

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-352

OTHER REVIEW(S)

EXECUTIVE SUMMARY

Mutual Pharmaceutical Company Inc. submitted a New Drug Application (NDA) on June 20, 2008, for Colchicine Tablets, USP, 0.6 mg, for the treatment of adults and children ≥ 4 years of age with Familial Mediterranean Fever, specifically for the _____

_____. The Maternal Health Team (MHT) was consulted to review the Pregnancy and Nursing Mothers section of the proposed colchicine labeling.

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Colchicine, a marketed, unapproved (as a single-active ingredient) drug product, has been used for years in the treatment of certain inflammatory conditions including Familial Mediterranean Fever (FMF). FMF is an autosomal recessive, autoimmune disorder characterized by recurrent episodes of inflammation in the peritoneum, pleura, and synovium, often accompanied by a fever and rash. This inflammatory process leads to amyloidosis in organs and tissues and most often renal failure. Continued, daily use of colchicine tablets has become the standard therapy for prevention of FMF attacks and amyloid deposition. Colchicine disrupts cellular processes including spindle formation and has demonstrated adverse early embryonic development and teratogenic effects in animal studies. Limited human data from pregnant and nursing women have not demonstrated adverse fetal or infant effects when colchicine is used at recommended doses.

The MHT agrees with the Sponsor proposed Pregnancy Category C designation and has provided revisions to the Sponsor 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, we have required regulatory language regarding colchicine use during pregnancy and lactation to the Highlights of Prescribing Information, Use in Specific Populations section of the labeling.

INTRODUCTION

On June 20, 2008, Mutual Pharmaceutical Company Inc. submitted a NDA for Colchicine Tablets, USP, 0.6 mg, for the treatment of adults and children ≥ 4 years of age with Familial Mediterranean Fever (FMF). The Maternal Health Team (MHT) was consulted to review the Pregnancy and Nursing Mothers section of the proposed colchicine labeling.

Colchicine is a tricyclic alkaloid with anti-inflammatory properties. It interacts with microtubules, inhibiting spindle fiber formation and disrupting cellular processes, including mitosis and meiosis. Colchicine also induces change at the transcriptional level. Through its mechanism of action, colchicine produces a stabilizing action on the cytoskeleton and cell membranes.¹

BACKGROUND

Regulatory History

Colchicine (Tablets) were approved as part of a combination product, NDA 12-383, ColBenemid (colchicine 0.5 mg and probenacid 500 mg) in 1961 (DESI review 1972) for the treatment of

¹ Ben-Chetrit E, Bergmann S, Sood R. Mechanism of the anti-inflammatory effect of colchicine in rheumatic diseases: a possible new outlook through microarray analysis. *Rheumatology* 2006; 44:274-282.

chronic gout. The current FDA approved versions of colchicine are colchicine tablets in combination with probenacid (Col-Probenacid from Watson Labs and Probenacid and Colchicine from IVAX Pharmaceuticals). Colchicine is not approved in the U.S. as a single-active ingredient drug; however, colchicine has been in use in the U.S. since the early 1900's and has been used (as an unapproved drug product) for 40 to 50 years in the treatment of Familial Mediterranean Fever, Behcet's Syndrome, Sweet's Syndrome, scleroderma, amyloidosis, liver cirrhosis, and other diseases.² Adverse early embryonic development and teratogenic effects have been demonstrated in animal studies; and because colchicine disrupts cellular processes, these same potential adverse effects have been a concern for colchicine-treated pregnant women.

In February 2008, FDA took enforcement action and ordered unapproved injectable colchicine products off-the-market for safety reasons (colchicine has a narrow margin between an effective dose and a toxic dose and can easily be administered in excessive doses when injected intravenously), and at the same time encouraged manufacturers of colchicine tablet products to pursue FDA approval.³ In response to this action, Mutual Pharmaceutical Company Inc. submitted a New Drug Application (NDA) on June 20, 2008, for Colchicine Tablets, USP, 0.6 mg, for the treatment of adults and children ≥ 4 years of age with Familial Mediterranean Fever (FMF), specifically for the _____

_____. The review division requested that MHT review the pregnancy and nursing mothers sections of labeling and supporting referenced articles submitted to the NDA by the Sponsor.

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Familial Mediterranean Fever and Colchicine

Familial Mediterranean Fever (FMF) is an autosomal recessive, autoimmune disorder primarily affecting people of Armenian, Arabic, Turkish, and Jewish ancestry. The incidence ranges from 1/250 people to 1/1000 people in these populations, and the condition occurs less commonly in other populations. FMF is characterized by recurrent episodes of inflammation in the peritoneum, pleura, and synovium, often accompanied by a fever and rash. Without treatment of the inflammatory process, amyloidosis occurs in organs and tissues, often leading to renal failure.^{4,5} Goldfinger, 1972⁶ reported on the effectiveness of colchicine in preventing acute attacks of FMF. Since this report, daily colchicine has become the standard therapy for prevention of FMF attacks and amyloid deposition.

REVIEW OF DATA

In addition to reviewing the sponsor's submitted labeling and supporting references, MHT conducted its own PubMed search for literature on colchicine and pregnancy, colchicine and breastfeeding, FMF and pregnancy, FMF and colchicine; and also searched Lactmed for data on colchicine use during lactation.

