# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-353**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

## CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA: 22-353 | Submission Date(s): 11/25/2008 |
| Brand Name | COLCRYS |
| Generic Name | Colchicine 0.6 mg tablet |
| Clinical Pharmacology Reviewer | Srikanth C. Nallani, Ph.D. |
| Team Leader | Suresh Doddapaneni, Ph.D. |
| OCP Division | Division of Clinical Pharmacology II |
| OND Division | Anesthesia, Analgesia and Rheumatology Products |
| Sponsor | Mutual Pharmaceutical Company, Inc. |
| Relevant IND(s) | 72,586 |
| Formulation; Strength(s) | Immediate release tablet; 0.6 mg |
| Indication | Prevention of Gout Flares |
| Proposed Dosage Regimen | 0.6 mg once or twice daily. Maximum dose 1.2 mg/day. |

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# 1 Executive Summary

## 1.1 Recommendation

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

## 1.2 Phase IV Commitments

None.

## 1.3 Summary of Clinical Pharmacology Findings

Mutual Pharmaceuticals Inc., submitted a 505(b)(2) NDA 22-353 supporting use of Colcrys tablets for prophylaxis of gout flares. All of the efficacy data pertaining to the use of colchicine for prevention of gout flares are derived from a comprehensive review of the worldwide published literature. Mutual is also relying upon the FDA's prior determination of safety and efficacy of colchicine for preventing gout flares (Col-Probenecid, ANDA 084-279).

Previously, Mutual Pharmaceutical Company submitted a 505(b)(2) NDA 22-352 for Colcrys, on 06/20/2008, for the ———————— of familial Mediterranean fever (FMF) , an orphan indication, in adults and children up to 4 years of age. Agency approved NDA 22-352 on 7/29/2009. In addition, Mutual Pharmaceutical Company also submitted a 505(b)(2) NDA 22-351 for Colcrys, colchicine tablets on 9/30/2008, for the treatment of gout flares (acute gout). Safety and efficacy of Colcrys for treatment of acute gout was evaluated in a single adequate well controlled clinical trial MPC-004-06-001. Agency approved NDA 22-351 on 7/30/2009.

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The sponsor is relying on literature for clinical pharmacology in special populations, safety and efficacy data in patients receiving colchicine for prevention of acute gout. Medical officer review documents the basis for efficacy of 0.6 mg colchicine in prophylaxis of gout. A recent publication has documented safe use of colchicine, up to 0.6 mg bid, for prophylaxis of gout (Borstad GC., et. al. J. Rheumatology 2004). Safety of 1.5 mg colchicine, administered as one tablet Colbenemid three times a day, for up to 109 months of therapy was evaluated by Paulus HE., 1974 (Arthritis Rheum. 17(5):609-614). In addition, published literature describes the safety of colchicine 0.6 mg tid in other less common inflammatory diseases *e.g.*, Familial Mediterranean Fever [FMF] (Dinarello et al., N Engl J Med 1974;291:934-937, Goldstein and Schwabe, Ann Intern Med 1974;81:792-794.).

No new clinical pharmacology information has been submitted to this NDA.

In support of NDA 22-352 (colchicine for familial Mediterranean Fever), Mutual had submitted four clinical PK studies in healthy volunteers to describe:

- single dose (Study #1001) and multiple dose (Study #1004) pharmacokinetics of colchicine and its metabolites

- relative bioavailability (Study#1001) of colchicine compared to col-probenecid (Watson Laboratories)
- food effect on Colcrys bioavailability (Study# 1001).

Study #1001 was a single-dose, three-way crossover comparative bioavailability and food effect study. In addition, four in vitro metabolism and drug interaction studies were also conducted. These studies were previously reviewed in clinical pharmacology review for NDA 22-352 dated 11/26/2008.

It is conceivable that a small number of subjects flare in spite of receiving colchicine for prophylaxis of gout. Hence, sponsor proposed the following labeling change

**Treatment of Gout Flares** ———————

The recommended dose of COLCRYS for treatment of a gout flare ——— ——— is 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. Wait 12 hours and then resume the prophylactic dose.

