

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204820Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204820	Biopharmaceutics Reviewer: Elsbeth Chikhale, PhD	
Submission Date:	November 11, 2013		
Division:	Division of Pulmonary, Allergy, and Rheumatology Products	Acting Biopharmaceutics Team Leader: John Duan, PhD	
Applicant:	Hikma Pharmaceuticals LLC	Acting Supervisor: Richard Lostritto, PhD	
Trade Name:	Colchicine Capsules	Date Assigned:	October 17, 2012
Generic Name:	Colchicine Capsules	Date of Review:	July 1, 2013
Indication:	Prophylaxis of gout flares	Type of Submission: 505(b)(2) Original New Drug Application	
Dosage form/strengths	Immediate release capsules/ 0.6 mg/capsule		
Route of Administration	Oral		

SUMMARY

Submission:

The proposed drug product is an immediate release gelatin capsule containing 0.6 mg colchicine as the active ingredient, indicated for prophylaxis of gout flares in adult patients. Colchicine is a water soluble alkaloid obtained from the colchicum plant. It is a highly potent drug. West Ward (US Agent for Hikma Pharmaceuticals LLC) has marketed 0.6 mg strength colchicine tablets for over 25 years. The proposed capsule formulation (b) (4)

The Applicant plans to rely on published literature to support the nonclinical profile, clinical pharmacology, clinical safety and efficacy of the proposed capsule drug product in this 505(b)(2) New Drug Application. A comparative bioavailability study of the proposed capsules versus reference tablets (0.5 mg colchicine/500 mg probenecid) has been conducted to support this NDA.

Review:

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of:

- 1) the proposed dissolution methodology, and
- 2) the dissolution acceptance criterion

RECOMMENDATION

The following dissolution method and acceptance criterion are acceptable:

Drugs Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance Criterion
Colchicine	IR Capsules	USP 2 (Paddle)	75	500 mL water with 2% SLS	Q= (b) (4) % at 20 minutes

From the Biopharmaceutics perspective, NDA 204820 for Colchicine Capsules containing 0.6 mg colchicine per capsule is recommended for **APPROVAL**.

Elsbeth Chikhale, Ph.D.
 Biopharmaceutics Reviewer
 Office of New Drug Quality Assessment

John Duan, Ph.D.
 Acting Biopharmaceutics Team Leader
 Office of New Drug Quality Assessment

BIOPHARMACEUTICS EVALUATION – REVIEWER NOTES

BIOPHARMACEUTICS INFORMATION:

Composition of the proposed drug product capsules:

Ingredient	Function	Mg/Capsule	% Composition
Colchicine, USP	Active	(b) (4)	(b) (4)
Microcrystalline Cellulose, NF (b) (4)	(b) (4)	(b) (4)	(b) (4)
Anhydrous Lactose, NF	(b) (4)	(b) (4)	(b) (4)
Sodium Starch Glycolate, NF (b) (4)	(b) (4)	(b) (4)	(b) (4)
Colloidal Silicon Dioxide, NF (b) (4)	(b) (4)	(b) (4)	(b) (4)
Magnesium Stearate, NF	(b) (4)	(b) (4)	(b) (4)
Total Fill Weight			100.0
Empty Gelatin Capsule			
Total Filled Capsule Weight			

DISSOLUTION METHOD:

The proposed dissolution method:

Rotating paddle apparatus (apparatus 2)

Dissolution medium: water with 2% SLS

Volume: 500 ml

Temperature: 37.0 °C

Agitation speed: 75 rpm

The original submission did not contain a dissolution development report. An information request dated 11/20/12 asked that the Applicant submit the dissolution method development report. A response was received on 4/17/13. The report was provided in section 3.2.P.5.3. The report describes the selection of the dissolution test conditions as shown below, however, the report did not include the requested data to show the discriminating capability of the dissolution method.

Selection of apparatus:

(b) (4)

Selection of dissolution medium:

(b) (4)

(b) (4)

Selection of rotation speed:

(b) (4)

Discriminatory power of the method:

The Applicant did not provide the requested data to demonstrate the discriminatory power of the dissolution procedure. Therefore, the Applicant was asked again to provide these data.

Information request dated 6/10/13:

Provide dissolution data to demonstrate the discriminating capability of your proposed dissolution method. For example, dissolution profile data indicating that the method can detect changes in drug substance particle size, changes in excipients, etc.

Applicant response e-mail dated 6/20/13:

Please note that we do not have dissolution data available to demonstrate the discriminating capability of the proposed dissolution method.

Evaluation of response:

Since the Applicant has agreed to tighten the acceptance criterion to $Q = \frac{(b)}{(4)}\%$ at 20 minutes (see below), the drug product dissolution specification (method and acceptance criterion) as part of the drug product quality control, will ensure that the proposed capsules will dissolve fast and completely in a timely manner, as expected for an immediate release dosage form. The proposed dissolution method is found acceptable as a quality control method.

Reviewer's Overall Assessment of the proposed dissolution method: Acceptable

The Applicant has justified the selected dissolution apparatus, rotation speed, and dissolution medium. Even though the discriminatory power of the dissolution method has not been demonstrated, the proposed dissolution method is found acceptable.

DISSOLUTION ACCEPTANCE CRITERION:

The proposed acceptance criterion is:

75% (Q) after 30 minutes

The Applicant states that the proposed acceptance criterion for colchicine capsules is based on the USP monograph for colchicine tablets that require at least 75% (Q) dissolved in 30 minutes.

Reviewer's Initial Assessment of the proposed dissolution acceptance criterion: Not Acceptable
Based on the provided dissolution data for the proposed drug product (profile 12) and the stability dissolution profile data (3.2.P.5.4), an acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 20 minutes is appropriate for the drug product.

Information request dated 6/10/13:

Revise your proposed dissolution acceptance criterion to $Q = \frac{(b)}{(4)}\%$ at 20 minutes.
Accordingly, provide a revised drug product specification sheet.

A telephone conference was held between FDA and the Applicant on June 19, 2013 during which the rationale for the tightening of the dissolution acceptance criterion was discussed.

Applicant response e-mail dated 6/20/13:

The Applicant has accepted the FDA proposed acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 20 minutes.

Reviewer's Overall Assessment of the proposed dissolution acceptance criterion: Acceptable

The revised dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 20 minutes is acceptable. The Applicant has committed to submit the response and the revised dissolution acceptance criterion officially to the NDA on 7/1/13.

RECOMMENDATION:

- The applicant's dissolution methodology, as summarized below is acceptable:
USP Apparatus II (paddle)
Temperature: 37 °C
Rotation speed: 75 rpm
Medium: 500 mL water with 2% SLS
- Dissolution acceptance criterion:
The following dissolution acceptance criterion is acceptable:
 $Q = \frac{(b)}{(4)}\%$ at 20 minutes

From the Biopharmaceutics perspective, NDA 204820 for Colchicine Capsules containing 0.6 mg colchicine per capsule is recommended for **APPROVAL**.

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

/s/

ELSBETH G CHIKHALE
07/01/2013

JOHN Z DUAN
07/01/2013

CLINICAL PHARMACOLOGY REVIEW

<i>NDA</i>	204820	<i>Submission Date(s)</i>	October 5, 2012
<i>Proposed Brand Name</i>	Mitigare		
<i>Generic Name</i>	Colchicine Capsules 0.6 mg		
<i>Reviewer</i>	Sheetal Agarwal, Ph.D.		
<i>Team Leader</i>	Suresh Doddapaneni, Ph.D		
<i>OCP Division</i>	DCP-2		
<i>OND Divisions</i>	Division of Pulmonary, Allergy and Rheumatology Products		
<i>Sponsor</i>	Hikma Pharmaceuticals (US Agent: West-ward)		
<i>Submission Type</i>	505 (b) (2) NDA referencing Col-Probenecid and literature		
<i>Formulation; Strength(s)</i>	0.6 mg capsules		
<i>Proposed Indication</i>	Prophylaxis of gout flares		
<i>Proposed Dosing Regimen</i>	0.6 mg BID or QD		

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1.0 Executive Summary

1.1 Recommendation:

NDA 204820 (0.6 mg Colchicine Capsules (Agency accepted brand name, Mitigare), for prophylaxis of gout flares) is acceptable from a Clinical Pharmacology perspective.

1.2 Phase 4 commitments:

None.

See Section 2.4.2 for this reviewer's assessment of this topic.

1.3 Summary of important Clinical Pharmacology findings:

On October 5, 2012, Hikma Pharmaceuticals through their U.S. agent, West-Ward, submitted a 505(b)(2) NDA for their 0.6 mg Colchicine Capsules, for the proposed indication of prophylaxis of gout flares. In this 505(b)(2) NDA, West-Ward is relying on FDA's finding of safety and effectiveness for Col-Probenecid and published literature for the efficacy and safety of colchicine for the proposed indication. Based on pre-submission discussions with FDA, the sponsor conducted DDI studies to support any proposed dose modification recommendations. West-Ward performed four DDI studies with their product - one with the weak CYP3A4 inhibitor cimetidine, one with the moderate CYP3A4 inhibitor fluconazole, one with the strong CYP3A4 inhibitor voriconazole, and one with the P-gp inhibitor propafenone.

The relative bioavailability of West-Ward's 0.6 mg capsule product was compared to Col-Probenecid (ANDA 084729). West-ward's product showed slightly higher C_{max} (~17% higher C_{max}) and equivalent AUC compared to dose-normalized C_{max} and AUC parameters respectively of the reference, Col-Probenecid (0.5 mg colchicine and 500 mg probenecid).

A food effect assessment was conducted with a 0.6 mg tablet formulation of colchicine instead of the proposed to be marketed 0.6 mg Colchicine Capsules (see regulatory history in Section 2.1.1 for additional discussion on the transition from previously proposed 0.6 mg tablet to the current 0.6 mg capsule presentation). The presence of a high-fat, high-calorie meal did not have much effect on colchicine PK (~11% lower C_{max}, 12% lower AUC). This food affect assessment was considered acceptable for the current 0.6 mg capsule formulation for the following 2 reasons: (a) (b) (4)

(b) The sponsor provided dissolution data for both tablet and capsule formulation indicating that dissolution profiles of the tablet and capsule formulations are similar.

In West-Ward's 4 DDI studies, colchicine did not interact to a significant extent with any of the 4 probe inhibitors employed, i.e., voriconazole, fluconazole, cimetidine or propafenone, except for a 40% increase in AUC of colchicine with fluconazole. An OSI inspection of the voriconazole-colchicine DDI study did not reveal any issues with the study conduct. The rest of the 3 DDI studies were also conducted at the same site. The sponsor explained their results with the 3 CYP3A4 inhibitors by postulating that colchicine's drug-drug interactions are due more to the involvement of P-gp rather than CYP3A4 and none of the 3 CYP3A4 inhibitors that they employed, i.e., voriconazole, fluconazole, cimetidine, inhibit P-gp potently. The sponsor explained a lack of interaction between the P-gp inhibitor that they employed, propafenone, and colchicine, by hypothesizing that propafenone and colchicine bind to different domains

of P-gp.