² Lange U, Schumann C, Schmidt KL. Current aspects of colchicine therapy-classical indications and new therapeutic uses. *Eur J Med Research* 2001 Apr 20; 6(4):150-60.

³ Questions and Answers about FDA's Enforcement Action Against Unapproved Injectable Colchicine Products. 2008 Feb 6.

⁴ Genetics Home Reference (<http://ghr.nlm.nih.gov/>)

⁵ Familial Mediterranean Fever; FMF (<http://www.ncbi.nlm.gov/entrez/ds>)

⁶ Goldfinger SE. Colchicine for Familial Mediterranean Fever. *NEJM* 1972; 287:1302

Pregnancy Section of Labeling

Sponsor's proposed Pregnancy section:

8.1 Pregnancy

Pregnancy Category C

_____ . *There are no adequate and well-controlled studies with colchicine in pregnant women.*
_____ *no evidence of an increased risk of miscarriage, stillbirths, or teratogenic effects.*

b(4)

Maternal Health Team Response

The proposed Pregnancy Category C is appropriate given that animal studies demonstrated teratogenic effects in offspring; however, the Sponsor failed to provide a summary of reproductive and developmental toxicity study findings. In order to properly label the product for use during pregnancy and lactation, these data should be submitted and described in terms of species exposed, timing of exposure, equivalent human doses, and maternal, fetal, and offspring outcomes. The Sponsor's proposed labeling does not include all required pregnancy category C regulatory language.

We recommend including all required pregnancy category C regulatory language along with the additional limited data on pregnant-exposed women in order to adequately communicate the potential risks of colchicine use during pregnancy to healthcare providers and patients. In addition, a complete brief summary of animal data should be included in the Pregnancy section.

Nursing Mothers Section of Labeling

Sponsor's proposed Nursing Mothers section:

8.3 Nursing Mothers

_____ *There are no published reports of adverse effects _____ in breast-feeding infants of mothers taking colchicine. Caution should be exercised when colchicine is administered to a nursing woman.*

b(4)

Maternal Health Team Response

The Sponsor presented accurate information; however, there are limited human data on use of colchicine during breastfeeding. The available data on dose and exposure in breastfed infants should be added to nursing mothers labeling to guide healthcare providers and patients in decision-making regarding lactation. The Drug and Lactation Database (Lactmed)⁷ summarizes limited study data indicating that exclusively breastfed infants receive less than 10 percent of the maternal weight-adjusted colchicine dose. We recommend including this information in the Nursing Mothers section.

DISCUSSION

Colchicine has demonstrated teratogenicity in animals; however, several small studies in pregnant women with FMF using colchicine have demonstrated no deleterious effects on the

⁷ The Drug and Lactation Database (<http://toxnet.nlm.nih.gov>)

mother or fetus. Even though colchicine inhibits cell mitosis and crosses the placenta, these limited human data do not show an association between human colchicine use during pregnancy and the teratogenic or mutagenic risks seen in animal studies.^{8,9} FMF inflammatory attacks appear to increase (including amyloid nephropathy) during pregnancy which can lead to adverse maternal and fetal outcomes including an increased risk of spontaneous abortion.¹⁰ Growing evidence suggests that continued daily treatment with colchicine not only improves the prognosis of women with FMF by preventing amyloidosis and the resulting nephropathy, but may also improve female fertility and pregnancy outcome.^{11,12}

The most common adverse events listed in the proposed colchicine label are gastrointestinal symptoms including abdominal pain, diarrhea, nausea, and vomiting. Worsening gastrointestinal symptoms are also the first sign of colchicine toxicity. None of these effects have been described in breastfed infants exposed to colchicine, and follow-up of a limited number of exposed infants has not shown any remarkable effects.¹³ As previously mentioned, The Drug and Lactation Database (Lactmed) summarizes colchicine drug levels and effects during lactation and reports that limited information indicates that exclusively breastfed infants receive less than 10 percent of the maternal weight-adjusted dose.

CONCLUSIONS

The Pregnancy and Nursing Mothers sections of the colchicine labeling should contain both FDA required regulatory language and clinically relevant data to guide healthcare providers and patients in making adequate risk/benefit decisions about colchicine use during pregnancy and lactation. In the recommendations section below, the MHT provides suggested revisions to the Sponsor proposed Pregnancy and Nursing Mothers sections of the colchicine labeling to reflect inclusion of required regulatory language and clinically relevant human data.

RECOMMENDATIONS

The Maternal Health team has the following labeling recommendations for colchicine:

1. Add the following statements to the HIGHLIGHTS OF PRESCRIBING INFORMATION, USE IN SPECIFIC POPULATIONS section of the labeling:
 - Pregnancy: Based on animal data, may cause fetal harm (8.1).
 - Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3).

⁸ Michael O, Goldman RD, Koren G. Safety of colchicine during pregnancy. *Canadian Family Physician* 2003 Aug; 49:967-9.

⁹ Mijatovic V, Hompes PG, Wouter MG. Familial Mediterranean Fever and its implications for fertility and pregnancy. *Eur J Obstet Gynecol Reprod Biol.* 2003 Jun10; 108(2):171-6.

¹⁰ Satnkovic K, Hentgen V, Grateau G. Auto-inflammatory syndromes and pregnancy. *Presse Medicale* 2008 Sep 23.

