports pertained to marrow or hematopoietic lineage specific suppression.

Musculoskeletal/Neuromuscular

Colchicine-induced neuromuscular toxicity has reported 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 post marketing 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.

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

Special safety Issues

Drs. Hull and Okada have also identified three safety issues associated with colchicine therapy which warrant specific discussion.

The first issue is colchicine's potential for drug-drug interactions, some of which can be result in exposure to lethal levels of colchicine. These interactions are described above, and more extensively by Dr. Nallani in the Clinical Pharmacology reviews. The Applicant has included a comprehensive list of potential drug interactions in the warning section of the proposed label. In addition to the table, and the dosage modification, the review team has concluded that a Medication Guide will be an important component of the label, as it is necessary for patient's safe and effective use of the product. Therefore, a Risk Evaluation and Mitigation Strategy (REMS), consisting of a Medication Guide will be required of the Applicant.

The second issue is the potential for colchicine toxicity in special populations. Dr. Okada has noted in her review that, 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. Further, a 2.5- to 10-fold lower clearance has been reported in cirrhotic patients, when compared to healthy subjects. The Applicant has not conducted formal pharmacokinetic studies in the elderly, but since the elderly are more likely to have significant renal or hepatic impairment, they are more at risk, and appropriate precautions should be taken. The applicant has not conducted any pharmacokinetic studies in the pediatric patient population; however, there is information in the medical literature regarding dosing in pediatric patients.

The third issue is the use of colchicine in women with FMF, specifically with respect to colchicine's effects on fertility, reproductive and developmental toxicity, and implications in lactating women. Dr. Okada notes that, since 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.

Dr. Leshin's review of studies submitted by the Applicant indicates that colchicine administration in animals induces significant reductions in fertility through direct effects on germ cells as well as hormonal alterations supporting the embryonic environment. Further, teratogenic effects have been noted in multiple species after maternal exposure to colchicine, and the degree and nature of the defects are dependent on the developmental stage of embryo exposure. Clinically, 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.

Dr. Okada notes in her review that 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.

The Applicant has proposed that 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. Dr. Okada acknowledges the limitations of the available human data, but notes that, "...overall, there does not appear to be a major negative impact of colchicine in therapeutic doses on fertility or development."

With respect to lactating women, Dr. Okada noted that colchicine distributes into breast milk, but ingestion *via* breast feeding results in doses that are estimated to be 1/10th to 1/20th therapeutic doses. She also noted that there are no published reports of adverse effects of colchicine in breastfeeding infants of mothers taking colchicine, citing a 1998 article in which 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.

Outstanding or Unresolved Issues

As noted by Dr. Okada, based on its mechanism of action and the nonclinical data to date, colchicine would be expected to be a teratogen; however, the limited clinical data in patients with FMF seem to indicate that, at therapeutic doses, it is not particularly unsafe and may actually be beneficial for a women with FMF to continue colchicine treatment during a pregnancy in order to minimize the inflammatory attacks, which are felt to be more detrimental. Drs. Leshin and Wasserman have suggested a pregnancy registry be instituted to obtain additional information; however, Drs. Hull and Okada believe that it will have limited utility, in part because it is unlikely to have very many enrollees who will not be taking colchicine to serve as a control, and it 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. Due to the incidence of FMF in the United States, I tend to agree with Drs. Hull and Okada that a pregnancy registry would have limited utility.

The other outstanding issue is the narrow therapeutic index of colchicine and the potentially lethal drug-drug and drug-disease interactions. Although a point can be made that these issues are generally known, the potential clinical significance of their adverse consequence is such that a Medication Guide should be required. Dr. Okada indicated in her review that since colchicine is widely available and used currently, she did not believe that the medication guide is necessary for the approval of this application, and could be required of the applicant as a post-marketing commitment. I believe that since it is part of the strategy that would critical for the safe use of the product, i.e., REMS, it should be required as part of the approval.