Although there are no published case reports for colchicine toxicity when co-administered with the 4 inhibitors that the sponsor employed, i.e., voriconazole, fluconazole, cimetidine and propafenone, several published case reports indicate that colchicine toxicity is observed when it is co-administered with drugs that are potent inhibitors of both P-gp and CYP3A4 (e.g., clarithromycin, ketoconazole), strong to moderate inhibitors of CYP3A4 (e.g., grapefruit juice, erythromycin) as well as potent P-gp inhibitors (e.g., cyclosporine). As such, although colchicine did not exhibit any PK interaction with the 4 inhibitors that the sponsor employed, its drug-drug interaction potential with other P-gp and CYP3A4 inhibitors (dual inhibitors) or even with more 'pure' P-gp inhibitors and strong to moderate CYP3A4 inhibitors cannot be ruled out. Based on available information, general cautionary language informing patients about DDI potential of colchicine will be included in label along with the suggestion that colchicine daily dose may be reduced if co-administered with dual inhibitors of CYP3A4 and P-gp as well as with strong to moderate CYP3A4 inhibitors or P-gp inhibitors.

Overall, West-ward provided adequate clinical pharmacology information to support their 505(b)(2) NDA for 0.6 mg Colchicine Capsules.

2. Question Based Review

2.1 General Attributes/Background:

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Colchicine was first isolated from colchicum in 1820 and made available in oral dosage forms during the 19th century. It has been used for gout prophylaxis since the 1930s. However, colchicine was first approved by the FDA in 1961 as part of combination with probenecid for the chronic treatment of gout (ColBenemid—colchicine 0.5 mg/probenecid 500 mg). ColBenemid underwent DESI review (FR Vol.37, No.146, 28 July 1972) which deemed the combination effective for the treatment of chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout.

Single-ingredient colchicine tablets were available for decades as marketed but unapproved products, in 0.6 mg strength. The first approved single-ingredient oral colchicine product was Mutual Pharmaceutical's colchicine 0.6 mg tablets (Colcrys), which was approved in July 2009 for treatment of familial Mediterranean fever (FMF) and treatment of acute flares of gout; approval for the prophylactic treatment of gout was given in October 2009. Approval of Colcrys for FMF was based on published literature and supported by Mutual's PK studies. Approval of Colcrys for prophylactic treatment of gout was based primarily on published literature and FDA's finding of safety and effectiveness for Col-Probenecid. For approval of colchicine in the treatment of acute flares of gout, Mutual performed a randomized controlled trial to supplement a single controlled trial available in the literature. Mutual submitted results from their randomized controlled trial, which supported the efficacy and improved safety profile of a lower dosing regimen of colchicine for the acute treatment of gout flares.

With these NDAs, Mutual provided information on DDI from a comprehensive DDI program which was the basis for extensive dose-modification recommendations in the approved label for Colcrys as shown below in Table 1. Colchicine's drug-drug interaction potential, as a P-gp and cytochrome P450 substrate (specifically CYP3A4), has long been reported in the literature. However, the DDI studies conducted by Mutual allowed for a more precise quantitative assessment of the interactions.

Table 1: Summary of Colcrys Dose Modification Recommendations for Prophylactic Use

Dosing for prophylaxis	(1) 0.6 mg BID or (2) 0.6 mg QD
With Strong CYP3A4 inhibitors	(1) 0.3 mg QD (2) 0.3 mg every other day
With Moderate CYP3A4 inhibitors	(1) 0.3 mg BID or 0.6 mg QD (2) 0.3 mg QD
With P-gp inhibitors	(1) 0.3 mg QD or (2) 0.3 mg every other day

The sponsor of the current NDA 204820 under review, West-Ward, began marketing Colchicine Tablets, 0.6 mg in the early 1970s, until it removed the product from the market in late 2010 in response to FDA's announcement of its intention to take enforcement action against unapproved single ingredient colchicine products in the October 1, 2010, Federal Register. (b) (4)

In November 2011, FDA met with West-Ward to discuss their development plan, and agreement was reached on a program that included 4 DDI studies—one each with a strong, moderate, and weak CYP3A4 inhibitor and a P-gp inhibitor, to be able to include relevant DDI information in West-ward's product label and recommend dose reductions if needed with any or some of these classes of inhibitors.

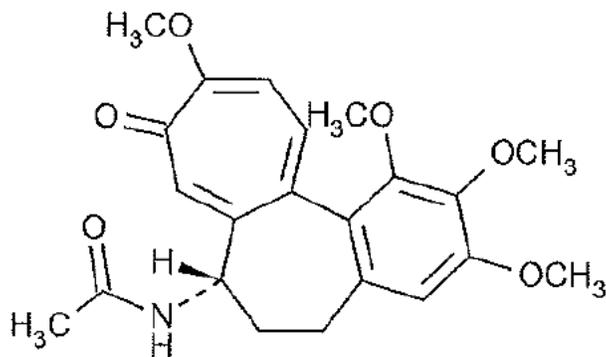
On October 5, 2012, Hikma Pharmaceuticals and their U.S. agent, West-Ward, submitted a 505(b)(2) NDA for their 0.6 mg Colchicine Capsules, for the proposed indication of prophylaxis of gout flares. The sponsor will still be referred to as West-Ward in the remainder of this document. In this 505(b)(2) NDA, West-Ward proposed to rely on FDA's finding of safety and effectiveness for Col-Probenecid and published literature for the efficacy and safety of colchicine for the proposed indication. In pre-submission meetings with FDA, the sponsor was advised to conduct DDI studies to support any proposed dose modification recommendations. West-Ward performed four DDI studies with their product—one with the weak CYP3A4 inhibitor cimetidine, one with the moderate CYP3A4 inhibitor fluconazole, one with the strong CYP3A4 inhibitor voriconazole, and one with the P-gp inhibitor propafenone.

An important distinction between this NDA and previously approved NDAs for single-ingredient colchicine, Colcris, is the indication for which approval is sought and related total daily dose. While prophylaxis of gout flares only requires a small dose of colchicine (0.6-1.2 mg), previously approved Colcris includes treatment of gout flares and FMF indications for which the recommended total daily dose ranges between 1.8-2.4 mg. In addition, in discussion with the clinical review team, it is believed that colchicine is generally titrated to effect and total daily dose could be higher than 2.4 mg if patients are able to tolerate the drug. As such, the risk associated with drug-drug interactions of colchicine, impact of hepatic and renal impairment and other factors that impact bioavailability of colchicine, is lower with Colchicine Capsules based on its proposed conditions of use as compared to previously approved Colcris. In addition, colchicine has been available in the U.S. market for several decades and the health-care community is generally aware of colchicine toxicity (which is observed even at low doses) from published literature. Colchicine related adverse events are frequently monitored in the clinical setting and dose is adjusted to patient's efficacy and safety. As such, general and cautionary dose reductions for this product are appropriate based on the DDI data obtained with this product, published adverse event reports and the proposed indication for this product in prophylactic treatment of gout flares. For additional discussion on this topic, refer to Dr. Keith Hull's clinical review as well as Dr. Sarah Yim's CDTL review.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Colchicine is an alkaloid chemically described as (S)N-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[alpha]heptalen-7-yl)acetamide with a molecular formula of C₂₂H₂₅NO₆ and a molecular weight of 399.4. The structural formula of colchicine is shown below in Figure 1.

Figure 1: Colchicine Structure



2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

The mode of action of colchicine in gout is unknown. It is not an analgesic, though its use results in relief of pain in acute attacks of gout. It is not a uricosuric agent and will not prevent progression of gout to chronic gouty arthritis. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks and to relieve the residual pain and mild discomfort that patients with gout occasionally feel.

Proposed Indications:

Prophylaxis of gout flares.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Proposed dosage(s): 0.6 mg BID or QD

Route of administration: Oral

2.1.5 What are the to-be-marketed formulations?

West-Ward had marketed unapproved Colchicine Tablets, 0.6 mg before submission of this NDA. In this NDA, they modified the tablet dosage form into a capsule dosage form. (b) (4)

The composition of the 0.6 mg capsules is listed below in Table 2:

Table 2: Composition of the 0.6 mg Colchicine Capsules

Ingredient	Function	0.6 mg	% Composition
Colchicine, USP	Active	(b) (4)	(b) (4)
Microcrystalline Cellulose, NF (b) (4)	(b) (4)	(b) (4)	(b) (4)
Anhydrous Lactose, NF	(b) (4)	(b) (4)	(b) (4)
Sodium Starch Glycolate, NF (b) (4)	(b) (4)	(b) (4)	(b) (4)
Colloidal Silicon Dioxide, NF (b) (4)	(b) (4)	(b) (4)	(b) (4)
Magnesium Stearate, NF	(b) (4)	(b) (4)	(b) (4)
Total Fill Weight			100.0
Empty Gelatin Capsule Weight			
Total Filled Capsule Weight			

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A total of 6 clinical pharmacology studies as listed below in Table 3 were reviewed. As indicated previously, the NDA is a 505 (b) (2) NDA referencing previously approved Col-Probenecid for findings of safety and effectiveness of colchicine as well as published literature for efficacy of colchicine for prophylaxis of gout flares. In addition to a relative bioavailability assessment and food effect assessment, 4 DDI studies were also conducted by West-ward to be able to adequately label their product with DDI information.

Table 3: Clinical Pharmacology Studies Reviewed for 0.6 mg Colchicine Capsules

Study #	Study design	Duration	Test products
AA95730-01	Open-label, randomized, single-dose, two-period, two-sequence, crossover, food-effect study in healthy adult volunteers. 28 enrolled, 27 completed study.	Two periods of approximately 5.5 days each separated by a 21-day washout period.	Test: 0.6 mg colchicine tablet with 240 mL of water, 30 minutes after administration of a standard high-fat breakfast meal. [Lot No.: (b) (4)]. Reference: 0.6 mg colchicine tablet with 240 mL of water, after a 10-hour overnight fast [Lot No.: (b) (4)].
CLI-P1-680	Single center, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover study. 36 enrolled, 35 completed study.	A single oral dose was administered under fasting conditions in each study period. The drug administrations were separated by a wash-out of 21 calendar days.	Test: Colchicine Capsule 0.6 mg Batch no.: (b) (4) Reference: Probenecid and Colchicine. Single dose of 1 x 500 mg/0.5 mg. Batch no.: (b) (4)
CLL-P1-	Single center, non-	Day 1: 0.6 mg	Test: Colchicine Capsule 0.6 mg

741	randomized, open-label, one-sequence, crossover study. 12 enrolled, 12 completed.	colchicine single dose Days 4-8: 200 mg voriconazole BID for 5 days Day 9: 0.6 mg colchicine + 200 mg voriconazole	Batch no.: (b) (4) Interacting drug: Vfend® (Voriconazole) 200 mg Film-Coated Tablet. Batch no.: (b) (4)
CLL-P1-742	Single center, non-randomized, open-label, one-sequence, crossover study. 12 enrolled, 12 completed.	Day 1: 0.6 mg colchicine single dose Day 4: 2 X 200 mg (400 mg) fluconazole (loading dose) Days 5-8: 200 mg fluconazole QD for 4 days Day 9: 0.6 mg colchicine + 200 mg fluconazole	Test: Colchicine Capsule 0.6 mg Batch no.: (b) (4) Interacting drug: Diflucan® (Fluconazole) 200 mg Tablet. Batch no.: (b) (4)
CLN-P1-743	Single center, non-randomized, open-label, one-sequence, crossover study. 12 enrolled, 12 completed.	Day 1: 0.6 mg colchicine single dose Days 4-8: 800 mg cimetidine BID for 5 days Day 9: 0.6 mg colchicine + 800 mg cimetidine	Test: Colchicine Capsule 0.6 mg Batch no.: (b) (4) Interacting drug: Cimetidine 800 mg Film-Coated Tablet USP. Batch no.: (b) (4)
CLN-P1-744	Single center, non-randomized, open-label, one-sequence, crossover study. 12 enrolled, 9 completed.	Day 1: 0.6 mg colchicine single dose Days 4-8: 225 mg propafenone BID for 5 days Day 9: 0.6 mg colchicine + 225 mg propafenone	Test: Colchicine Capsule 0.6 mg Batch no.: (b) (4) Interacting drug: Rythmol® (Propafenone) 225 mg Film-Coated Tablet. Batch no.: (b) (4)

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Dedicated PK studies were not conducted by the sponsor to address the influence of age, race, bodyweight, pregnancy and organ dysfunction. Dosing reduction in the presence of renal impairment is proposed by the sponsor based on published data and PK simulations.