¹¹ Ben-Chetrit E, Levy M. Reproductive system in Familial Mediterranean fever; an overview. *Annals of Rheumatolgy Disease* 2003 Oct; 62(10):916-9

¹² Kallanich T, et al. Colchicine use in children and adolescents with Familial Mediterranean Fever: literature review and consensus statement. *Pediatrics* 2007; 119:474-483.

¹³ Kallanich T, et al. Colchicine use in children and adolescents with Familial Mediterranean Fever: literature review and consensus statement. *Pediatrics* 2007; 119:474-483.

2. Revise the Pregnancy section as follows:

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with colchicine in pregnant women.

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[P/T Reviewer: Add a sentence summarizing animal study outcomes.] Colchicine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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3. As noted above, the Pharmacology/Toxicology reviewer should revise the animal data information to describe species exposed, equivalent human doses, and maternal, fetal, and offspring outcomes.
4. Revise the Nursing Mothers section as follows:

8.3 Nursing Mothers

Colchicine is excreted into human milk. Limited information indicates that exclusively breastfed infants receive less than 10 percent of the maternal weight-adjusted dose. There are no published reports of adverse effects of colchicine in breast-feeding infants of mothers taking colchicine. Caution should be exercised when colchicine is administered to a nursing woman.

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5. The MHT requests to re-review the Pregnancy section of the labeling after the Pharmacology/Toxicology reviewer has summarized and added appropriate animal data information.

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/s/

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DRUG SAFETY OFFICE REVIEWER

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MEDICAL OFFICER
Concur

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: March 3, 2009

To: **Margarita Tossa**
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products
(DAARP)

From: **Michael Sauers**
Regulatory Review Officer
Division of Marketing, Advertising, and Communications (DDMAC)

Subject: NDA 22-352
DDMAC labeling comments for Colchicine Medication Guide

DDMAC has reviewed the proposed Medication Guide for colchicine and offer the following comments. These comments are provided using the updated proposed Medication Guide and PI forwarded via email by Margarita Tossa on February 25, 2009.

5 Page(s) Withheld

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 √ § 552(b)(5) Deliberative Process

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Michael A Sauers
3/3/2009 10:19:09 AM
DDMAC CONSUMER REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 19, 2009
To: Bob Rappaport, M.D., Director
**Division of Analgesics, Anesthetics and Rheumatology
Products**

Through: Claudia Karwoski, PharmD, Director (Acting)
Division of Risk Management

Jodi Duckhorn, MA, Team Leader
**Patient Labeling and Education Team
Division of Risk Management**

From: LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Product Information Reviewer
**Patient Labeling and Education Team
Division of Risk Management**

Subject: Review of Patient Labeling (Medication Guide) and
Proposed Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): Colchicine 0.6mg Tablets

Application
Type/Number: NDA 22-352

Applicant/sponsor: Mutual Pharmaceutical Company, Inc.

OSE RCM #: 2009-98

1 INTRODUCTION

This review is written in response to a request from the Division of Analgesics, Anesthetics and Rheumatology Products (DAARP) for the Division of Risk Management's Patient Labeling and Education Team to review the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) for colchicine tablets 0.6mg, which includes the draft Medication Guide (MG) and Timetable for Submission of Assessments of the effectiveness of the REMS.

FDA has determined that colchicine poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of colchicine. FDA has 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; colchicine is a product for which patient labeling could help prevent serious adverse events.

2 MATERIAL REVIEWED

- Draft TRADENAME (colchicine) Prescribing Information (PI) submitted January 22, 2009 and revised by the Review Division throughout the current review cycle.
- Draft TRADENAME (colchicine) Medication Guide (MG) submitted on January 22, 2009 and revised by the review division throughout the review cycle.
- TRADENAME (colchicine) proposed Risk Evaluation and Mitigation Strategy (REMS), submitted on January 22, 2009, and the Amendment to the Proposed REMS submitted on February 9, 2009.
- TRADENAME (colchicine) Container Labels for oral tablets: 0.6mg submitted October 2, 2008.

3 BACKGROUND

Mutual Pharmaceutical Company, Inc. submitted a New Drug Application (NDA 22-352) for colchicine tablets on June 20, 2008. The proposed indication for colchicine is for the treatment of familial Mediterranean fever (FMF) _____ in adults and children 4 years of age and older.

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The DAARP reviewed the colchicine PPI on January 7, 2009. The clinical team determined that a Medication Guide was warranted to alert patients to the potential for serious drug-drug interactions with colchicine and to the increased susceptibility to severe colchicine toxicity in patients with renal or hepatic impairment.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to provide FDA with new authorities to require sponsors of approved drugs to develop and comply with section 505-1 of the FDCA if FDA finds that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. These provisions took effect on March 25, 2008.

In an email dated January 7, 2009 DAARP informed the sponsor that a REMS is necessary for colchicine. The only elements of the REMS will be a Medication Guide and a timetable of submission of assessments of the REMS.

The sponsor submitted a proposed REMS for colchicine on January 22, 2009, and following feedback from the Agency submitted an amendment to the proposed REMS on February 9, 2009.

