

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204820Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 204820

SUPPL #

HFD # 570

Trade Name Mitigare

Generic Name colchicine

Applicant Name Hikma Pharmaceuticals (US Agent – West-Ward Pharmaceuticals)

Approval Date, If Known September 26, 2014

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

#### **505(b)(2)**

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?  
YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?  
YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 12383

Colbenemid (colchicine, probenecid)

NDA# 22352 Colcris (colchicine)  
ANDA# 84279 Col-Probenecid (colchicine, probenecid)  
ANDA# 40618 Probenecid and colchicine

***There are several additional ANDAs that were approved for colchicine and probenecid combination products, and are listed in the discontinued section of the Orange Book***

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

***The applicant submitted published literature on the safety and efficacy of colchicine for the prophylactic treatment of gout to support approval of this 505(b)(2) application, which also relies on the Agency's finding of safety and effectiveness for Col-Probenecid (ANDA 84-279). The applicant neither requests nor qualifies for three years of exclusivity based on these published studies.***

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # YES  ! NO   
! Explain:

Investigation #2 !  
IND # YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Michelle Jordan Garner  
Title: Senior Regulatory Management Officer  
Date: 9/24/14

Name of Office/Division Director signing form: Badrul A. Chowdhury  
Title: Director, DPARP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHELLE Y JORDAN GARNER  
09/26/2014

BADRUL A CHOWDHURY  
09/26/2014

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 204820 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Mitigare Established/Proper Name: colchicine Dosage Form: 0.6 mg capsule		Applicant: Hikma Pharmaceuticals LLC Agent for Applicant (if applicable): West-Ward Pharmaceutical
RPM: Michelle Jordan Garner		Division: DPARP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)            Date of check: 9/10/14</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>9/28/14</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None    8/5/13
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
*(confirm chemical classification at time of approval)*

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s): (AP)9/26/14; (CR) 8/5/13
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>Review(s) <i>(indicate date(s))</i></li> </ul>	6/20/14; 3/6/13 5/2/13
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 7/8/13 DMEPA: 9/3/14; 8/1/13 DMPP/PLT (DRISK): 9/9/14; 6/17/13 OPDP: 9/9/14; 6/19/13 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	9/10/14(completed 12/12)
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	(AP)6/4/14; (CR)7/9/13
	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>6/12/13</u> If PeRC review not necessary, explain: _____</li> </ul>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	9/17/14; 9/12/14; 9/10/14; 8/25/14;4/11 and 4/14; 6/10/13; 4/25 and 15/13; 4/11/13; 3/18 and 7/13; 2/4/13; 12/20/12; 12/19/12; 12/18/12; 11/28,20 and 5/12; 10/25/12
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Reg Briefing MM (9/19/14)
❖ Minutes of Meetings <ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 12/23/11 ( <i>IND 78601</i> ) <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9/26/14; 8/5/13
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9/11/14; 7/15/13
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews <ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review 7/9/13; 11/16/12 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Clinical review 7/9/13(pg.12)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None

❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/5/13
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/21/13; 12/10/12
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input type="checkbox"/> None requested 4/11/13
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 7/8/13
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 7/1/13; 11/15/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ <b>Product Quality Discipline Reviews</b>	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/7/14; 7/29/13; 6/6/13; 4/24/13; 1/17/13; 12/5/12;
❖ <b>Microbiology Reviews</b> <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ <b>Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer</b> <i>(indicate date of each review)</i>	<input type="checkbox"/> None 7/1/13; 11/21/12(Biopharm)
❖ <b>Environmental Assessment (check one) (original and supplemental applications)</b>	
<input checked="" type="checkbox"/> <b>Categorical Exclusion</b> <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	4/24/13
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ <b>Facilities Review/Inspection</b>	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: 6/26/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
• Finalize 505(b)(2) assessment	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHELLE Y JORDAN GARNER  
09/26/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

The PI attached to the approval letter, dated 9/26/14 was incorrect with the omission of minor editorial changes. Therefore, RPM sent a Word version of the corrected PI (see attached) 9/26/14 via email, so that corrections could be made prior to the applicant's distribution of the product and before submission of the labeling in SPL format.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** September 19, 2014

**TO:** Badrul A. Chowdhury, MD, PhD  
Director, DPARP

**FROM:** Michelle Jordan Garner, MS, OTR/L  
Senior Regulatory Management Officer

**SUBJECT: The Curious Case of Colchicine: What to Do About Conflicting Drug Interaction Study Results for the Same Molecular Entity**

**APPLICATION/DRUG:** NDA 204820/Hikma Pharmaceuticals-West-Ward/Mitigare (colchicine 0.6 mg capsule)

**BACKGROUND:**

The purpose of the regulatory briefing was to discuss the unexplained difference between Hikma/West-Ward's colchicine 0.6 capsules and the approved 0.6 mg colchicine tablets (Colcrys) with respect to Drug-Drug Interaction (DDI) studies. Based on the DDI studies with Hikma/West-Ward's 0.6 mg colchicine capsules, these capsules do not appear to have a significant interaction with drugs. The unexpected results conflict with historical information on colchicine from the published literature, as well as results from DDI studies conducted by Mutual Pharmaceuticals for Colcrys. The Division sought input regarding the optimal regulatory approach for the Hikma/West-Ward colchicine 505(b)(2) NDA (NDA 204820) and proposed labeling.