Colchicine is known to be excreted in urine. Ben-Chitrit et. al. 1994 (J. Rheumatology, 21(4): 710) published a report on PK of colchicine in patients with FMF (Familial Mediterranean Fever) with and without severe renal impairment who were on dialysis. Using data from this study, the current sponsor

West-ward conducted PK simulations using their own PK data with Colchicine Capsules and suggested the following dosing recommendations for patients with renal impairment:

‘Colchicine Capsules dosing must be individualized according to the patient’s renal function. For prophylaxis of gout flares in patients with mild (estimated creatinine clearance Clcr 60 – 89 mL/min) renal function impairment, adjustment of the recommended dose is (b) (4), but patients should be monitored closely for adverse effects. For patients with moderate renal impairment, (estimated creatinine clearance Clcr 30-59 mL/min), a (b) (4) % dosing reduction is recommended, which can be accomplished by reducing the daily dose to (b) (4) % of the normal dose or reducing the frequency of the dose to (b) (4) % of the normal frequency. Patients should be closely monitored for adverse effects. For patients with severe renal impairment, (estimated creatinine clearance Clcr 15-29 mL/min), a (b) (4) % dosing reduction is recommended, which can be accomplished by reducing the daily dose to (b) (4) % of the normal dose or reducing the frequency of the dose to (b) (4) % of the normal frequency. Patients should be closely monitored for adverse effects. Colchicine therapy should not be initiated in patients undergoing dialysis. If, however, colchicine therapy is necessary, the dose should be reduced to (b) (4) % of the normal dose and the patient closely monitored for adverse effects.’

Reviewer’s comments: The sponsor’s proposed labeling recommendations for renal impairment subjects are too prescriptive and the available PK data from the published study does not lend itself to this type of fine dose adjustment for the different renal impairment categories. Keeping in mind, that colchicine toxicity is regularly monitored in a clinical setting and the total daily dose of Colchicine Capsules for proposed indication ranges 2 fold, i.e., between 0.6-1.2 mg, a general cautionary language for renal impairment subjects including those on dialysis can be included in the label and the choice for dose reduction can be left to physician’s judgment.

2.3.2. What is the pediatric plan?

Hikma/West-ward requested a full waiver for PREA studies because gout is extremely rare in children and studies would be impossible or highly impracticable. The waiver was considered acceptable by the PeRC committee which reviewed the proposal on 6/12/2013.

2.4 Extrinsic Factors

2.4.1 How does food affect colchicine bioavailability?

The rate and extent of absorption of colchicine tablets (0.6 mg) was compared following a single dose, with and without the presence of a high fat meal, in study AA95730. West-ward is relying on its earlier food effect study for the tablet on the basis of a comparative dissolution study and the quantitative and qualitative equivalence of the two formulations, which is deemed acceptable.

The 90% CIs of the ratios of LSM derived from the analyses of the ln-transformed PK parameters AUC_{0-t}, AUC_{inf}, and C_{max} for colchicine when administered with or without food were within the 80.00% – 125.00% limits. Under fed conditions, the median t_{max} of colchicine was delayed by ~45 minutes when compared to fasting conditions. The PK parameters and the statistical analysis are shown below:

Table 4: PK Parameters of Colchicine in the Presence and Absence of Food (Treatment A: colchicine with high fat, high calorie breakfast, Treatment B: colchicine control)

PK Parameters	Treatment A		Treatment B	
	Mean ± SD	Geom. Mean (%CV)	Mean ± SD	Geom. Mean (%CV)
C _{max} (ng/mL)	2.08 ± 0.604	1.99 (31.4%)	2.34 ± 0.859	2.15 (48.4%)
AUC _{0-t} (ng·h/mL)	16.3 ± 4.16	15.8 (29.2%)	18.6 ± 5.81	17.6 (36.0%)
AUC _{inf} (ng·h/mL)	18.1 ± 4.23	17.6 (26.0%)	20.3 ± 5.93	19.4 (32.9%)
t _{max} * (h)	2.00 (0.50, 4.00)	.	1.25 (0.75, 3.00)	.
t _{1/2} (h)	31.0 ± 5.67	.	29.9 ± 5.36	.

Table 5: Statistical Analysis on Colchicine PK Parameters for Food Effect

Colchicine in Plasma West-ward 0.6 mg Colchicine Tablets – FED (A) Versus West-ward 0.6 mg Colchicine Tablets – FAST (B) (N = 27)		
Parameter	Ratio of LSM (A/B) (%)	90% CIs (%)
AUC _{0-t}	89.2	82.0 – 97.0
AUC _{inf}	90.3	83.5 – 97.6
C _{max}	92.4	82.6 – 103.4

2.4.2 What is the potential for drug-drug interactions between colchicine and CYP3A4 or P-gp inhibitors?

West-ward is relying on previous findings of safety and efficacy of Col-Probenecid and conducted their own DDI studies to be able to include adequate DDI information in their product label. They evaluated DDI potential of their product when co-administered with strong CYP3A4 inhibitor, voriconazole, a moderate CYP3A4 inhibitor, fluconazole, a weak CYP3A4 inhibitor, cimetidine, and a P-gp inhibitor propafenone. Study designs are listed below in Table 6. Blood samples for pharmacokinetic measurements were collected prior to and up to 72 hours (serial sampling) after each colchicine administration.

Table 6: Study Designs of the 4 Drug-Drug-Interaction Studies Conducted by West-Ward

Voriconazole	single center, non-randomized, open-label, one-sequence, crossover design in healthy male subjects.	Days 4-8: 1 x Vfend (Voriconazole) 200 mg film-coated tablet given twice daily for 5 consecutive days	Day 1: colchicine 0.6 mg Day 9: colchicine 0.6 mg + 200 mg Vfend
Fluconazole	single center, non-randomized, open-label, one-sequence, crossover design in healthy male subjects	Day 4: 2 x Diflucan (Fluconazole) 200 mg tablet Days 5-8: 1 x Diflucan (Fluconazole) 200 mg tablet given once-daily for 4 consecutive days	Day 1: colchicine 0.6 mg Day 9: colchicine 0.6 mg + 200 mg Diflucan
Cimetidine	single center, non-randomized, open-label, one-sequence, crossover	Days 4-8: 1 x Cimetidine 800 mg film-coated tablet USP given twice daily for 5	Day 1: colchicine 0.6 mg Day 9: colchicine 0.6 mg + 800 mg cimetidine

	design in healthy male and female subjects	consecutive days	
Propafenone	single center, non-randomized, open-label, one-sequence, crossover design in healthy male subjects	Days 4-8: 1 x Rythmol (Propafenone) 225 mg film-coated tablet given twice daily for 5 consecutive days	Day 1: colchicine 0.6 mg Day 9: colchicine 0.6 mg + 225 mg Rythmol

Plasma profiles of colchicine in the presence and absence of these inhibitors and associated PK data is shown below in Tables 7 and 8. Box plots indicating distribution of C_{max}, AUC_{inf} and T_{1/2} around the median are also shown in Appendix 2. The whiskers in the box plots depict the maximum and the minimum values. In addition, individual colchicine PK data in the presence and absence of any one inhibitor was evaluated for any trends in PK changes or existence of any outliers and is shown in Appendix 3.

Table 7: Plasma Profiles of Colchicine in the Presence and Absence of Various Inhibitors
 VCZ= voriconazole, FCZ = fluconazole, CMN= cimetidine, PFN = propafenone

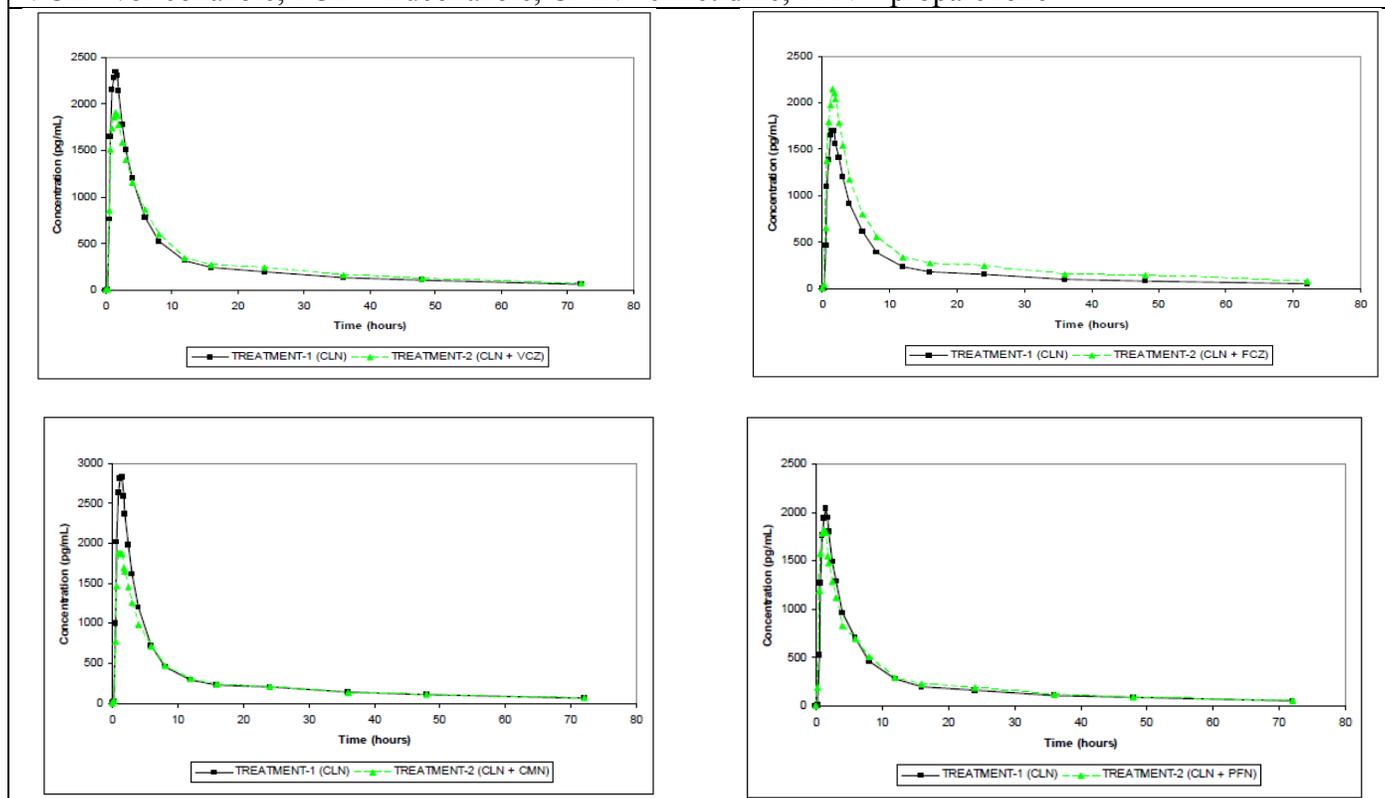


Table 8: PK parameters of Colchicine in the Presence and Absence of Various Inhibitors