4 DISCUSSION

4.1 MEDICATION GUIDE

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the sponsor has a Flesch Kinkaid grade level of 9.5, and a Flesch Reading Ease score of 49.5%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level).

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers. See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4.2 PROPOSED REMS

- a. Goal

The Sponsor has proposed the following REMS goal:

The goal of this REMS is to _____ increased susceptibility to colchicine toxicity in patients with renal or hepatic impairment and potential serious drug-drug interactions with colchicine.

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The primary purpose for requiring a REMS is to communicate the serious risks associated with colchicine specifically the risk of increased susceptibility to colchicine toxicity in patients with renal or hepatic impairment and potential drug-drug interactions with colchicine, through use of a Medication Guide. We suggest broadening the goal slightly to address other risks associated with TRADENAME (colchicine). We recommend the following goal:

The goal of the REMS is to inform patients of the serious risks associated with the use of TRADENAME (colchicine), including the risks of increased susceptibility to colchicine toxicity in patients with renal or hepatic impairment, and potential serious drug-drug interactions with colchicine.

b. REMS Elements

- Medication Guide- colchicine tablets are provided in unit-of-use packaging. The sponsor's proposed REMS states that the MG will be dispensed with each TRADENAME (colchicine tablets, USP), in accordance with 21CFR208.24. The sponsor also proposes that the MG may be available through use of tear pads or on a website.
- The Timetable for Submission of Assessments is as follows:
 - 1st assessment: 18 months after approval
 - 2nd assessment: 3 years after approval
 - 3rd assessment: 7 years after approval

In the original REMS proposal the sponsor proposed a communication plan consisting of a _____ They subsequently submitted an amendment to the proposed REMS on February 9, 2009, following feedback from the Agency requesting _____ the REMS.

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4.3 Carton and Container

The sponsor must comply with 21 CFR 208.24(d), which requires a statement alerting pharmacists to dispense the MG with the product is on the carton and container on all strengths and formulations. The Sponsor submitted carton and containers for TRADENAME (colchicine) 30, 60, 250, 500, tablets and Professional Sample 1, and 3 tablets. The statement on the carton and container labels states the following:

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The statements above are not in compliance with MG regulation 21 CFR208.24(d) and are not acceptable. We propose the following language dependent upon whether the Medication Guide accompanies that product or is enclosed in the carton e.g., unit-of-use.

- We recommend the sponsor revise the proposed statement to read:
“Dispense the enclosed Medication Guide to each patient.” or
“Dispense the accompanying Medication Guide to each patient.”

5 CONCLUSIONS AND RECOMMENDATIONS

DRISK believes that the sponsor’s proposed REMS and Medication Guide for colchicine generally meets the statutory requirements outlined in section 505-1 of FDAAA and in 21 CFR 208. However, we have the following comments and recommendations:

We have the following comments on the proposed REMS:

1. We recommend the REMS goal be revised as follows:
The goal of the REMS is to inform patients of the serious risks associated with the use of TRADENAME (colchicine), including the risks of increased susceptibility to colchicine toxicity in patients with renal or hepatic impairment, and potential serious drug-drug interactions with colchicine.
2. See the appended TRADENAME REMS proposal (Appendix A) for additional track changes corresponding to comments in this review.
3. The statements on the carton and container to satisfy the requirements under 21 CFR208.24(d) are not acceptable. We recommend the following language dependent upon whether the Medication Guide accompanies that product or is enclosed in the carton e.g., unit-of-use.
“Dispense the enclosed Medication Guide to each patient.” or
“Dispense the accompanying Medication Guide to each patient.”
4. The sponsor should submit for review a detailed plan to evaluate the patients’ understanding about the safe use of colchicine at least 2 months before they plan to conduct the evaluation. The submission should include:
 - All methodology and instruments that will be used to evaluate the patients’ understanding about the safe use of colchicine. This should include, but not be limited to:
 - Sample size and confidence associated with that sample size
 - How the sample will be determined (selection criteria)
 - The expected number of patients to be surveyed
 - How the participants will be recruited
 - How and how often the surveys will be administered
 - Explain controls used to minimize bias
 - Explain controls used to compensate for the limitations associated with the methodology
 - The survey instruments (questionnaires and/or moderator’s guide).

- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

We have the following comments on the proposed Medication Guide:

1. In the section ‘What is the most important information I should know about TRADENAME?’ To avoid a long list of HIV protease inhibitors, we have instead listed the drug class. Patients are not likely to read through a whole “laundry list” of products.
2. In the section “What is the most important information I should know about TRADENAME” the sponsor should list all brand and generic names of the drugs listed. If all drugs in a class are not listed, patients may incorrectly think that they are “safe” if their medicine is not specifically listed.
3. In the section “What should I tell my healthcare provider before taking TRADENAME?” medications were added from section 7 of the PI. The sponsor should add to this list all brand and generic names for drugs listed. If all drugs in a class are not listed, patients may incorrectly think that they are “safe” if their medicine is not specifically listed. If this list becomes too long, it might be more appropriate to simply say “It is important for you to tell your healthcare provider about all the medicines you take”.
4. In the section “How should I take TRADENAME?” the statement _____
_____ has been removed. This information is not listed in the PI. For consistency, if the sponsor wishes to add this to the PPI it must be added to the PI. **b(4)**
5. In the section “What should I avoid while taking TRADENAME?” the sponsor should clarify what is considered a _____ of grapefruit juice. **b(4)**
6. In the section ‘What are the possible side effects of TRADENAME?’ We recommend that the sponsor list the signs and symptoms of fatal overdose and of drug interactions between TRADENAME and CYP3A4 inhibitors and P-gp in the PI so that they can be listed in the PPI. See warning and precautions, 5.1 Fatal overdose and 5.3 drug interactions.
7. In the section “How should I store TRADENAME? A temperature range was added from the PI as it is more realistic to provide an acceptable temperature storage range.
8. In the section “General Information about TRADENAME” the sponsor should provide website information if available.
9. We have added the following statement to the end of the section, “What are the possible side effects of TRADENAME?”:
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
This verbatim statement is required for all Medication Guides.