**Background and Regulatory History of Colchicine**

Colchicine, an alkaloid originally derived from the autumn crocus (*Colchicum autumnale*), has a long history of medicinal use, dating back to its first use as a purgative agent in ancient Egypt and Greece, more than 3000 years ago. Its first use as a selective treatment for gout dates back to 6 A.D. Colchicine is well known to have dose-related toxicity. The most common toxicity of colchicine is gastrointestinal (with nausea, vomiting, abdominal pain, and diarrhea), which is reversible with discontinuation of colchicine. Although gastrointestinal toxicity does not necessarily indicate an overdose of colchicine, it may be the first sign of more serious toxicity to follow, particularly with oral administration. Overdose toxicity can include electrolyte imbalance, bone marrow suppression, cardiovascular collapse, renal failure, rhabdomyolysis, seizures, mental status changes and death. Colchicine is estimated to be effective at doses of

approximately 0.015 mg/kg, toxic in doses greater than 0.1 mg/kg, and typically lethal at doses of approximately 0.8 mg/kg. In the therapeutic range, plasma levels are approximately 0.5 to 3 ng/ml.<sup>1</sup>

Colchicine was first isolated from colchicum in 1820 and made available in oral dosage forms during the 19<sup>th</sup> century. It has been used in small doses 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 “chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout,” or essentially, prophylactic treatment of gout flares.

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 was asked to perform a randomized controlled trial to supplement a single controlled trial available in the literature. Mutual performed and 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. Colchicine’s drug-drug interaction potential, as a P-gp<sup>2</sup> and cytochrome P450<sup>3</sup> substrate (specifically CYP3A4<sup>4</sup>), has long been reported in the literature. However, the DDI studies conducted by Mutual allowed for a more precise quantitative assessment of the interactions. Before the approved labeling for Colcrys, there were no widely-accepted specific recommendations for dose reduction in the setting of potential concomitant use of drugs with known interactions, other than avoidance when possible and caution when necessary, with vigilant monitoring of clinical signs of toxicity. Based on Mutual’s DDI studies, the Colcrys label has detailed dose modification information.

In November 2010, Mutual filed a Citizen Petition requesting, among other things, that any single-ingredient oral colchicine product must reference Colcrys and include all drug-drug interaction information in Colcrys labeling, including relevant dose adjustments needed to prevent unnecessary toxicity. Mutual’s citizen petition was granted in part, and denied in part. FDA disagreed that any single-ingredient oral colchicine product submitted through the

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<sup>1</sup> E Niel and JM Scherrmann, “Colchicine Today” Joint Bone Spine 2006; 73:672-678.

<sup>2</sup> AR Safa, ND Mehta, M Agresti, “Photoaffinity labeling of P-glycoprotein in multidrug resistant cells with photoactive analogs of colchicine.” Biochem and Biophys Res Com, 1989; 162(3):1402-1408

<sup>3</sup> AL Hunter, CD Klassen, “Biliary excretion of colchicine.” J Pharmacol Exp Ther, 1974; 192:605-17

<sup>4</sup> T Tateiski, et al. “Colchicine biotransformation by human liver microsomes: identification of CYP3A4 as a major isoform responsible for colchicine demethylation.” Biochem Pharmacol, 1997; 10:111-16

505(b)(2) pathway must necessarily cite Colcrys as its listed drug, irrespective of whether the proposed product shares the same strength, PK profile, or other characteristics such as dosage form or conditions of use. With respect to drug-drug interaction labeling, FDA agreed that product labeling for any single-ingredient oral colchicine product needs to include adequate information on drug-drug interactions, including relevant dose adjustments needed to prevent unnecessary toxicity.

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. The protocols were not reviewed by the FDA, and the data were not discussed with FDA before submission.

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 capsule, for the proposed indication of prophylaxis of gout flares. In this 505(b)(2) NDA, Hikma/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 presubmission 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 colchicine capsules—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. Unexpectedly, all four DDI studies demonstrated no significant effect on the pharmacokinetics of the West-Ward colchicine capsule. Study sites were inspected and no issues were identified. Further details are described in the Clinical Pharmacology section below.

**Product Information**

The drug product is colchicine capsules and each immediate release capsule contains 0.6 mg of colchicine. The drug product is formulated as gelatin capsule with a formulation comprised of colchicine and the following excipients: anhydrous lactose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and colloidal silicon dioxide. The drug substance has the USAN name “colchicine” and a monograph appears in the current edition of the USP. The drug substance provided by (b) (4) is an (b) (4).

**Clinical Pharmacology Overview**

Table 1, below, summarizes the DDI data submitted by West-Ward for their product, along with the corresponding DDI data from Mutual’s submission for Colcrys.

**Table 1: Summary of DDI Study Results**

	Capsules WESTWARD	Tablets MUTUAL (Colcrys)
Weak CYP3A4 inhibitor	With cimetidine: -33% Cmax, -15% AUC	With azithromycin: 21.6% ↑ Cmax, 57% ↑ AUC

Moderate CYP3A4 inhibitor	With fluconazole: 13% ↑ Cmax, 40% ↑ AUC	With verapamil: 40% ↑ Cmax, 103% ↑ AUC
Strong CYP3A4 inhibitor	With voriconazole: 20% ↑ Cmax, 10% ↑ AUC	With ketoconazole: 102% ↑ Cmax, 212% ↑ AUC With clarithromycin: 227% ↑ Cmax, 282% ↑ AUC With ritonavir: 184% ↑ Cmax, 296% ↑ AUC
P-gp inhibitor	With propafenone: no change	With cyclosporine: 270% ↑ Cmax, 259% ↑ AUC

For reasons that are not fully understood, Hikma/West-Ward's product did not show a significant PK based interaction with any of the 4 probe inhibitors employed in their DDI studies. 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 attempted to explain their results by postulating that colchicine's drug-drug interactions are due more to the involvement of P-gp rather than CYP3A4. Since strong, moderate, and weak CYP3A4 inhibitors did not show interaction with their product, the sponsor inferred that CYP3A4 does not play a significant role in drug interactions of colchicine. Since P-gp inhibitor propafenone did not show an interaction, the sponsor explained this lack of interaction by hypothesizing that propafenone and colchicine bind to different domains of P-gp. However, a notable difference between the interacting drugs chosen in the two DDI programs is that cimetidine, fluconazole, voriconazole, and propafenone are not dual inhibitors of CYP3A4 and P-gp, whereas azithromycin, verapamil, ketoconazole, clarithromycin, ritonavir, and cyclosporine all inhibit both CYP3A4 and P-gp.