VCZ= voriconazole, FCZ = fluconazole, CMN= cimetidine, PFN = propafenone

	- VCZ	+ VCZ	-FCZ	+FCZ	-CMN	+CMN	-PFN	+PFN
C _{max} (pg/mL)	2663	2058	1926	2299	2997	2109	2118	2206
AUC (pg.h/mL)	19605	20731	14939	21270	20382	18082	16626	16777
CL _{tot} /F (L/h)	33	28	37	26	28	34	34	33
T _{1/2el} (h)	30	31	34	35	35	32	30	28
K _{el} (1/h)	0.02	0.02	0.02	0.02	0.02	0.02	0.024	0.026

Reviewer's comments: Sponsor's studies revealed that colchicine PK (C_{max}, AUC_{inf} or T_{1/2}) was not affected significantly by any of the 4 inhibitors, a strong CYP3A4 inhibitor, voriconazole, a moderate CYP3A4 inhibitor, fluconazole (a mean of 40% increase in colchicine AUC_{inf} with fluconazole), a weak CYP3A4 inhibitor, cimetidine, and a P-gp inhibitor propafenone. Although some individuals showed some increase in colchicine PK in the presence of any of the 4 inhibitors (appendix 3), no trend in increase in colchicine PK in the presence of any of the 4 inhibitors was observed. These results initially seemed to not align with known DDI information for colchicine, i.e., its PK is affected severely by concomitant administration of CYP3A4 and/or P-gp inhibitors. However, upon a closer look at the existing DDI information of colchicine in published literature as well as several other factors that could have played into the DDI behavior of colchicine as observed in the DDI studies conducted by the sponsor, new insight into the disposition of colchicine was gained.

First, a search for DDI reports of colchicine was carried out using the University of Washington DDI database to check if any interactions have been reported with the 4 inhibitors that the sponsor employed. (<http://www.druginteractioninfo.org/>). The results (Appendix 4) indicated that no adverse event case reports have been published in literature with colchicine and any of the 4 inhibitors that the sponsor employed, this could mean that colchicine does not interact severely with these 4 drugs.

With respect to other drugs which significantly interact with colchicine (as indicated by > 20% inhibition in the UW database), the drugs that have been reported more than once, to interact severely with colchicine are clarithromycin, erythromycin, cyclosporine, and azithromycin. All these 4 drugs are known to inhibit both CYP3A4 mediated metabolism and P-gp mediated efflux to varying extent as noted in the most recent draft DDI Guidance published by the Agency (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>). Whereas clarithromycin is considered a strong CYP3A4 inhibitor and a potent P-gp inhibitor, cyclosporine is considered a potent P-gp inhibitor and a weak CYP3A4 inhibitor. Erythromycin and azithromycin are considered moderate to weak CYP3A4 inhibitors with some P-gp inhibition potential. As compared to these 4 drugs, the 4 inhibitor probes that the sponsor employed, i.e., the 3 CYP3A4 inhibitors, voriconazole, fluconazole and cimetidine, and the P-gp inhibitor, propafenone are not known to inhibit both the pathways. As such, the 4 drugs that the sponsor employed may be considered more 'pure' inhibitors of CYP3A4 (voriconazole, fluconazole and cimetidine) and P-gp (propafenone) respectively.

As such, it is possible that dual inhibition, i.e., inhibition of both CYP3A4 and the P-gp pathways for colchicine disposition is needed to observe significant DDI of colchicine.

Published literature was reviewed to evaluate contribution of CYP3A4 mediated metabolism and P-gp mediated efflux to colchicine disposition and if P-gp inhibition may play a more dominant role over CYP3A4 inhibition in colchicine DDI. An in vitro study published in 1997 (Tateishi T et al., 1997, *Biochemical Pharmacology*, 53, 111:116) showed that following the incubation of colchicine (5 nM) with human liver microsomes in the presence of an NADPH generating system for 60 min, 9.8% and 5.5% of the substrate were metabolized mainly by CYP3A4 to 3-demethyl colchicine (3-DMC) and 2-demethyl colchicine (2-DMC) respectively. From this in vitro study, it seems that colchicine is stable in human liver microsomes up to 60 minutes as only ~15% of colchicine was metabolized after 60 minutes. As such, it may be hypothesized that CYP3A4 may not play a major role in colchicine metabolism as colchicine is stable in human liver microsomes, a well acknowledged in vitro model to assess CYP mediated metabolism of drugs. This hypothesis is supported by the 3 DDI studies conducted by the sponsor with 3 CYP3A4 inhibitors ranging from strong inhibition potential to weak inhibition potential that did not interact with colchicine, indicating that DDI through CYP3A4 mediated pathways may not be as important for colchicine as previously believed. Having said that, the role of CYP3A4 in colchicine metabolism (in humans) cannot be ruled out completely. It is not clear how colchicine is metabolized in humans, no human ADME study has been conducted with colchicine. Also, some published case reports indicate that colchicine PK is affected by grapefruit juice, which is known to be primarily a CYP3A4 inhibitor and not a P-gp inhibitor.

In looking at whether P-gp inhibition may be more relevant for colchicine DDI as compared to CYP3A4 inhibition, a published study in rats that evaluated effect of P-gp inhibition vs. CYP inhibition on colchicine PK using somewhat specific inhibitors for the 2 pathways was reviewed. Chen et al., 2007 published a study evaluating effect on colchicine PK in rats when it is co-administered with cyclosporine (a potent P-gp inhibitor with weak to negligible CYP3A4 inhibition potential) and proadifen (a non-specific CYP inhibitor, per the authors). Cyclosporine increased colchicine systemic levels dramatically whereas proadifen increased liver concentrations of colchicine dramatically. As such, it is possible that colchicine systemic levels are affected mainly by P-gp inhibition and effect of CYP3A4 inhibition may be more prominent if localized liver concentrations are measured. This could be one of the reasons for not observing any DDI with the 3 CYP3A4 inhibitors that the sponsor used, i.e., voriconazole, fluconazole and cimetidine. All these 3 inhibitors do not inhibit P-gp and as such no change in systemic levels of colchicine was observed when co-administered with these 3 drugs. The sponsor did not measure any CYP or conjugation (UGT) metabolites in these studies. It is possible that the metabolite levels are affected by these 3 inhibitors, not levels of unchanged colchicine.

The doses and dosing regimen of the 4 inhibitors employed by the sponsor in their DDI studies were assessed for their appropriateness. Voriconazole, fluconazole and cimetidine are classified as strong, moderate and weak inhibitors of CYP3A4 based on several published DDI studies with sensitive CYP3A4 substrates. The doses and dosing regimens of each of these 3 inhibitors employed by the sponsor in the DDI studies are commonly studied doses and dosing regimens for these 3 inhibitors respectively to observe related CYP3A4 inhibition. However, there is uncertainty with regards to consistent CYP3A4 inhibition by voriconazole, for e.g., it does not increase systemic exposure of indinavir, a well-known CYP3A4 substrate, in humans (Purkins L et al., *Br J Clin Pharmacol* 2003;56 (Suppl I):62-68). As such it is possible that the best probe inhibitor for strong CYP3A4 inhibition was not employed by the sponsor, and perhaps use of more reliable and consistent strong CYP3A4 inhibitors such as ketoconazole or clarithromycin may have resulted in different observations. With regards to the choice of fluconazole as a moderate CYP3A4 inhibitor, it did result in a 40% increase in AUC of colchicine. This could be due to inhibition of CYP3A4 mediated metabolism of colchicine, due to which, the role of CYP3A4 cannot be

ruled out completely at this stage. It is also possible that fluconazole inhibited UGT-mediated conjugation pathways of colchicine in addition to inhibiting CYP3A4 mediated metabolism (colchicine is known to be glucuronidated in animals).

With regards to using propafenone as a P-gp inhibitor, its choice is not clear as there are other known and potent P-gp inhibitors such as quinidine, cyclosporine etc., that are routinely used as P-gp inhibitors in DDI assessments. Although the package insert for propafenone indicates that it enhances PK of digoxin in human studies, the package insert does not indicate whether it is a P-gp inhibitor or not. Additionally, it is possible that the right dose of propafenone was not employed to observe the effects of potent P-gp inhibition. Upon search in public database for reports indicating propafenone's interaction with digoxin, a well-known P-gp substrate, it was found that the doses of propafenone that affected digoxin PK were higher than the 225 mg BID X 5 days employed by the sponsor. Additionally, a published study reported that the IC₅₀ value of propafenone for digoxin inhibition was 6.8 microM in Caco-2 cells (Bachmakov et al., 2005. *Naunyn Schmiedebergs Arch Pharmacol.* 371(3):195-201). The plasma concentration of propafenone at 225 mg BID is projected to be lower than 6.8 microM and it is possible that propafenone systemic concentrations achieved with a 225 mg BID dose are insufficient to block P-gp activity in humans.

In summary, it appears that the sponsor employed CYP3A4 inhibitors that are either not potent and consistent inhibitors of CYP3A4 or are not dual inhibitors of CYP3A4 and P-gp and as such did not cause any significant changes in PK of colchicine in humans. This is a new insight related to colchicine DDI potential. It is also possible that the sponsor employed a P-gp inhibitor, propafenone which may not inhibit P-gp at the concentration employed in the colchicine-propafenone DDI study. Since in vitro studies indicate that CYP3A4 may not play a meaningful role in colchicine metabolism, it is possible that CYP3A4 inhibition by itself does not lead to a meaningful change in colchicine PK and P-gp inhibition is necessary to observe any significant changes in colchicine PK in humans. However, since case reports reporting colchicine toxicity have been published with moderate to strong CYP3A4 inhibitors such as erythromycin, grapefruit juice etc., the role of CYP3A4 in colchicine metabolism in humans cannot be completely ruled out with available data. Overall, based on published case reports, it is clear that dual inhibitors of CYP3A4 and P-gp such as clarithromycin, ketoconazole etc., exhibit clinically significant DDI with colchicine. In addition, P-gp inhibitors such as cyclosporine also exhibit clinically significant DDI with colchicine. Based on all available DDI information for colchicine (published adverse event reports and sponsor's DDI data), the labeling for colchicine will include cautionary language informing patients and health-care community with regards to DDI potential of colchicine along with the recommendation that colchicine daily dose may be reduced if co-administered with dual inhibitors of CYP3A4 and P-gp as well as with strong to moderate CYP3A4 inhibitors or P-gp inhibitors.