Please let us know if you have any questions.

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 √ § 552(b)(5) Deliberative Process

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 17, 2009

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia and Rheumatology Products

Thru: Kristina C. Arnwine, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Lorretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Colchicine Tablets USP
0.6 mg

Application Type: NDA 22-352

Applicant: Mutual Pharmaceutical Company, Inc.

OSE RCM #: 2008-1133

Contents

EXECUTIVE SUMMARY	3
1 BACKGROUND	3
1.1 Introduction.....	3
1.2 Regulatory History.....	3
1.3 Product Information.....	3
2 METHODS AND MATERIALS.....	4
2.1 Label and Labeling Risk Assessment	4
2.2 AERS Selection of Medication Error Cases	4
3 RESULTS	5
3.1 Label and Labeling Risk Assessment	5
3.2 AERS Selection of Medication Error Cases	5
4 DISCUSSION.....	5
4.1 Label and Labeling Risk Assessment	5
5 CONCLUSIONS.....	7
6 RECOMMENDATIONS.....	8
6.1 Comments to the Division.....	8
6.2 Comments to the Applicant.....	8
7 REFERENCES	9
APPENDICES	10

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment identified areas of vulnerability that could lead to medication errors. Specifically, improvements can be made to increase the prominence of information on the container labels, including a medication guide statement, and adding important information concerning administration of the product in the insert labeling (e.g., whether the tablets can be crushed or mixed with food to facilitate administration to those who are unable to swallow tablets).

The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products for assessment of the container labels and insert labeling for Colchicine Tablets USP, NDA 22-352.

1.2 REGULATORY HISTORY

This is a 505(b)(2) new drug application. The reference listed drug (RLD) for this NDA is Col-Probenecid (ANDA 84-279) which contains Colchicine 0.5 mg and Probenecid 500 mg. Colchicine is indicated for treatment and relief of pain in attacks of acute gouty arthritis. It is also recommended for regular use between attacks as a prophylactic measure, and is often effective in aborting an attack when taken at the first sign of articular discomfort.

The single ingredient, Colchicine, is a pre-1938 drug for which there is no currently approved NDA.

1.3 PRODUCT INFORMATION

Colchicine is a beta-tubulin interactor indicated in adults and children (4 years of age and older) with Familial Mediterranean Fever (FMF) _____

Colchicine is not indicated for treatment of acute attacks of FMF. Colchicine tablets are administered orally, without regard to food. The total daily dose may be administered in one or two divided doses. The recommended dosing is as follows (see chart below):

Age	Daily Dose	
	Usual	Maximum
Adults and children > 12 years	_____	2.4 mg
Children > 6 to 12 years	_____	_____
Children 4 to 6 years	0.3 _____	_____

The dose is to be increased or decreased as indicated and as tolerated in increments of 0.3 mg/day, not to exceed the maximum recommended daily dose of 2.4 mg. For patients with severe renal failure (estimated creatinine clearance less than 10 mL/min), the dosage should be 1.2 mg/day or less.

Colchicine will be available in 0.6 mg scored tablets in the following bottles sizes: 30-, 60-, 100-, 250-, 500-, and 1000-count. _____

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2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis staff conducting a label, labeling, and/or packaging risk assessment (see 2.1 Label and Labeling Risk Assessment). The primary focus for the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the United States Pharmacopeia-Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because the Division of Medication Error Prevention and Analysis staff analyzes reported misuse of drugs, the DMEPA staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. The Division of Medication Error Prevention and Analysis uses Failure Mode and Effects Analysis and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

The Division of Medication Error Prevention and Analysis reviewed the following container labels and insert labeling submitted by the Applicant on October 2, 2008. See Appendix A for pictures of the labels.

- Container Labels (30-, 60-, 100-, 250-, and 500-count bottles)
- _____
- Insert Labeling (no image).

b(4)

2.2 AERS SELECTION OF MEDICATION ERROR CASES

Since Colchicine tablets are currently marketed in the U.S. (various manufacturers), DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) for medication errors associated with the use of Colchicine tablets. Errors associated with the use of Colchicine should be taken into consideration when reviewing the labels and labeling for this NDA in order to prevent such errors from occurring with this product after it is introduced into the marketplace. DMEPA searched AERS using the High Level Group Term "Medication Errors", the Preferred Term "Pharmaceutical Product Complaint", and the

¹ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

active ingredient term "colchicine%". The cases were manually reviewed to determine if medication errors occurred involving the labels/labeling of Colchicine. Those cases that did not describe a medication error were excluded from further analysis.