Based on these DDI results, modifications in colchicine dosing regimens are not warranted when the Hikma/West-Ward product is co-administered with drugs from any of the 4 classes of probe inhibitors, i.e., strong, moderate, weak CYP3A4 inhibitors and P-gp inhibitors. However, these results are not consistent with historical knowledge and previous drug interaction data with colchicine, and it is not clear why. These data suggest potentially new insights into colchicine drug interactions, but additional data would be required to understand what those are.

### **QUESTIONS:**

1. Do these unexpected results justify a complete response action for NDA 204820?
  - a) If so, what response should be required to address the deficiency?
  - b) Please comment on why you believe West-Ward's proposal to label based on published literature and conduct clarifying studies post-approval is not acceptable.
2. If not, and you believe the application should be approved:
  - a) How should the product be labeled pending clarifying DDI study(ies)?
  - b) What issues does the panel see with having different labeling for the two different single-ingredient oral colchicine products and how should these be addressed?

**DISCUSSION:**

Dr. Hull presented an overview on the history and regulatory background of colchicine, as described in Section 1 above. Dr. Hull also described the history of colchicine drug-drug interaction knowledge, which dates back to 1974, when colchicine was first identified as a cytochrome P450 substrate and 1989 when it was identified as a P-glycoprotein substrate. This included literature reports of colchicine's interaction with various drugs, such as clarithromycin, azithromycin, cyclosporine, and erythromycin, and review articles as early as 1998 recommending caution and careful monitoring of colchicine when coadministered with agents metabolized by the cytochrome system. As additional context, Dr. Hull discussed the Colcrys NDA, which represented the first approval for colchicine as a single-ingredient product, and the presubmission regulatory interactions with West-Ward.

Dr. Agarwal then presented a summary of the West-Ward DDI study results and the possible explanations that were considered for these results, which were different than expected based on the Colcrys data described in product labeling and the literature. Possibilities included differences in the formulation, DDI study design or conduct issues, and differences in the probe inhibitors tested. Formulation and DDI study design/conduct issues were investigated but ruled out. The probe inhibitors used by West-Ward were different than those previously reported to interact with colchicine and were thought to be a possible explanation. Cimetidine was used as a weak CYP3A4 inhibitor, fluconazole as a moderate CYP3A4 inhibitor, and voriconazole as a strong CYP3A4 inhibitor. Propafenone was used as a P-gp inhibitor. Dr. Agarwal then presented the data for each inhibitor tested, along with the sponsor's explanation for the apparent lack of interaction, as described in Section 1 above. In contrast to known interacting drugs, which inhibit both CYP3A4 and P-gp, the probe inhibitors tested in the West-Ward DDI studies are not known to have effects on both pathways. Overall, the West-Ward DDI studies raised the question of whether CYP3A4 or P-gp interactions alone would present a DDI risk with colchicine. Dr. Agarwal then described additional data that might be helpful to clarify the observed differences.

The regulatory briefing panel then asked clarifying questions regarding the DDI study results and the particular probe inhibitors tested.

Dr. Yim then presented the Division's considerations in determining the next course of action for the Hikma/West-Ward NDA and the possible action scenarios. These included requiring additional data before approval, approving the NDA with labeling that had literature-based drug interaction precautions, labeling that included the West-Ward DDI data, or a combination of the latter two scenarios.

The regulatory briefing panel opined that the unexpected results, on their own, did not warrant a complete response action for NDA 204820. It was noted that the results from the Hikma/West-Ward studies actually did not contradict historical information on colchicine from published literature or DDI study results described in Colcrys labeling, but instead provided data on different probe inhibitors. The panel discussed whether additional data should be requested to clarify observed differences among P-gp inhibitors and between dual P-gp/CYP3A4 inhibitors

and single inhibitors. The panel also discussed the necessity of such studies given that the drugs of most concern appear to be dual inhibitors, for which there is adequate qualitative data regarding drug interactions in published literature. Overall, the panel considered that available data and information in published literature reflecting the long history of clinical use of colchicine and Hikma/West-Ward's study data supported approval of the NDA despite certain questions raised by the West-Ward DDI study data. Discussion then proceeded to Question 2.

The regulatory briefing panel discussed the possibilities for labeling in light of the available information on colchicine DDI. The panel recommended that the West-Ward DDI studies should be included in labeling with the caveat that these results may not apply to other drugs that have not been studied. The panel agreed that the West-Ward DDI studies raise questions about the generalizability of detailed dose modification recommendations to drugs that have not been directly studied and asked the team whether safety concerns had arisen based on the detailed dose modification recommendations in the Colcris labeling. The team was not aware of any data that would suggest a specific safety concern related to the detailed dose modification recommendations, but noted that the Colcris dose modification recommendations were not tested clinically and the Colcris labeling could be misleading if interpreted to mean that following dose modification instructions would avoid a problem. The regulatory briefing panel also considered the labeling in light of FDA's earlier consideration of drug-drug interaction information for colchicine in the context of a citizen petition submitted by Mutual in 2010. In FDA's 2011 response to the citizen petition, FDA agreed that product labeling for single-ingredient oral colchicine products would need to include adequate information on drug-drug interactions and relevant dose adjustments needed to prevent unnecessary toxicity. However, in light of the new information provided by the West-Ward DDI studies, and the questions about the generalizability of dose modification recommendations, the regulatory briefing panel opined that it was reasonable to forego detailed dose modification recommendations and include Warnings and Precautions about drug interactions with colchicine based on the case reports in the literature, which suggest that dual inhibitors of CYP3A4 and P-gp are particularly problematic when administered with colchicine, and co-administration should be avoided. If avoidance is not possible, a general precaution to reduce the daily dose and monitor closely for colchicine toxicity is reasonable, given the uncertainty about generalizability and variability among individuals.