Need for post-marketing studies:

Because of what seems to be gaps in metabolism and excretion information for colchicine moiety as a whole and from the DDI package submitted by the sponsor in this NDA, the need for post-marketing studies was discussed in detail internally within the Agency. As already discussed, although initially the DDI data submitted by the sponsor seemed not to align with historical DDI information for colchicine, a review of all the pieces of information available from sponsor as well as from literature, generated new insights in understanding colchicine disposition.

Table 9 includes a list of studies that were discussed as potential post-marketing studies, however as indicated below for each study, enough scientific information was gathered to not have the sponsor conduct these studies post marketing.

Table 9: A list of potential post-marketing assessments discussed internally along with the available information that mitigated the need for the assessment.

Potential new assessment	Potential new information that can be generated from the assessment	Available information that mitigated the need for the assessment
An in vitro study in MDR1 over-expressing cells assessing P-gp inhibition potential of propafenone (including assessment of IC50 values for P-gp inhibition) using both colchicine and digoxin as positive control	This study may provide insight on the negative drug-drug interaction study of propafenone with colchicine	Based on in vitro inhibition potential of propafenone and its DDI case reports and studies with digoxin, a known, P-gp substrate, one can postulate that the dose of propafenone employed in the DDI study may not have been enough to demonstrate enough P-gp inhibition potential in humans
A human ADME study with radioactive colchicine	This study may provide quantitative information on colchicine disposition in humans	Based on case reports reporting colchicine toxicity in subjects with renal and hepatic impairment, it can be postulated that hepatobiliary and renal excretion are important pathways for renal metabolism and clearance and new quantitative information is not likely to significantly aid in the clinical management of colchicine in this patient population
An in vitro study evaluating metabolic pathways of colchicine, i.e., CYP mediated metabolism in human liver microsomes and UGT mediated metabolism in hepatocytes.	This study may provide insight on whether CYPs play an important role in colchicine metabolism and may help explain the negative drug-drug interaction studies of voriconazole and cimetidine with colchicine	This information is already available in a published in vitro study in hepatic liver microsomes indicating that about ~16% of colchicine is metabolized by CYP3A4 after 60 minutes of incubation
An in vivo study with a potent P-gp inhibitor such as quinidine or cyclosporine	This study may confirm the hypothesis that colchicine does interact significantly with potent P-gp inhibitors and the negative DDI with propafenone should not be extrapolated to other P-gp inhibitors	Case reports reporting fatal interactions of colchicine with cyclosporine in subjects with hepatic and/or renal impairment exist that confirm role of P-gp in colchicine disposition. Since the total daily dose of colchicine for the proposed indication is relatively on the low end with a two fold range in total dose of 0.6 to 1.2 mg, and healthcare providers regularly monitor patients colchicine dose with reference to GI and other adverse events, cautionary language informing health-care community on the risks of DDI of

		colchicine with P-gp inhibitors should suffice. Colchicine is contraindicated in patients with hepatic and/or renal impairment who are on CYP3A4+P-gp (dual) inhibitors.
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2.5 General Biopharmaceutics

2.5.1 What is the relative bioavailability of the proposed test product when compared to the approved reference products?

Study CLI-P1-680 evaluated relative bioavailability of West-ward's 0.6 mg Colchicine Capsules against Col-Probenecid (0.5 mg colchicine, 500 mg probenecid). The study demonstrated that dose adjusted C_{max} was slightly higher than that from Col-Probenecid, however dose-adjusted AUC parameters were equivalent. The test to reference C_{max} ratio of geometric LS means was 117.08% (90%CI: 105.78 to 129.58%) and the test to reference AUC_t ratio of geometric LS means was 109.97% (90%CI: 102.14 to 118.41%). The median T_{max} was 1.33 and 1.17 hours for the test and reference formulations, respectively. Overall, the dose adjusted bioavailability was similar between the two products. The plasma profiles obtained for colchicine from both test and reference colchicine products as well as PK parameters for colchicine and statistical analysis for bioequivalence are shown below.

Table 10: Plasma Profiles of Colchicine When Administered as 0.6 mg Colchicine Capsules or 0.5mg/500 mg Colchicine-Probenecid

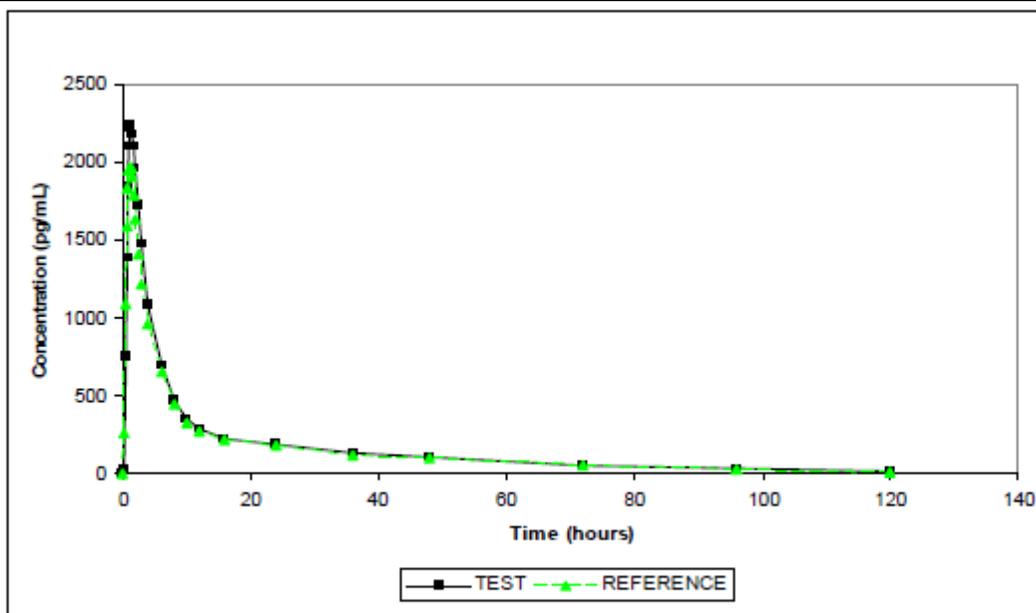


Table 11: PK Parameters for Colchicine in the Relative Bioavailability Study Bridging PK for 0.6 mg Colchicine Capsules to Reference, Col-Probenecid

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (pg/mL)	3046.0	40.4	2155.4	36.7
$\ln(C_{max})$	7.9399	5.3	7.5976	5.6
T_{max} (hours) [§]	1.33	35.1	1.17	38.9
AUC_T (pg·h/mL)	24175.0	37.6	18271.8	34.1
$\ln(AUC_T)$	10.0289	3.6	9.7496	3.9
AUC_{∞} (pg·h/mL)	25575.8	37.3	19508.7	32.7
$\ln(AUC_{\infty})$	10.0876	3.5	9.8207	3.7
$AUC_{T/\infty}$ (%)	94.32	1.9	93.17	2.6
K_{el} (hours ⁻¹)	0.0227	15.4	0.0226	18.4
$T_{1/2el}$ (hours)	31.26	17.1	31.79	20.1

[§] For T_{max} , the median is presented

Table 12: Bioequivalence Analysis on Colchicine PK Parameters when Administered as Test (0.6 mg Colchicine Capsules) or Reference (Col-Probenecid 0.5 mg colchicine, 500 mg probenecid)

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	25.5	2804.6	1996.3	140.49	126.94	155.49
AUC_T	18.4	22649.3	17163.8	131.96	122.56	142.08
AUC_{∞}	17.7	24017.5	18425.8	130.35	121.41	139.94

* units are pg/mL for C_{max} and pg·h/mL for AUC_T and AUC_{∞}

2.6 Analytical Methods

2.6.1 What bioanalytical methods are used to assess concentrations?

A validated HPLC method using MS/MS detection was employed in determining sample concentrations of colchicine in human plasma. The analytical assay was adequately validated. All samples were stored at -20°C nominal for about 27 days. The long-term stability of colchicine in human plasma covered 51 days at -20°C nominal. Sample pre-treatment involved the liquid-liquid extraction of colchicine from 0.200 mL of human plasma; Colchine-D6 was used as the internal standard. The compounds were identified and quantified using reverse-phase HPLC with MS/MS detection over a theoretical concentration range of 20 pg/mL to 18000 pg/mL. Office of Scientific Investigations audit of study CLL-P1-741 did not identify any significant issues with the analytical data.

3. Labeling Recommendations

Sponsor's proposed package insert with Agency's suggested revisions (underlined text showing additions and strikethrough text showing deletions) at the time of finalizing this review is shown in Appendix 4. Since this language is more than likely to undergo further revisions based on further internal discussions and negotiations with sponsor, see the approved package insert for final language.

Appendix 1: Box plots

Table 13: Box Plots Indicating Colchicine Cmax Distribution Along the Median in the Presence and Absence of Various Inhibitors