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

3.1.1 Lack of a 0.3 mg Strength

The proposed product will only be available in a 0.6 mg scored, film-coated tablet. The recommended starting dose for children 4 to 6 years of age is 0.3 mg. Thus, the tablet will have to be split/halved in order to obtain a 0.3 mg dose.

3.1.2 General Comment for All Container Labels

The established name is not at least ½ the size of the proprietary name.

The label lacks a Medication Guide statement.

3.1.3 Container Labels

3.1.3.1 Container Labels (Trade)

The statement of strength lacks prominence on the label.

3.1.3.2 Container Label _____,

On the upper part of the label, the established name and the _____ are printed in _____ that is difficult to read. **b(4)**

The statement _____ is not prominent on the label.

3.1.4 Insert Labeling

In Full Prescribing Information, Section 2, *Dosage and Administration*, there are no directions for means to facilitate administration of the product to those who have difficulty swallowing tablets (e.g., pediatric patients).

The Error-prone symbol — is used in the Dosage and Administration section.

In Full Prescribing Information, Section 3, *Dosage Forms and Strengths*, two units of measure are used to specify the tablet strength [i.e., "0.6 mg _____"]. **b(4)**

3.2 AERS SELECTION OF MEDICATION ERROR CASES

DMEPA did not identify any medication error cases concerning colchicine tablets that were relevant to this review.

4 DISCUSSION

4.1 LABEL AND LABELING RISK ASSESSMENT

Our analysis identified several areas of needed improvement that may help to prevent medication errors.

4.1.1 Lack of a 0.3 mg Strength

The current proposal is to market one tablet strength (0.6 mg) despite the fact that the starting dose for children aged 4 to 6 years of age is 0.3 mg and dosage increases or decreases for all ages are recommended to be done in 0.3 mg increments. In order to achieve a 0.3 mg dose of Colchicine, the 0.6 mg tablet will have to be split/halved. This is problematic as studies have shown that tablet splitting may result in doses with substantial deviations from the intended dose. Even when a tablet is scored, it does not always split evenly. In one study of manually split tablet portions, 41.3% deviated from ideal weight by more than 10% and 12.4% deviated by more than 20% when split by adults³. In another study, there was a deviation between 9% and 37% of the intended dose when tablets were split in half by the elderly⁴.

Other potential sources of medication errors include misinterpretation of "1/2 tablet" as "1-2 tablets" and patients forgetting to split the tablet and inadvertently taking a whole tablet. These types of medication errors could lead to Colchicine overdose. Marketing a 0.3 mg tablet decreases the potential that patients will take the wrong amount of drug because of tablet splitting or that dispensing errors from misinterpretation of the dose "1/2" will occur.

We expressed our concerns to the Division that uneven splitting of tablets could result in deviations from the desired dose and asked for their input on the clinical consequences should this occur. We were informed by the medical officer via email on November 5, 2008 that *"there is no clinically significant safety or efficacy concerns with a difference in dosage that would result from a mis-scored colchicine tablet in either the adult or pediatric patient population."*

Additionally, per the Cross-Discipline Team Leader Review, dated December 1, 2008: *"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)."* We believe their response has adequately addressed this concern.

4.1.2 Container Labels (Trade _____)

b(4)

The established name appears less than ½ the size of the proprietary name. The size of the established name should be increased to at least ½ the size of the proprietary name (taking into consideration the font, type, etc.) in order to comply with 21 CFR 201.10(g)(2).

This product has an associated Medication Guide, however, the label lacks a Medication Guide statement. Therefore, a Medication Guide statement must be included on the label and it should be conspicuous, state that a Medication Guide must be provided to each patient, and also state how the Medication Guide is provided.

4.1.3 Container Label (Trade)

The statement of strength lacks prominence. Increasing the size of the statement of strength (0.6 mg) will increase its visibility and, thus, better facilitate product identification and selection from the pharmacy shelf.

³ Mcdevitt JT, Gurst AH, Chen Y. Accuracy of tablet splitting. *Pharmacotherapy*. 1998;18:193-197.

⁴ Peek BT, Al-Achi A, Coombs SJ. Accuracy of tablet splitting by elderly patients. *JAMA*. 1998;288:451-2.

4.1.4 Container Label _____

_____ at the upper part of the label lack sufficient contrast. The established name and the _____ are included in this area so adjusting the background color to improve contrast will improve the visibility and readability of this information. b(4)

The statement _____ is not prominent on the label. This statement concerns _____ and, therefore, needs more prominence and visibility.

4.1.5 Insert Labeling

4.1.5.1 Full Prescribing Information

Section 2

There is no information concerning whether the product can be crushed and/or mixed with food to facilitate administration of the product to those who have difficulty swallowing tablets. Since this product is labeled for use in children as young as 4 years of age, information should be provided, if available, that addresses means by which the product can be administered to those who are unable to swallow tablets.