5. Advisory Committee Meeting

The convening of an advisory committee meeting for discussion of this application was deemed to be unnecessary. This decision was reached in view of the observation that colchicine has a long history of medicinal use, the clinical experience with colchicine and the specific indication being sought in the application (FMF), and the lack of any specific issues identified in the application that would warrant discussion at an advisory committee meeting.

6. Pediatrics

After consultation with the staff of the Pediatric Review Committee (PeRC), it was concluded that, since the Applicant had secured orphan product status for this indication, it would not be necessary to take the application in front of the committee.

As noted above, although the Applicant did not conduct any pharmacokinetic studies in pediatric patients, the Applicant did propose dosing for the pediatric patient population, based on the available published medical literature.

7. Other Relevant Regulatory Issues

Consultations were obtained from the Division of Drug Marketing and Communications (DDMAC), the Division of Risk Communication (DRISK), the Division of Medication Error Prevention and Analysis (DMEPA), and the Pediatric and Maternal Health (PMH) staff. Their recommendations were reviewed and incorporated in the appropriate places in the label.

There were no clinical sites to inspect; therefore, the Division of Scientific Investigations was not consulted.

There are no other unresolved relevant regulatory issues.

8. Labeling

The Applicant had originally requested the name "Colstat" as the proprietary name, but it was found to be unacceptable because it contained the United States Adopted Names (USAN) Council stem '-stat'. This particular USAN stem has the USAN definition of "enzyme inhibitors," and since the product is not an enzyme inhibitor, the use of this stem in the proposed proprietary name would be inconsistent with the USAN definition. The Applicant had also submitted the name "Colcrys" as an alternative; this was found to be acceptable.

As noted above, a Medication Guide is being required because we have determined that colchicine meets two of the three criteria for a Medication Guide as set forth in 21 CFR 208.1: colchicine is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use colchicine; and colchicine is a product for which patient labeling could help prevent serious adverse events. Therefore, a Medication Guide is necessary for patients' safe and effective use of colchicine.

9. Decision/Action/Risk Benefit Assessment

- Regulatory Action
  Approval

- Risk Benefit Assessment

The Applicant has presented information to demonstrate that colchicine therapy is effective in reducing the number of attacks in patients with familial Mediterranean fever. I concur with Drs. Hull and Okada that, overall, when colchicine is taken in therapeutic doses, and when the prescriber exercises vigilant monitoring with respect to the appropriate reduction of dosage in susceptible populations, or with potentially interacting drugs, colchicine is generally safe and well-tolerated.

- Recommendation for Post marketing Risk Management Activities

Due to the potentially serious drug-drug interactions that have been identified, it will be necessary for Colcrys to have a medication guide. This will increase the probability that a patient will accurately report to the prescribing health professional all the concomitant medications that they may be taking, and avoid a serious complication.

- Recommendation for other Post marketing Study Requirements

I concur with Dr. Wasserman's recommendation that colchicine should be evaluated for its carcinogenic potential in a standard 2-year rat bioassay, as well as in a 6-month transgenic mouse study, in view of the fact that familial Mediterranean fever affects a younger population that may end up requiring treatment for the remainder of their life and, therefore, may be at an increased risk for tumor development. I also concur with the rationale that, in view of the existing clinical experience, the severity of this disease and its associated morbidity and mortality, these studies do not need to be conducted prior to approval.

With respect to the potential for the presence of photo-degradants which contain a structural alert for mutagenicity (identified as β- and γ-lumicolchicine), which has not been adequately addressed in the submission, I concur with Dr. Wasserman's recommendation that the Applicant must improve their detection assays to allow reduction of the specifications for the photo-degradant impurities β- and γ-lumicolchicine to a limit of not more than 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.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22352	ORIG 1	MUTUAL PHARMACEUTICAL CO INC	COLCRYS TABLETS,6MG

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

/s/

RIGOBERTO A ROCA
07/29/2009