With respect to having different labeling for the two single-ingredient oral colchicine products (i.e., Colcris and the Hikma/West-Ward product), the regulatory briefing panel did not believe this was a major issue. There was some discussion of whether the Colcris labeling should be revised. However in the absence of information suggesting that one approach was superior to the other, in terms of safety, either approach could be considered reasonable.

# The Curious Case of Colchicine



What to do about conflicting drug-drug interaction  
study results for the same molecular entity

May 31, 2013

## Outline

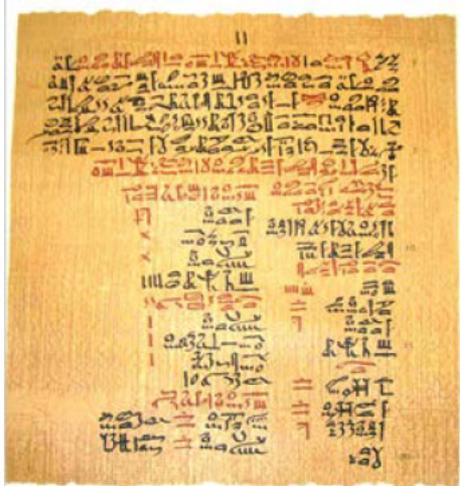
- Colchicine history and regulatory background: Dr. Keith Hull
- Colchicine drug-drug interaction studies: Dr. Sheetal Agarwal
- Considerations for path forward: Dr. Sarah Yim
- Discussion of questions: Dr. Sarah Yim



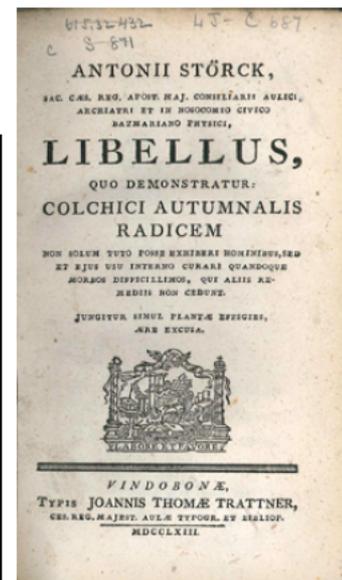
# Colchicine History and Regulatory Background

Dr. Keith Hull

# Colchicine: abbreviated history



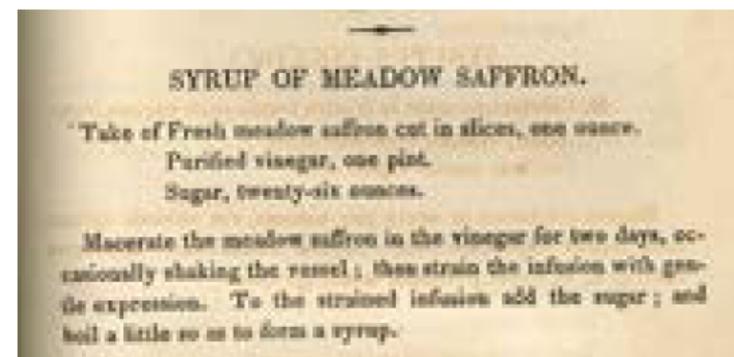
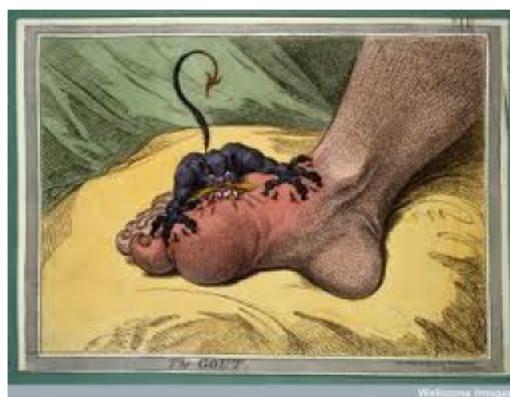
1500 BC  
Ancient  
Egypt / Greece  
Purgative agent



1760s  
Vienna  
Colchicine  
revival

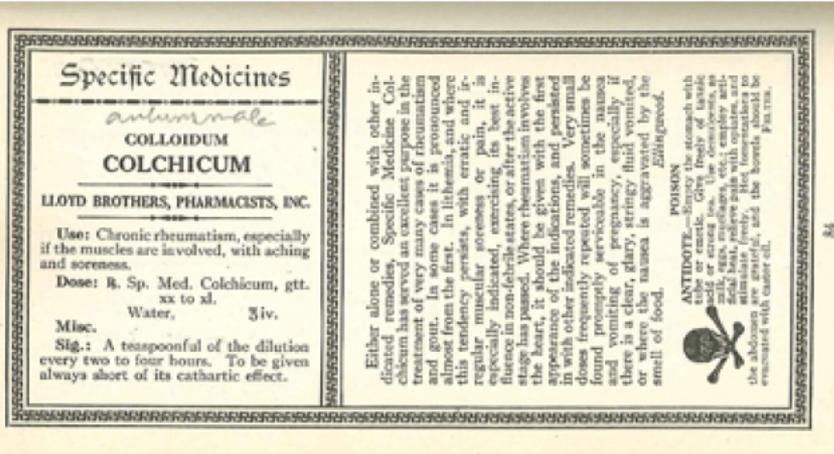
1300s-1600s—**toxicity concerns drop use**