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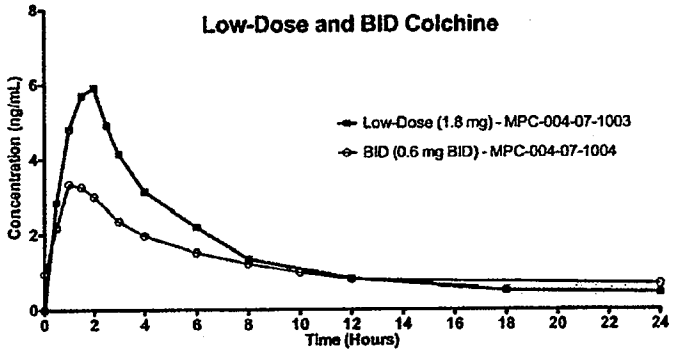
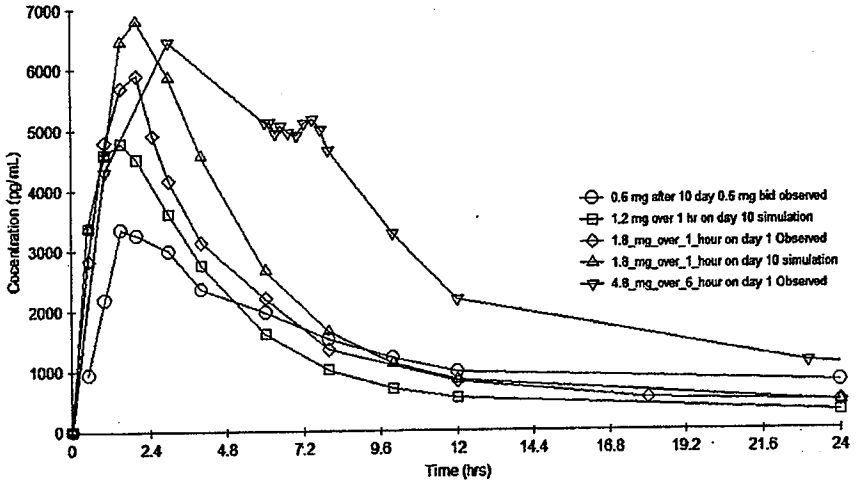
Justification provided by the sponsor:

Added dosage recommendation for treatment of gout flares during prophylaxis and waiting 12 hours before resuming the prophylactic dose. Our data shows that patients taking 0.6 mg BID after 10 days have a peak concentration of approximately 3 ng/mL and a 12 hour trough of approximately 1 ng/mL. Following a 3 tablet regimen to treat an acute flare, a higher peak is seen at approximately 2 hours but by 12 hours the trough concentration is also 1 ng/mL( i.e., the same as seen with 0.6 mg BID prophylaxis dosing.) Hence it would be safe to re assume dosing 12 hours later in either case.




Additional simulations were conducted to confirm if the plasma levels of colchicine would be between the clinical experience of low-dose (1.8 mg over 1 hour) and standard dose (4.8 mg over 6 hours). The plasma concentration data of colchicine on Day 10 of 0.6 mg bid dosing was fit to a two compartment model employing WinNonlin version 5.2. The PK parameters generated (V1_F= 161 L, K01 = 1.37 /hr, K10 = 0.1836 /hr, K12 = 0.14/hr, K21 = 0.0467/hr) using the observed data were employed to simulate different

dosing regimen were simulated. As shown in the figure below, simulated plasma concentrations of 1.2 mg over 1 hour (upward triangle), 1.8 mg over 1 hour (open square) on Day 10 are bracketed between the 1.8 mg colchicine administered over 1 hr (diamonds) and 4.8 mg administered over 6 hours (inverted triangle). Observed plasma concentration data following 0.6 mg (circle) administered on day 10 is indicated for comparison. Hence, the administration of up to 1.8 mg colchicine over 12 hours is acceptable when patients are already on colchicine for prophylaxis of gout. Patients should, however, be advised to stop dosing upon incidence of gastrointestinal adverse events such as diarrhea and vomiting.




*Intrinsic Factors:*

Pharmacokinetic studies were not conducted by the sponsor to address the influence of age, race, bodyweight, pregnancy and organ dysfunction. However, several publications addressing these intrinsic factors were submitted to the NDA 22-352. These studies were previously reviewed in clinical pharmacology review for NDA 22-352 dated 11/26/2008.

*Extrinsic Factors:*

In vitro studies show that colchicine is a substrate of P-glycoprotein and it is metabolized by CYP3A4. Hence, sponsor evaluated the effect of different strong, moderate, weak CYP3A4 inhibitors and a P-gp inhibitor on the pharmacokinetics of colchicine.