The error-prone symbol— is used in the Dosage and Administration section. This symbol— which means _____, is on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations. The symbol is problematic because it may be mistaken as opposite of intended. For example, the symbol for— may be misinterpreted as _____. Therefore, this symbol should not be used. The phrase should be written out in order to prevent this type of misinterpretation from occurring. In an effort to reduce confusion and prevent medication errors that can result from the use of unnecessary and error-prone medical abbreviations in labels and labeling, the FDA and the Institute for Safe Medication Practices launched a nationwide health professional education campaign in June 2006 aimed at reducing the number of common but preventable sources of medication mix-ups and mistakes caused by the use of unclear and dangerous medical abbreviations. As part of this campaign, the FDA agreed not to use such abbreviations in the approved labels and labeling of drug products. b(4)

Section 3

Two units of measure are used to specify the tablet strength [i.e., “0.6 mg _____”. The strength as stated on the container labels and elsewhere in the insert labeling is 0.6 mg. Introducing the _____ of measure is error prone because it offers prescribers the opportunity to prescribe the dose as _____ (or multiples thereof). Thus, calculation errors when converting between _____ and mg are likely to occur and may result in dosing errors. This issue can be resolved by deleting the _____ strength designation. b(4)

5 CONCLUSIONS

The Division of Medication Error Prevention expressed concerns to the Division that marketing this product in only a 0.6 mg strength, while recommending a 0.3 mg dose, increases the potential for medication errors from splitting the 0.6 mg tablet since inaccurate splitting could result in doses that deviate from the intended dose. After seeking input from the Division on this matter, we were informed that there are no clinically significant safety or efficacy concerns due to deviations in dose that could result from inaccurate splitting of the tablets. Thus, we believe their response has adequately addressed this concern.

Additionally, we found the prominence of information on the container labels needs to be increased in order to minimize confusion.

The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

The Division of Medication Error Prevention and Analysis believes the label and labeling risks we have identified can be addressed and mitigated prior to drug approval, and provide recommendations in Section 6.2 that aim at reducing the risk of medication errors.

We would appreciate feedback on the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any correspondence to the Applicant pertaining to this issue. If you have further questions or need clarifications, please contact Chris Wheeler, OSE Project Manager, at 301-796-0151.

6.2 COMMENTS TO THE APPLICANT

A. General Comments for All Container Labels

1. Submit revised container labels that contain the proposed proprietary name for our review and comment.
2. The established name appears less than ½ the size of the proprietary name. Ensure that the established name is at least ½ the size of the proprietary name (taking into consideration the font, type, etc.) as per 21 CFR 201.10(g)(2).
3. The labels lack a Medication Guide statement. Add a Medication Guide statement as per 21 CFR 208.24(d).
4. Provide details on how many medication guides will be included with each container size.
5. Provide details on how the Medication Guide will be provided (e.g., inside bottle, attached to the insert labeling, tear-off sheet, etc.)

B. Container Labels (Trade)

1. Increase the size of the statement of strength (0.6 mg).
2. If the 30-count bottle is a "unit-of-use" bottle to be dispensed on an outpatient basis, ensure that the bottle has a Child Resistant Closure as per the Poison Prevention Act.

C. Container Labels _____

1. At the topmost part of the label, the established name and the _____ are printed in _____ that is difficult to read due to the _____ Readability. Revise so that there is sufficient color contrast to improve readability.
2. Increase the prominence of the statement _____

b(4)

D. Insert Labeling

1. In Full Prescribing Information, Section 2, *Dosage and Administration*, there are no directions for means to facilitate administration of the product (e.g., crushing or mixing with

food) to those who have difficulty swallowing tablets (e.g., pediatric patients). Include this type of information, if available, in the labeling.

2. The error-prone symbol— is used in the *Dosage and Administration* section of the insert labeling. Delete the symbol and use the appropriate phrase instead.
3. In Full Prescribing Information, Section 3, *Dosage Forms and Strengths*, two units of measure are used to specify the tablet strength [i.e., “0.6 mg ————”]. Delete the ———— strength designation.

b(4)

7 REFERENCES

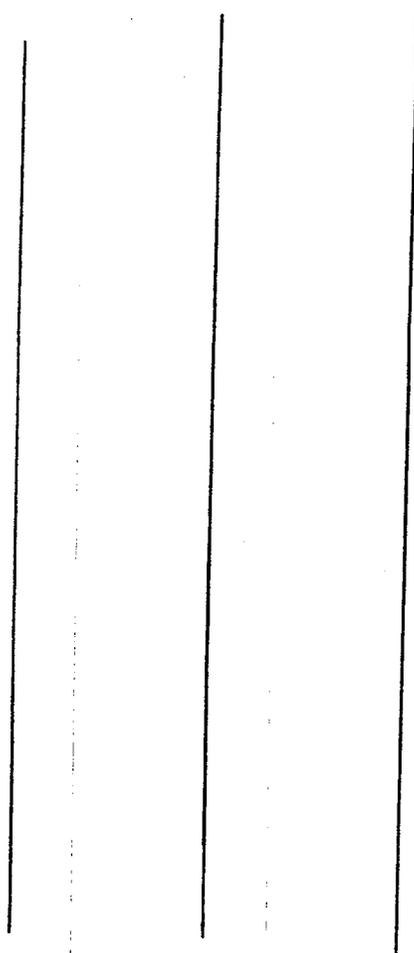
Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

APPENDICES

Appendix A:

Container Labels (not to scale)



b(4)

Container Labels: 30, 60, 100, 250, and 500-count



b(4)