Byzantine  
gout tx  
6 AD



1<sup>st</sup> ed. USP 1820

# Colchicine: abbreviated history



1930  
Individual  
Pharmacy  
Formulations

1961-2009 No approved single-ingredient colchicine



1961  
First FDA  
approval as  
part of the  
combination  
Colchicine-  
Probenecid  
for chronic  
gout



DESI review and endorsement  
July 1972

2009: First single-  
ingredient colchicine  
approved—Colcryls 0.6  
mg tablets

- FMF
- Acute Gout Tx
- Chronic Gout Tx

## History of Colchicine Drug-Drug Interactions

- Ca 1974: Colchicine is a Cytochrome P450 substrate
- Ca 1989: Colchicine is a P-glycoprotein (P-gp) substrate
- Ca 1997: Colchicine is a CYP3A4 substrate
- 1998, Ben Chetrit and Levy:
  - “Thus, coadministration of medications and substances metabolized by the cytochrome system, in principle, may lead to an increase of one or more of the drugs exposing the patient to a higher risk of toxicity. Caution should be exercised in such cases, especially when the patient also has disturbed liver or kidney function.”
- 2006, Niel and Scherrmann:
  - “Adverse events are not uncommon, most notably when colchicine is used in combination with drugs that interact with CYP3A4 and/or P-glycoprotein...Careful monitoring in this situation is effective in preventing the development of toxicity.”

# Colchicine case reports: Strong DDI potential of colchicine

Overall Effect	Object	Precipitant	Therapeutic Class	Accession # or NDA #	Published	Case Report
In Vivo Inhibition > 20% Effect	colchicine	azithromycin and cyclosporine	Other	Accession #: <a href="#">21169852</a>	2011 Jan	Yes
In Vivo Inhibition > 20% Effect	colchicine	clarithromycin	Antibiotics	Accession #: <a href="#">11269688</a>	2001 Feb	Yes
In Vivo Inhibition > 20% Effect	colchicine	clarithromycin	Antibiotics	Accession #: <a href="#">15494379</a>	2004 Dec	Yes
In Vivo Inhibition > 20% Effect	colchicine	clarithromycin	Antibiotics	Accession #: <a href="#">16144178</a>	2005 Aug	Yes
In Vivo Inhibition > 20% Effect	colchicine	clarithromycin	Antibiotics	Accession #: <a href="#">17048210</a>	2006 Jul-Aug	Yes
In Vivo Inhibition > 20% Effect	colchicine	clarithromycin	Antibiotics	Accession #: <a href="#">18490798</a>	2008 May	Yes
In Vivo Inhibition > 20% Effect	colchicine	clarithromycin	Antibiotics	Accession #: <a href="#">19734738</a>	2009 Sep	Yes
In Vivo Inhibition > 20% Effect	colchicine	cyclosporine	Immunosuppressants	Accession #: <a href="#">10455999</a>	1999 Aug	Yes
In Vivo Inhibition > 20% Effect	colchicine	cyclosporine	Immunosuppressants	Accession #: <a href="#">1604496</a>	1992 Jun	Yes
In Vivo Inhibition > 20% Effect	colchicine	cyclosporine	Immunosuppressants	Accession #: <a href="#">9170024</a>	1997 Apr	Yes
In Vivo Inhibition > 20% Effect	colchicine	disulfiram	Alcoholic Deterrents	Accession #: <a href="#">19580840</a>	2009 Oct 1	Yes
In Vivo Inhibition > 20% Effect	colchicine	erythromycin	Antibiotics	Accession #: <a href="#">1578471</a>	1992 Mar	Yes
In Vivo Inhibition > 20% Effect	colchicine	grapefruit juice	Food Products	Accession #: <a href="#">11131346</a>	2000 Dec	Yes

Azithromycin: Weak CYP3A + P-gp inhibitor

Clarithromycin: Strong CYP3A + P-gp inhibitor

CsA: Weak CYP3A + multiple transporter inhibitor

Erythromycin: Moderate CYP3A + P-gp inhibitor

Grapefruit juice: Strong/moderate CYP3A inhibitor (may/may not inhibit P-gp)

Disulfiram: Weak CYP3A inhibitor (may/may not inhibit P-gp)

## Regulatory background: Colcrys, first single-ingredient colchicine NDA

- A 0.6 mg scored tablet formulation of colchicine was approved in July 2009 (NDAs 22-351 and 22-352) and October 2009 (NDA 22-353) submitted by AR Holding/Mutual Pharma
  - 505(b)(2) applications referencing Col-Probenecid + published literature for FMF, treatment of gout flares (acute treatment), and prophylaxis of gout flares (chronic treatment)
  - Acute gout NDA also included a clinical trial considered necessary for approval for this indication
  - 3-year marketing exclusivity for treatment of gout flares, expired on July 30, 2012
  - 7-year marketing exclusivity for the orphan indication to expire on July 29, 2016

# Mutual NDAs supported by extensive DDI data

## Drug Interactions: Pharmacokinetic Parameters for COLCRYS (colchicine, USP) tablets in the Presence of the Co-Administered Drug

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of COLCRYS (mg)	N	% Change in Colchicine Concentrations from Baseline (Range: Min - Max)	
				C <sub>max</sub>	AUC <sub>0-t</sub>
Cyclosporine	100 mg single-dose	0.6 mg single-dose	23	270.0 (62.0 to 606.9)	259.0 (75.8 to 511.9)
Clarithromycin	250 mg BID, 7 days	0.6 mg single-dose	23	227.2 (65.7 to 591.1)	281.5 (88.7 to 851.6)
Ketoconazole	200 mg BID, 5 days	0.6 mg single-dose	24	101.7 (19.6 to 219.0)	212.2 (76.7 to 419.6)
Ritonavir	100 mg BID, 5 days	0.6 mg single-dose	18	184.4 (79.2 to 447.4)	296.0 (53.8 to 924.4)
Verapamil	240 mg daily, 5 days	0.6 mg single-dose	24	40.1 (-47.1 to 149.5)	103.3 (-9.8 to 217.2)
Diltiazem	240 mg daily, 7 days	0.6 mg single-dose	20	44.2 (-46.0 to 318.3)	93.4 (-30.2 to 338.6)
Azithromycin	500 mg × 1 day, then 250 mg × 4 days	0.6 mg single-dose	21	21.6 (-41.7 to 222.0)	57.1 (-24.3 to 241.1)
Grapefruit Juice	240 mL BID, 4 days	0.6 mg single-dose	21	-2.55 (-53.4 to 55.0)	-2.36 (-46.4 to 62.2)