VCZ= voriconazole, FCZ = fluconazole, CMN= cimetidine, PFN = propafenone

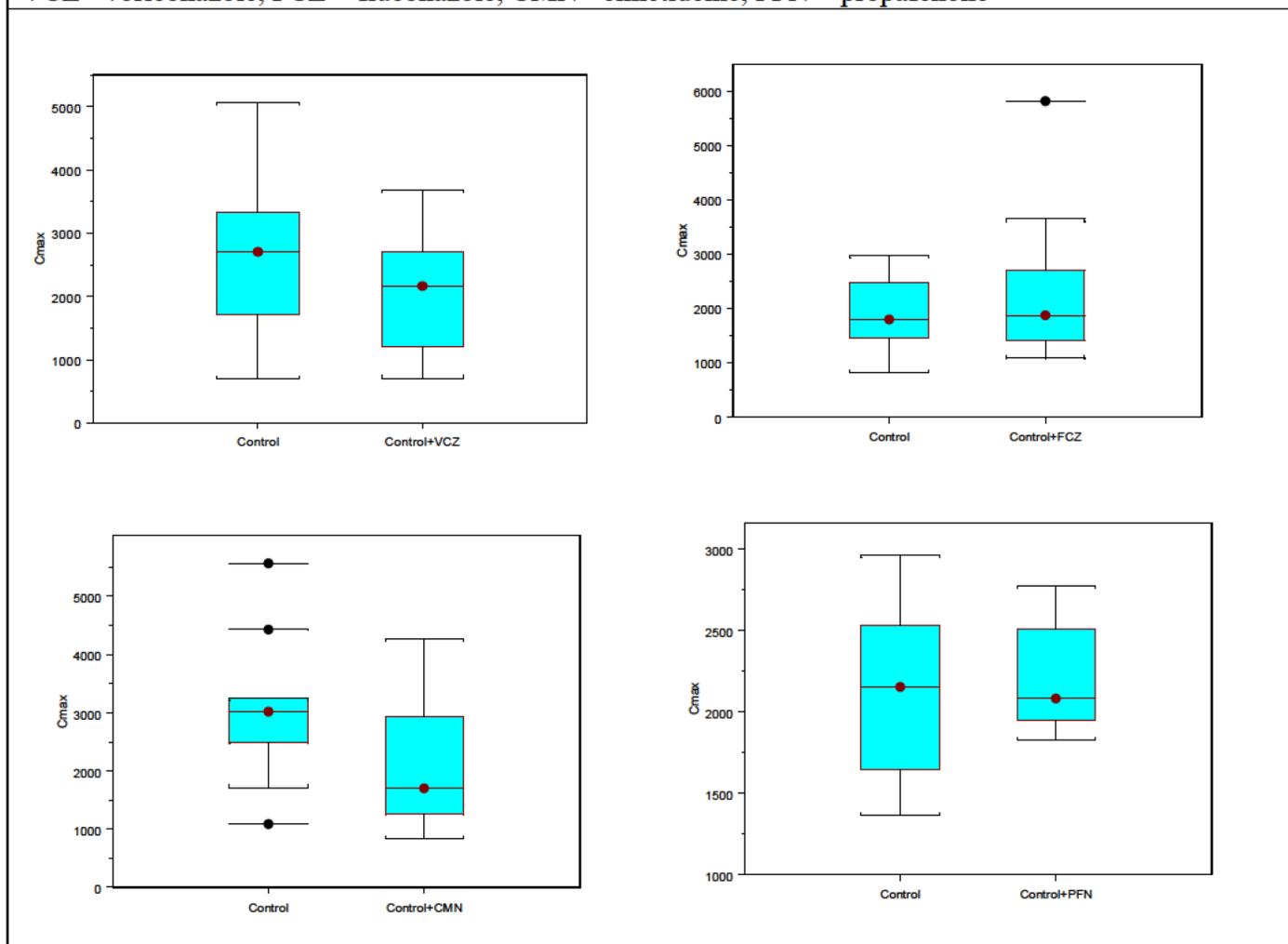


Table 14: Box Plots Indicating Colchicine AUCinf Distribution Along the Median in the Presence and Absence of Various Inhibitors

VCZ= voriconazole, FCZ = fluconazole, CMN= cimetideine, PFN = propafenone

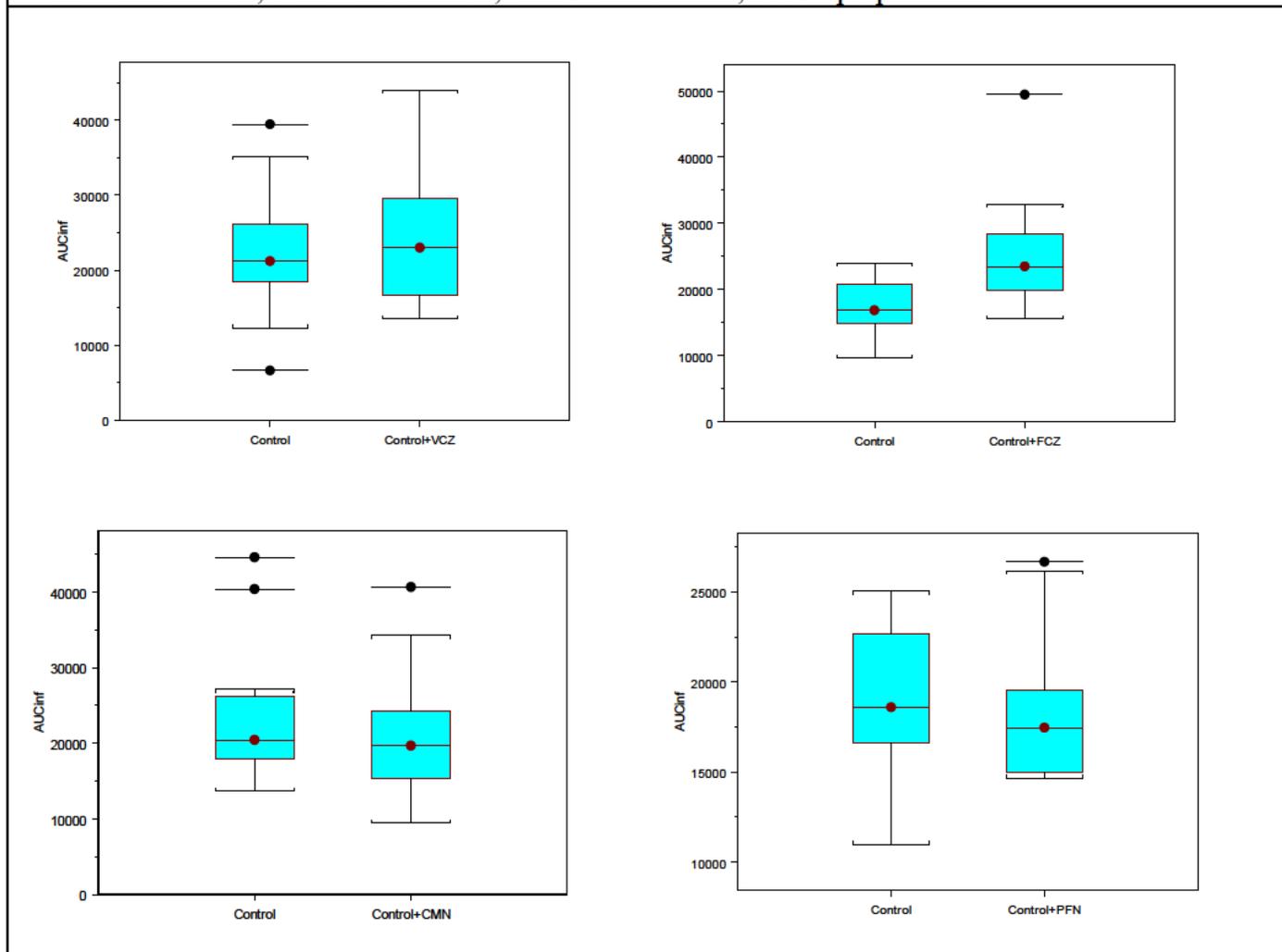
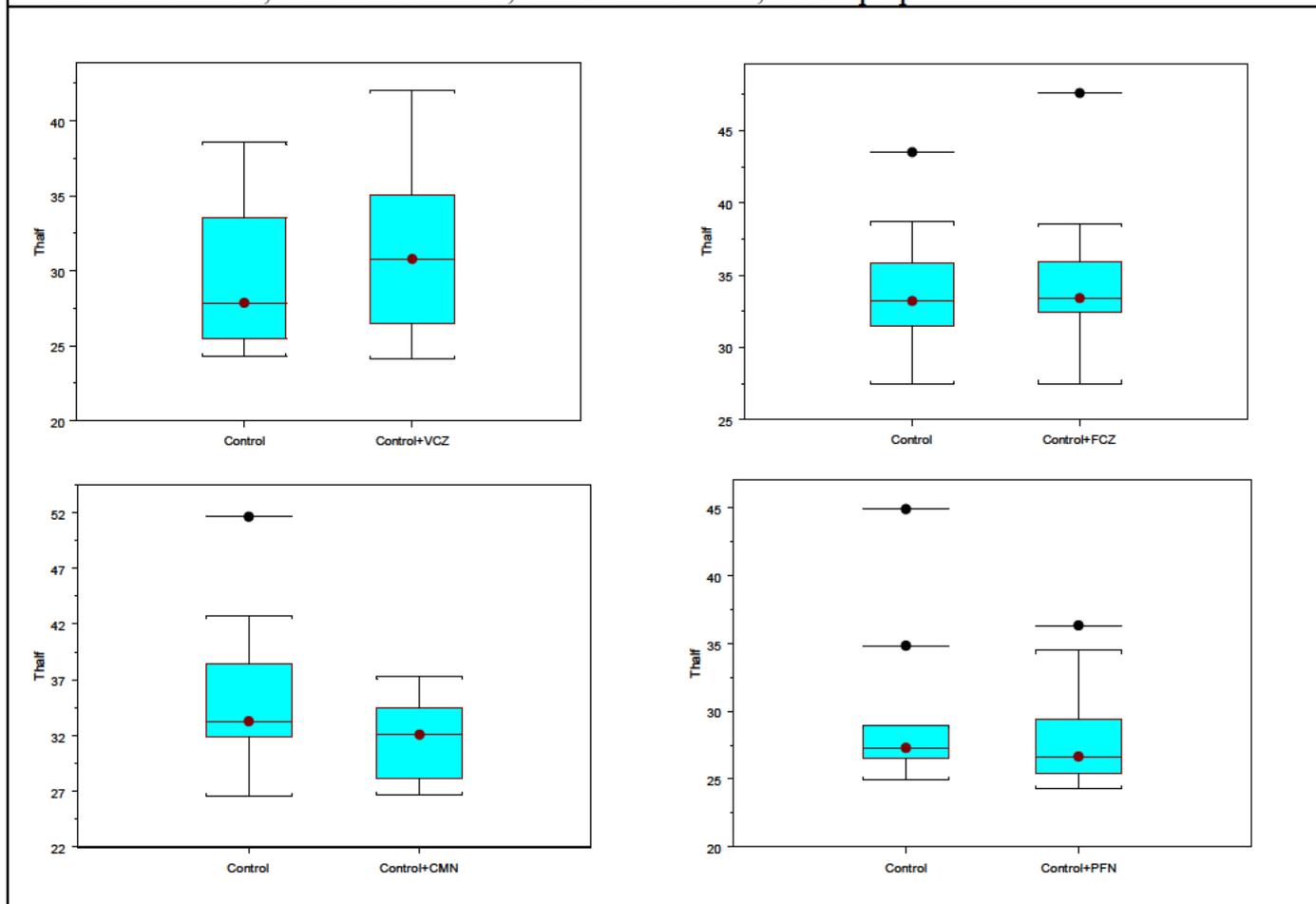


Table 15: Box Plots Indicating Colchicine Thalf Distribution Along the Median in the Presence and Absence of Various Inhibitors

VCZ= voriconazole, FCZ = fluconazole, CMN= cimetideine, PFN = propafenone



Appendix 2: Individual C_{max} and AUC_{inf} values in the presence and absence of a CYP3A4 inhibitor or a P-gp inhibitor observed in the colchicine DDI studies.