The drug interaction study results were noted in previous clinical pharmacology reviews dated 11/28/2008 and 6/5/2009.

Strong CYP3A4 inhibitors increase colchicine systemic exposure by 3- to 4-fold. Hence, a 75% decrease in dose is necessary to compensate for the increase in exposure.

Moderate CYP3A4 inhibitors cause a 2-fold increase in colchicine AUC when coadministered. Hence, a 50% decrease in dose is necessary to compensate for the increase in exposure.

P-gp inhibition by cyclosporine resulted in 3.5-fold increase in Cmax and AUC of colchicine. Hence, a 75% decrease in dose is necessary to compensate for the increase in exposure.

Dosage adjustment in patients who are on strong or moderate CYP3A4 inhibitors and P-glycoprotein inhibitors is indicated in the tablet below, based on the noted % change in Cmax and AUC of colchicine with interacting drug:

| Co-administered Drug | % Change in Colchicine Concentrations from Baseline (Range: Min – Max) | | Original dose | Adjusted dose when coadministering with interacting drug |
|---|---|---|---|---|
| | $C_{max}$ | $AUC_{0-t}$ | | |
| **Strong CYP3A4 Inhibitors** | | | | |
| Single Dose colchicine 0.6 mg + Clarithromycin 250mg bid 7-day regimen (Study #1006) N=24 | 227.2 (65.7 to 591.1) | 281.5 (88.7 to 851.6) | 0.6 mg twice a day | 0.3 mg once a day |
| Single Dose colchicine 0.6 mg + Ketoconazole 200mg bid 5-day regimen (Study #1012) N=24 | 101.7 (19.6 to 219.0) | 212.2 (76.7 to 419.6) | 0.6 mg once a day | 0.3mg once every other day |
| Single Dose colchicine 0.6 mg + Ritonavir 100 mg bid 5-day regimen (Study #1013) N=18 | 184.4 (79.2 to 447.4) | 296.0 (53.8 to 924.4) | | |
| **Moderate CYP3A4 Inhibitors** | | | | |
| Single Dose colchicine 0.6 mg + Verapamil ER 240 mg qd 5-day regimen (Study #1014) N=24 | 40.1 (-47.1 to 149.5) | 103.3 (-9.8 to 217.2) | 0.6 mg twice a day | 0.3 mg twice a day |
| Single Dose colchicine 0.6 mg + Diltiazem ER capsule 240 mg qd 7-day regimen (Study #1015) N=24 | 44.2 (-46.0 to 318.3) | 93.4 (-30.2 to 338.6) | 0.6 mg once a day | 0.3 mg once a day |
| Single Dose colchicine 0.6 mg + Grapefruit Juice 4-day regimen | -2.55 (-53.4 to | -2.36 (-46.4 to | | |

| | | | | |
|---|---|---|---|---|
| (Study #1017) N=21 | 55.0) | 62.2) | | |
| **Weak CYP3A4 Inhibitors** | | | | |
| Single Dose colchicine 0.6 mg + Azithromycin 250 mg 5-day regimen (Study #1011) N=24 | 21.6<br><br>(-41.7 to 222.0) | 57.1<br><br>(-24.3 to 241.1) | 0.6 mg twice a day<br><br>0.6 mg once a day | No dose adjustment needed |
| **P-gp Inhibitors** | | | | |
| Single Dose colchicine 0.6 mg + Cyclosporine 100mg single dose (Study #1016) N=23 | 270.0<br><br>(62.0 to 606.9) | 259.0<br><br>(75.8 to 511.9) | 0.6 mg twice a day<br><br>0.6 mg once a day | 0.3 mg once a day<br><br>0.3 mg once every other day |

Overall, the clinical pharmacology submission is acceptable.

## 2 QBR

### 2.1 General Attributes

Mutual Pharmaceuticals Inc., submitted a 505(b)(2) NDA 22-353 supporting use of Colcrys tablets for prophylaxis of gout flares. All of the efficacy data pertaining to the use of colchicine for prevention of gout flares are derived from a comprehensive review of the worldwide published literature. Mutual is also relying upon the FDA's prior determination of safety and efficacy of colchicine for preventing gout flares (Col-Probenecid, ANDA 084-279).