## Colcrys dosing recommendations in the presence of CYP3A4/P-gp inhibitors based on DDI data

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

## Post Colcrys approval

- Colcrys label included specific dosing changes when colchicine is co-administered with strong, moderate CYP3A4 inhibitors and with a P-gp inhibitor
- FDA published a FR notice announcing its intention to take enforcement action against unapproved single-ingredient oral colchicine products. FDA noted that the labeling for the unapproved products does not reflect the most current data regarding the safety and effectiveness of single-ingredient oral colchicine
- The price of colchicine increased from as little as a nickel per pill to \$5 per pill (about 100 times) for Colcrys
- Significant media and community backlash

## Mutual's Citizen Petition

- On November 26, 2010, Mutual filed a citizen petition requesting, among other things, that any single-ingredient oral colchicine product must reference Colcrys and include all DDI information in Colcrys labeling, including relevant dose adjustments needed to prevent unnecessary toxicity
- Mutual's citizen petition was granted in part, and denied in part
- FDA's response relevant to DDI labeling is as follows:
  - FDA has concluded there is a risk for severe drug interactions in certain patients treated with colchicine and concomitant P-gp or strong CYP3A4 inhibitors and the new dosing recommendations for concomitant use will help mitigate this risk. This determination was based on FDA's review of a significant volume of published literature as well as Mutual's DDI studies
  - FDA agrees that product labeling for any single-ingredient oral colchicine product needs to include adequate information on drug-drug interactions, including relevant dose adjustments needed to prevent unnecessary toxicity.

## Regulatory background for West-Ward colchicine

- October 14, 2009
  - IND protocol evaluating relative BA of their 0.6 mg tablets vs. Col-

(b) (4)



## Regulatory background for West-Ward colchicine

- November 30, 2011
  - FDA met with West-Ward to discuss their development plan
  - Agreement reached to conduct 4 DDI studies, one each with a strong, moderate and weak CYP3A4 inhibitor and a P-gp inhibitor
  - Protocols were not reviewed by the Agency, data were not discussed with the Agency before submission
- October 5, 2012
  - Present 505(b)(2) NDA received for prophylactic treatment of gout, Hikma as sponsor, West-Ward as US agent
  - Formulation changed to 0.6 mg capsules, references Col-Probenecid
  - Data from 4 DDI studies as discussed were included in the NDA, Sponsor used completely different probe inhibitors (compared to what were used for Colcrys); they mentioned doing this to avoid potential patent issues
  - 74-day filing comments, post-mid-cycle review telecon with sponsor



# Colchicine Drug-Drug Interaction Studies

Dr. Sheetal Agarwal

## DDI data obtained with West-ward's product (compared to Colcrlys)

	Caps WEST-WARD	Tabs Colcrlys MUTUAL
Weak 3A4 inhibitor	With cimetidine: -33% Cmax, -15% AUC	With azithromycin: 21.6% ↑ Cmax, 57% ↑ AUC
Moderate 3A4 inhibitor	With fluconazole: 13% ↑ Cmax, 40% ↑ AUC	With verapamil: 40% ↑ Cmax, 103% ↑ AUC
Strong 3A4 inhibitor	With voriconazole: 20% ↑ Cmax, 10% ↑ AUC	With ketoconazole: 102% ↑ Cmax, 212% ↑ AUC With clarithromycin: 227% ↑ Cmax, 282% ↑ AUC With ritonavir: 184% ↑ Cmax, 296% ↑ AUC
P-gp inhibitor	With propafenone: no change	With cyclosporine: 270% ↑ Cmax, 259% ↑ AUC

## Possible explanations for West-Ward DDI results

- Differences in the formulation
- DDI study design or conduct issues
- Differences in the probe (interacting) drugs tested

## No significant formulation differences in Colcrys and Westward's product identified

- 
-  (b) (4)
- A of colchicine from capsules to Col-Probenecid is similar to that observed with tablets to Col-Probenecid
- Food effect on capsules very similar to that on tablets (no significant food effect)

## West-Ward DDI studies: Right doses and durations studied, OSI inspection clean

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 design in healthy male and female subjects	Days 4-8: 1 x Cimetidine 800 mg film-coated tablet USP given twice daily for 5 consecutive days	Day 1: colchicine 0.6 mg Day 9: colchicine 0.6 mg + 800 mg cimetidine
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

Blood samples for pharmacokinetic measurements were collected prior to and up to 72 hours (serial sampling) after each colchicine administration.

Colcris: 96 hours sampling

## Differences in the probe (interacting) drugs

	Caps WEST-WARD	Tabs Colcrys MUTUAL
Weak 3A4 inhibitor	With cimetidine (not P-gp): -33% Cmax, -15% AUC	With azithromycin (also P-gp inhibitor): 21.6% ↑ Cmax, 57% ↑ AUC
Moderate 3A4 inhibitor	With fluconazole (not P-gp, inhibits UGTs) : 13% ↑ Cmax, 40% ↑ AUC	With verapamil (also P-gp inhibitor): 40% ↑ Cmax, 103% ↑ AUC
Strong 3A4 inhibitor	With voriconazole (not P-gp) : 20% ↑ Cmax, 10% ↑ AUC	With ketoconazole: 102% ↑ Cmax, 212% ↑ AUC With clarithromycin: <b>227% ↑ Cmax, 282% ↑ AUC</b> With ritonavir, 184% ↑ Cmax, 296% ↑ AUC <b>All are P-gp inhibitors</b>
P-gp inhibitor	With propafenone (not CYP3A4 inhibitor) : <b>no change</b>	With cyclosporine (also inhibits CYP3A4 to certain extent): <b>270% ↑ Cmax, 259% ↑ AUC</b>