Table 16: Individual C_{max} and AUC_{inf} values for Colchicine in 12 subjects in the Presence and Absence of Voriconazole (VCZ)

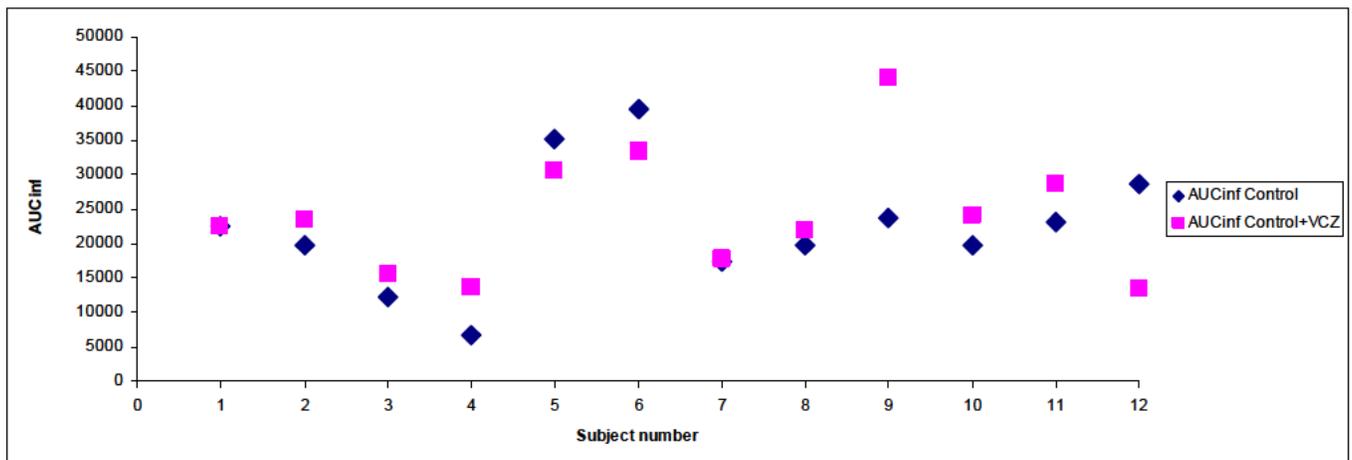
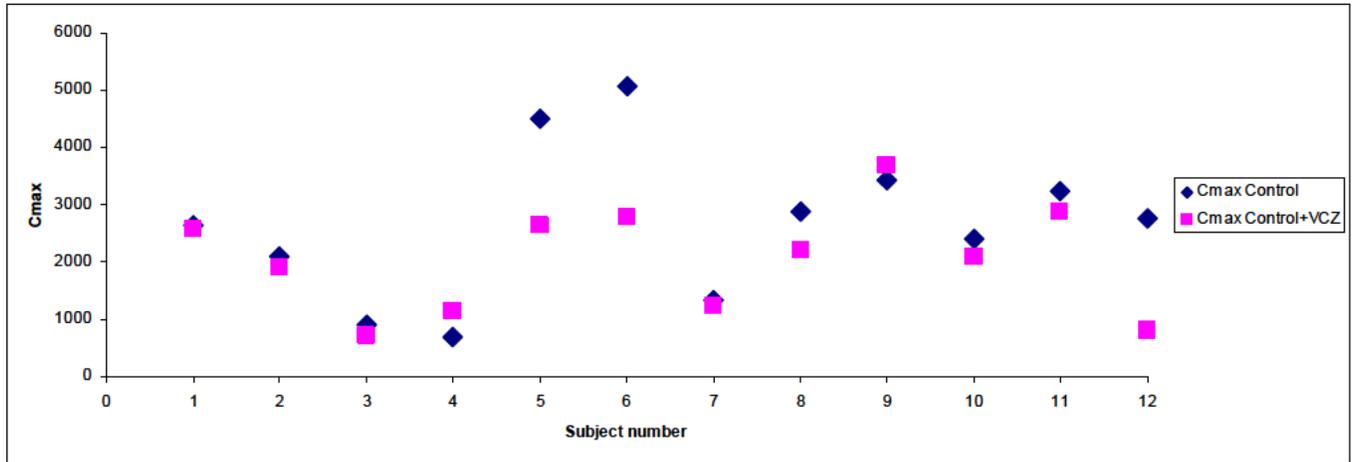


Table 17: Individual Cmax and AUCinf values for Colchicine in 12 subjects in the Presence and Absence of Fluconazole (FCZ)

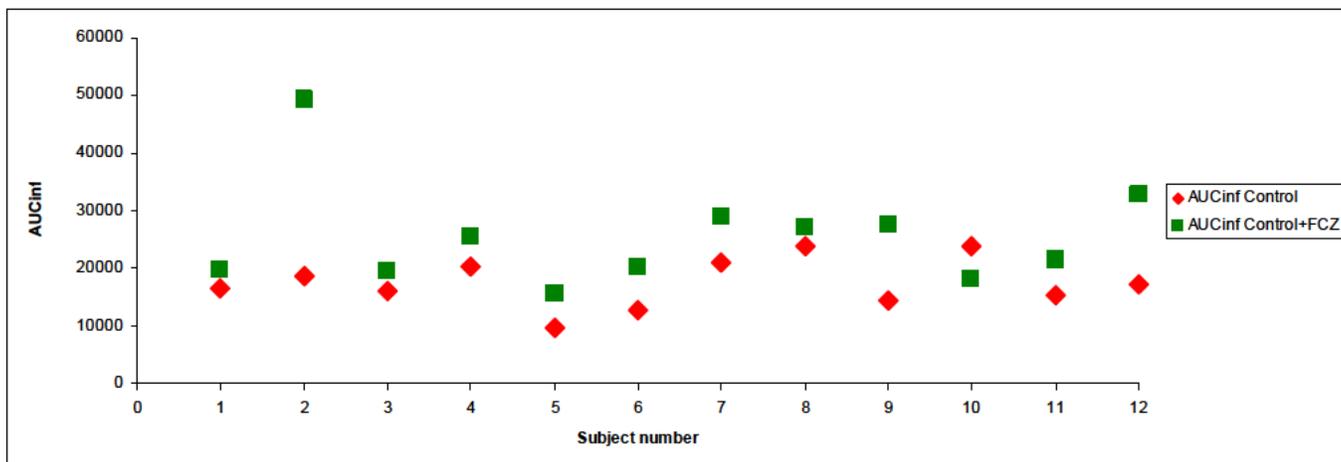
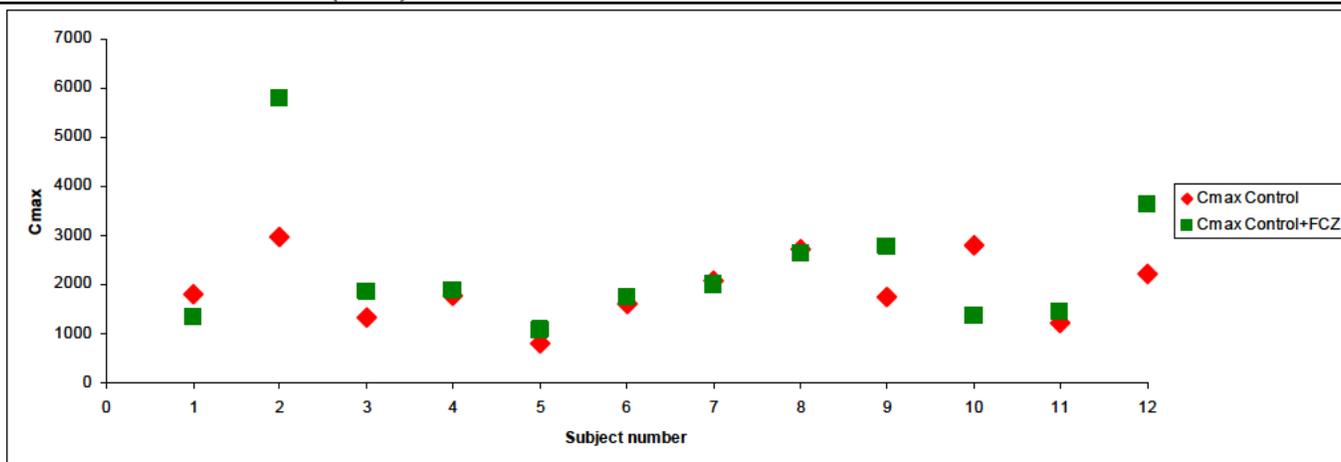


Table 18: Individual Cmax and AUCinf values for Colchicine in 12 subjects in the Presence and Absence of Cimetidine (CMN)