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The sponsor is relying on literature for clinical pharmacology in special populations, safety and efficacy data in patients receiving colchicine for prevention of acute gout.

Mechanism of action: Several publications suggest that colchicine has anti-inflammatory properties. However, the exact mechanism of the anti-inflammatory actions is unknown and it is an active area of research.

### 2.2 General Clinical Pharmacology

Mutual is also relying upon the FDA's prior determination of safety and efficacy of colchicine for preventing gout flares (Col-Probenecid, ANDA 084-279). Medical officer review documents the basis for efficacy of 0.6 mg colchicine in prophylaxis of gout. A recent publication has documented safe use of colchicine, up to 0.6 mg bid, for prophylaxis of gout (Borstad GC., et. al. J. Rheumatology 2004). Safety of 1.5 mg colchicine, administered as one tablet Colbenemid three times a day, for up to 109 months of therapy was noted by Paulus HE., 1974 (Arthritis Rheum. 17(5):609-614). In addition, published literature describes the safety of colchicine 0.6 mg tid in other less common inflammatory diseases *e.g.*, Familial Mediterranean Fever [FMF] (Dinarello et al., N Engl J Med 1974;291:934-937, Goldstein and Schwabe, Ann Intern Med 1974;81:792-794.).

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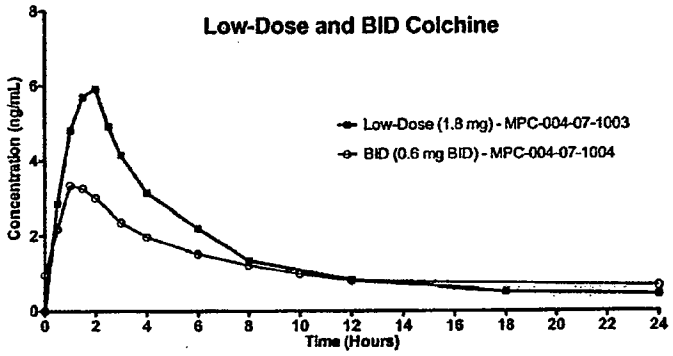


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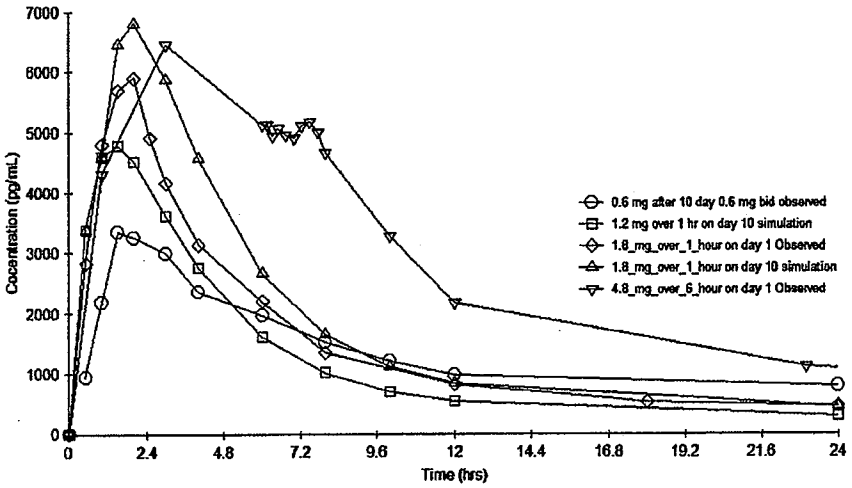


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**1) Are there any in vivo drug-drug interaction studies that indicate the exposure alone are different when drugs are co-administered? If so, is any dosage adjustment necessary?**

*The drug interaction study results were noted in previous clinical pharmacology reviews dated 11/28/2008 and 6/5/2009.*

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**2.5 General Biopharmaceutics**

Not applicable.

**2.6 Analytical**

Not applicable.

## 3 Labeling

**Sponsor proposed labeling is indicated below. Additions by the sponsor to the existing label for acute gout and FMF treatment are in color font. Additions by the reviewer are in bold text and deletions are in strike through text.**

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# 12 Page(s) Withheld

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

√ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

# 4 Appendix

## 4.1 Proposed labeling

To be inserted.

## 4.2 Individual Study Reviews

Not applicable.

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

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/s/

SRIKANTH C NALLANI
08/17/2009

SURESH DODDAPANENI
08/17/2009