**Gradation in extent of interaction**

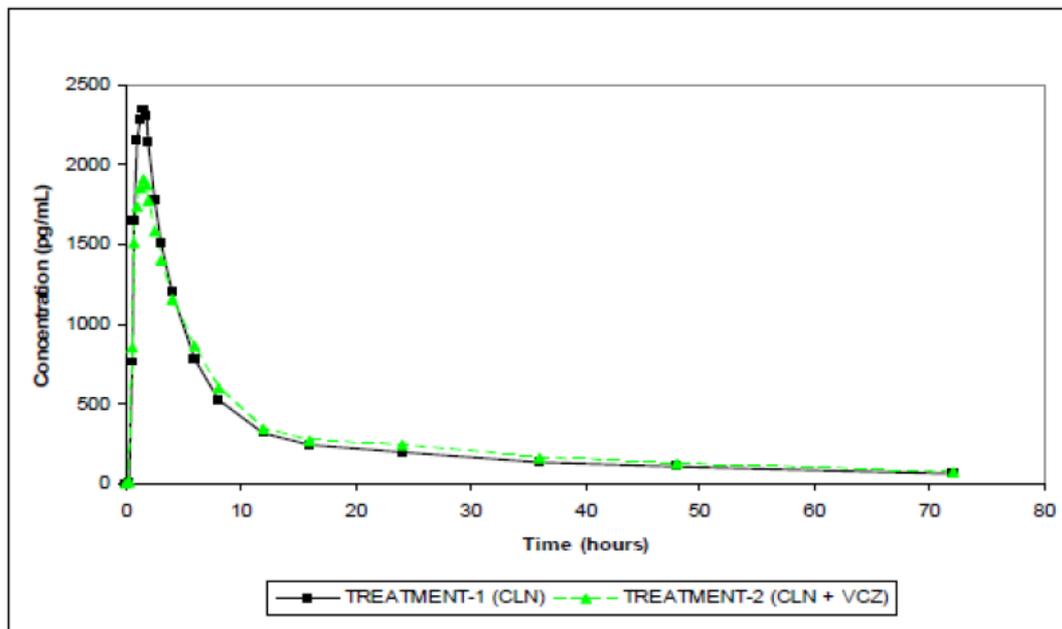
## Sponsor's explanation for lack of interactions: Response to 74-day filing comments

Cimetidine	Employed as a weak CYP3A4 inhibitor	Cimetidine is a weak CYP3A4/P-gp inhibitor. Colchicine may possess more affinity for CYP3A4 than cimetidine.
Fluconazole	Employed as a moderate CYP3A4 inhibitor	Effect on AUC and not Cmax indicates that it may inhibit other metabolism pathways of colchicine such as conjugation. Not known to be a P-gp inhibitor.
Voriconazole	Employed as a strong CYP3A4 inhibitor	Has variable effects as inhibitor. Effects not consistent and variable. May not inhibit P-gp. With indinavir, a known CYP3A4 substrate, did not show any interaction

## Sponsor's explanation for lack of interactions: Response to 74-day filing comments

Propafenone	Employed as a P-gp inhibitor	Propafenone and colchicine may be binding to different domains of the P-gp protein.
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## Voriconazole-colchicine DDI

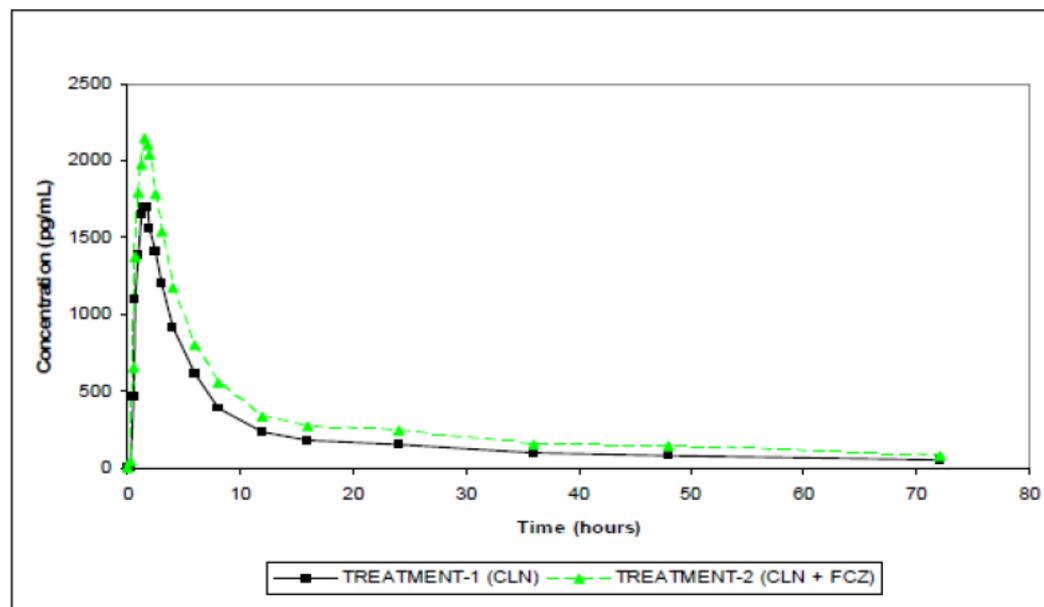


	- vori	+ vori
Cmax (pg/mL)	2663	2058
AUC (pg.h/mL)	19605	20731
CLtot/F (L/h)	33	28
T1/2el (h)	30	31
Kel (1/h)	0.02	0.02