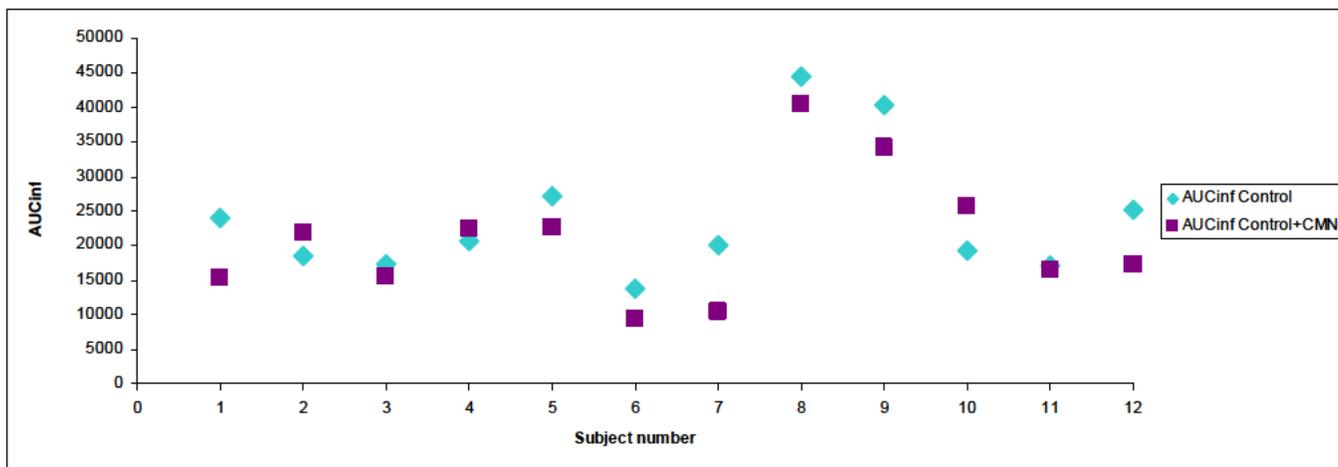
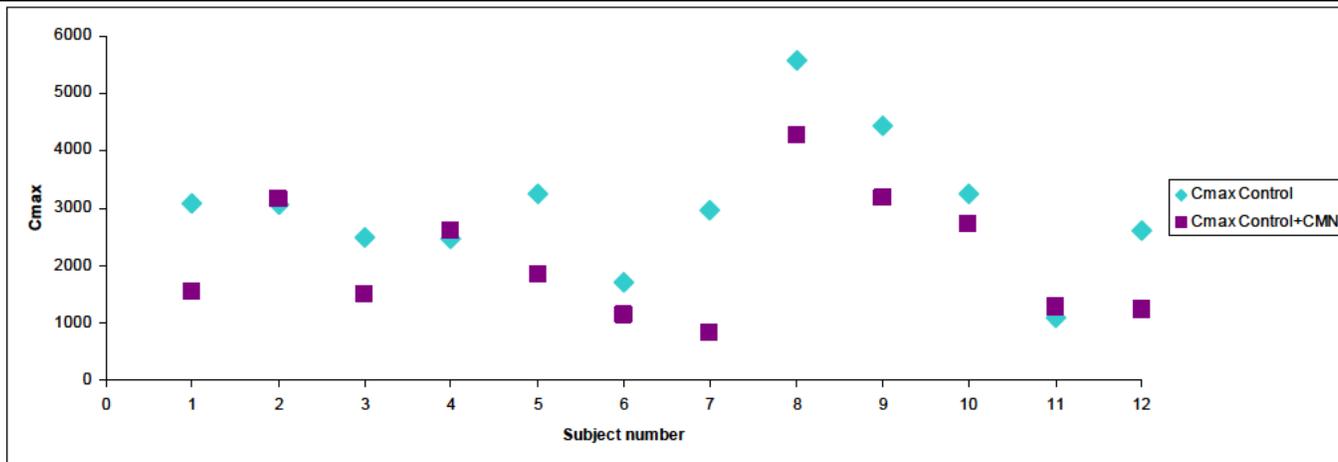
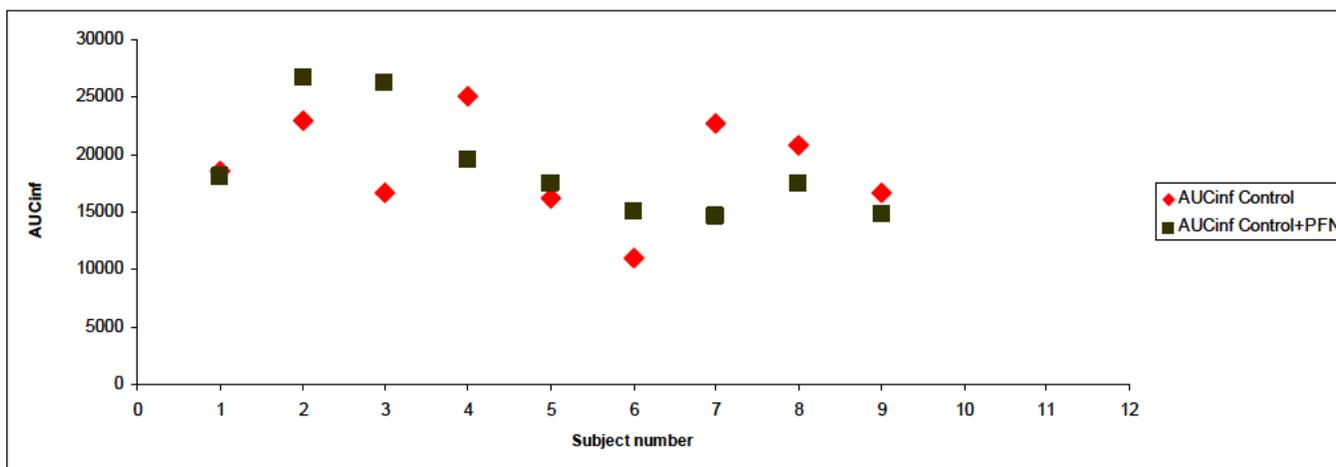
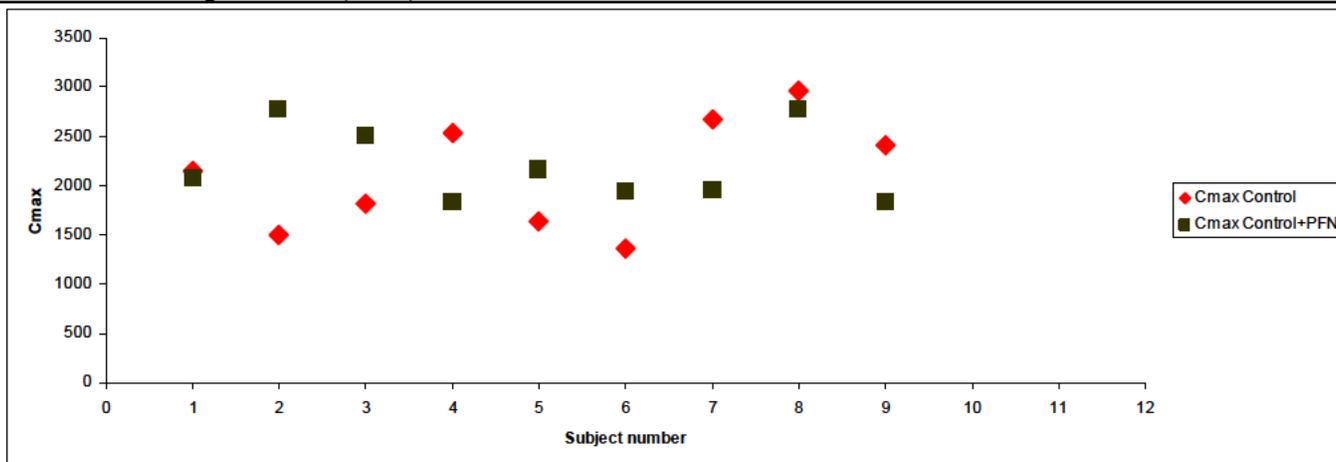


Table 19: Individual Cmax and AUCinf values for Colchicine in 9 subjects in the Presence and Absence of Propafenone (PFN)



Appendix 3: University of Washington Drug Metabolism and Transport Database
(<http://www.druginteractioninfo.org>)" adverse event reports for colchicine

Overall Effect	Object	Precipitant	Therapeutic Class	Accession # or NDA #	Published	Case Report
In Vivo Inhibition > 20% Effect	colchicine	azithromycin and cyclosporine	Other	Accession #: 21169852	2011 Jan	Yes
In Vivo Inhibition > 20% Effect	colchicine	clarithromycin	Antibiotics	Accession #: 11269688	2001 Feb	Yes
In Vivo Inhibition > 20% Effect	colchicine	clarithromycin	Antibiotics	Accession #: 15494379	2004 Dec	Yes
In Vivo Inhibition > 20% Effect	colchicine	clarithromycin	Antibiotics	Accession #: 16144178	2005 Aug	Yes
In Vivo Inhibition > 20% Effect	colchicine	clarithromycin	Antibiotics	Accession #: 17048210	2006 Jul-Aug	Yes
In Vivo Inhibition > 20% Effect	colchicine	clarithromycin	Antibiotics	Accession #: 18490798	2008 May	Yes
In Vivo Inhibition > 20% Effect	colchicine	clarithromycin	Antibiotics	Accession #: 19734738	2009 Sep	Yes
In Vivo Inhibition > 20% Effect	colchicine	cyclosporine	Immunosuppressants	Accession #: 10455999	1999 Aug	Yes
In Vivo Inhibition > 20% Effect	colchicine	cyclosporine	Immunosuppressants	Accession #: 1604496	1992 Jun	Yes
In Vivo Inhibition > 20% Effect	colchicine	cyclosporine	Immunosuppressants	Accession #: 9170024	1997 Apr	Yes
In Vivo Inhibition > 20% Effect	colchicine	disulfiram	Alcoholic Deterrents	Accession #: 19580840	2009 Oct 1	Yes
In Vivo Inhibition > 20% Effect	colchicine	erythromycin	Antibiotics	Accession #: 1578471	1992 Mar	Yes
In Vivo	colchicine	grapefruit juice	Food Products	Accession #: 11	2000	Yes

Inhibition > 20% Effect				131346	Dec	
In Vivo Inhibition > 20% Effect	colchicine	pristinamycin	Antibiotics	Accession #: 22137286	2012 Apr	Yes
In Vivo Inhibition > 20% Effect	colchicine	sunitinib	Kinase Inhibitors	Accession #: 23448320	2013 Jun	Yes
In Vivo Inhibition > 20% Effect	colchicine	verapamil	Calcium Channel Blockers	Accession #: 16148013	2005 Sep 17	Yes
Copyright University of Washington 1999-2013. UW Metabolism and Transport Drug Interaction Database (http://www.druginteractioninfo.org), accessed on May 30, 2013						

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

SHEETAL S AGARWAL
06/21/2013

SURESH DODDAPANENI
06/21/2013

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA 204820	Proposed Brand Name	Colcaps
OCP Division (I, II, III, IV, V)	II	Generic Name	Colchicine
Medical Division	DPARP	Drug Class	Anti-inflammatory
OCP Reviewer	Sheetal Agarwal	Proposed Indication(s)	Prophylaxis of gout flares
OCP Team Leader	Suresh Doddapaneni	Dosage Form	Capsules
Date of Submission	October 5, 2012	Dosing Regimen	For prophylaxis of gout flares, the recommended dosage of Colchicine Capsules is 0.6 mg once or twice daily for adults and adolescents older than 16 years of age. The maximum dose is 1.2 mg per day.
Estimated Due Date of OCP Review		Route of Administration	Oral
Medical Division Due Date		Sponsor	Hikma Pharmaceuticals US agent: Westward Pharma
PDUFA Due Date	August 5, 2013	Priority Classification	S

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	6	6	Includes 4 DDI studies, 1 food effect study and 1 relative BA study comparing the final to be marketed capsule formulation to an approved colchicine formulation (colchicine/probenecid 0.5/500 mg)
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				

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multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	4	4	Includes effects of strong, moderate and weak CYP3A4 inhibitor on colchicine and a P-gp inhibitor on colchicine
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	X	1	1	Single Dose Crossover Comparative Bioavailability Study of Colchicine 0.6 mg Capsules versus Colchicine/Probenecid 0.5 mg/500 mg Tablets in Healthy Male and Female Volunteers / Fasting State.
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	1	1	A Phase 1, Open-Label, Randomized, Single-Dose, Two-Way, Study to Investigate the Effect of the Consumption of a High-Fat Meal on the Bioavailability of West-ward 0.6 mg Colchicine Tablets in Healthy Adult Volunteers
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		6	6	Includes 4 DDI studies, 1 food effect study and 1 relative BA study.

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On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	

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17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

None.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The following 2 comments should be sent to the sponsor as part of the 74-day letter:

1. We note that data obtained in your four DDI studies, CLL-P1-741 (with voriconazole, a strong CYP3A4 inhibitor), CLL-P1-742 (with fluconazole, a moderate CYP3A4 inhibitor), CLN-P1-743 (with cimetidine, a weak CYP3A4 inhibitor), and CLN-P1-744 (with propafenone, a P-gp inhibitor) indicated that co-administration with inhibitors of either CYP3A4 or P-gp, does not have a significant effect on pharmacokinetics of colchicine in humans. However, most of the available in vitro and in vivo DDI information for colchicine in published literature (see references below), indicates that colchicine is metabolized by CYP3A4 and is a substrate of P-gp and co-administration with inhibitors of either CYP3A4 or P-gp, significantly alters pharmacokinetics of colchicine in humans. Therefore, your DDI data for colchicine is not in agreement with the published DDI information for colchicine. Please provide a justification/rationale for this discrepancy.
2. We note that in spite of not observing any significant changes in pharmacokinetics of colchicine when co-administered with either strong/moderate/weak CYP3A4 inhibitors or a P-gp inhibitor, you are recommending changes to dosing of colchicine when co-administered with these classes of drugs in your proposed label. Please provide a justification/rationale for this discrepancy.

Literature references for DDI information for colchicine:

1. Colchicine biotransformation by human liver microsomes. Identification of CYP3A4 as the major isoform responsible for colchicine demethylation. *Biochem Pharmacol* 1997; 53:111–116.
2. In vitro p-glycoprotein inhibition assays for assessment of clinical drug interaction potential of new drug candidates: a recommendation for probe substrates. *Drug Metab Dispos.* 2006 May; 34(5):786-92. Epub 2006 Feb 2.
3. Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. *Arthritis Rheum.* 2011 Aug; 63(8):2226-37. doi: 10.1002/art.30389.
4. Colchicine poisoning: the dark side of an ancient drug. *Clin Toxicol (Phila).* 2010 Jun;48(5):407-14.

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5. Colchicine update: 2008. Semin Arthritis Rheum. 2009 Jun;38(6):411-9. Epub 2008 Oct 29.

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

/s/

SHEETAL S AGARWAL
12/10/2012

SURESH DODDAPANENI
12/10/2012