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/s/

Loretta Holmes
2/17/2009 10:19:27 AM
DRUG SAFETY OFFICE REVIEWER

Kristina Arnwine
2/17/2009 11:28:11 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/17/2009 04:39:29 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/19/2009 02:06:42 PM
DRUG SAFETY OFFICE REVIEWER

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: December 10, 2008
To: **Margarita Tossa**
Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products
(DAARP)
From: **Michael Sauers**
Consumer Promotion Analyst
Division of Marketing, Advertising, and Communications (DDMAC)
Subject: 22-352
DDMAC PPI labeling comments for Colchicine, Tablets 0.6mg

DDMAC appreciates the opportunity to provide comments. We have reviewed the proposed PPI for Colchicine, Tablets 0.6mg and offer the following comments:

b(5)

b(4)

2 Page(s) Withheld

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

 √ § 552(b)(4) Draft Labeling

 √ § 552(b)(5) Deliberative Process

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/s/

Michael A Sauers
12/10/2008 04:08:39 PM
DDMAC REVIEWER

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: December 2, 2008

To: Margarita Tossa, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products
(DAARP)

From: Mathilda Fienkeng Pharm.D.
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 22-352 COLSTAT™ (Colchicine) Tablets USP for oral use

DDMAC has reviewed the proposed product labeling (PI) for COLSTAT™ (Colchicine) Tablets USP for oral use (Colstat) submitted for consult on June 20, 2008 and offers the following comments for the Professional section of the label.

NOTE: Comments on the patient labeling (PPI) section will be sent separately:

b(5)

b(4)

10 Page(s) Withheld

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

 √ § 552(b)(4) Draft Labeling

 √ § 552(b)(5) Deliberative Process

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/s/

Mathilda Fienkeng
12/2/2008 12:22:36 PM
DDMAC REVIEWER



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

MEMORANDUM

DATE: January 26, 2009

TO: File, NDA 22-352, Mutual's Colchicine for FMF

From: Sarah Okada, M.D.
Clinical Team Leader, DAARP

Through: Rigoberto Roca, M.D.
Deputy Director, DAARP
ODE II, Office of New Drugs
Center for Drug Evaluation and Research

RE: Risk Evaluation and Mitigation Strategy (REMS) Requirements

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) for an approved drug if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

1. The estimated size of the population likely to use the drug involved;
2. The seriousness of the disease or condition that is to be treated with the drug;
3. The expected benefit of the drug with respect to such disease or condition;
4. The expected or actual duration of treatment with the drug;
5. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;

6. Whether the drug is a new molecular entity.

During the review of NDA 22-352 it became evident that colchicine, in therapeutic doses, has been associated with fatal drug-drug interactions involving strong P-glycoprotein (P-gp) inhibitors such as clarithromycin. Although not reported in the literature or in the FDA postmarketing Adverse Event Reporting System (AERS) database to the same degree, a similarly dangerous interaction is anticipated with other strong P-gp inhibitors such as ritonavir and ketoconazole.

We have determined that a REMS is necessary to ensure that the benefits of colchicine outweigh its risks. In reaching this determination we considered the following:

1. Familial Mediterranean fever (FMF) is an orphan indication, and is estimated to affect approximately 5000 patients in the US.
2. FMF, if untreated, is associated with end-organ damage and premature mortality as a consequence of uncontrolled inflammation (i.e., secondary amyloidosis).
3. Colchicine is the only known efficacious treatment for FMF.
4. Patients with FMF must remain on colchicine treatment chronically (i.e., life-long) in order to prevent recurrent inflammatory attacks.
5. Although the toxicity of colchicine is well known and described in the medical literature, the number of patients reported with fatal non-overdose colchicine toxicity related to clarithromycin (60/117 or 51% of non-overdose fatalities reported to AERS through June 30, 2007) suggests that the severity of the potential interaction between colchicine and clarithromycin may not be widely understood. Patient awareness of potential serious drug-drug interactions with colchicine is especially important, since clarithromycin may be prescribed by different healthcare providers seeing the patient for an acute illness and, likewise, a healthcare provider seeing the patient for chronic conditions may not be aware of a new prescription for clarithromycin given for an acute illness.
6. Colchicine is not a new molecular entity, having been approved as part of a combination with probenecid (FDA approved 1961, DESI review, 1972) for the treatment of chronic gout. Single-entity colchicine is currently widely available as marketed unapproved product that is most commonly used in the United States for the treatment and prevention of gout flares. NDA 22-352 for colchicine in FMF would represent the first FDA approval of single-entity colchicine in the United States. Although colchicine is not a new molecular entity, based on the information in NDA 22-352 a REMS is warranted.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that colchicine (NDA 22 352) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of colchicine. FDA has determined that colchicine is a product that has serious risks (relative to benefits) of which patients should be made aware because information

NDA 22-352

concerning the risks could affect patients' decision to use, or continue to use, colchicine. FDA has also determined that colchicine is a product for which patient labeling could help prevent serious adverse events.

The only elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

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/s/

Margarita Tossa
2/3/2009 11:35:26 AM
CSO

Dear Sarah & Rigo please sign the REMS memo.

Sarah Okada
2/3/2009 11:42:44 AM
MEDICAL OFFICER

Rigoberto Roca
2/3/2009 12:40:11 PM
MEDICAL OFFICER