**Tmax voriconazole: 1-2 h, T1/2: 6-9 h**

**Tmax colchicine: 1-3 h**

## Fluconazole-colchicine DDI



	- flu	+ flu
C <sub>max</sub> (pg/mL)	1926	2299
AUC (pg.h/mL)	14939	21270
CL <sub>tot</sub> /F (L/h)	37	26
T <sub>1/2el</sub> (h)	34	35
K <sub>el</sub> (1/h)	0.02	0.02

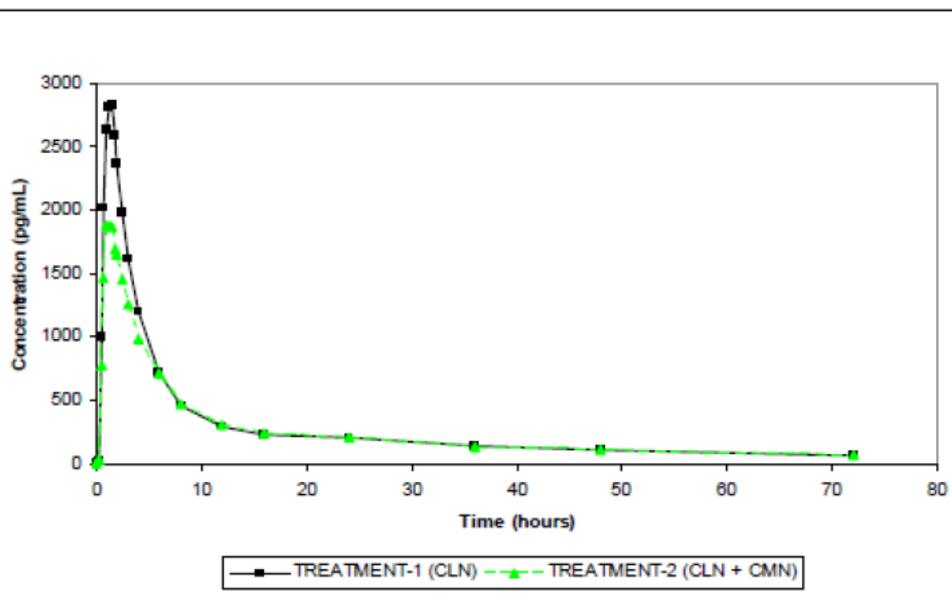
**T<sub>max</sub> fluconazole: 1-2 h, T<sub>1/2</sub>: 20-50 h**

**T<sub>max</sub> colchicine: 1-3 h**

## About fluconazole

- Report in literature indicating it significantly inhibits UGT 2B7 (Uchaipichat V et al., (Br J Clin Pharmacol. 2006 Apr;61(4):427-39)
- Sponsor suggests fluconazole could inhibit a 'conjugation pathway' of colchicine
- Its possible that fluconazole inhibits glucuronidation of colchicine

## Cimetidine-colchicine DDI

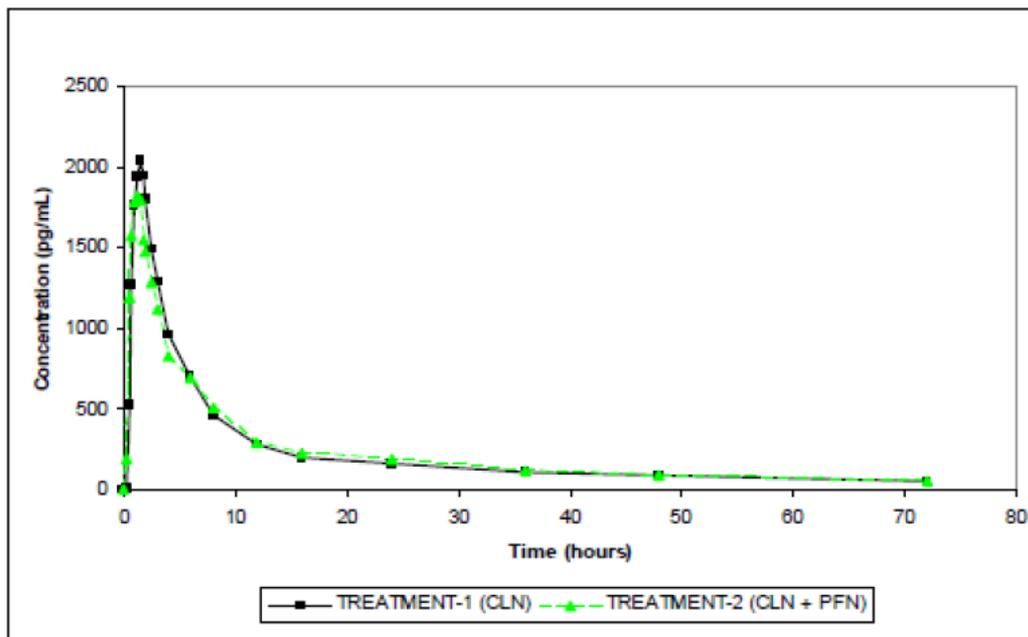


**Tmax cimetidine: 45-90 min. T1/2: 1-2 h**

**Tmax colchicine: 1-3 h**

	- cimet	+ cimet
Cmax (pg/mL)	2997	2109
AUC (pg.h/mL)	20382	18082
CLtot/F (L/h)	28	34
T1/2el (h)	35	32
Kel (1/h)	0.02	0.02

## Propafenone-colchicine DDI



**Tmax propafenone: 3-8 h, T1/2: 2-10 h**

**Tmax colchicine: 1-3 h**

	- prop	+ prop
Cmax (pg/mL)	2118	2206
AUC (pg.h/mL)	16626	16777
CLtot/F (L/h)	34	33
T1/2el (h)	30	28
Kel (1/h)	0.024	0.026

## Propafenone: A good probe for P-gp inhibition?

- From propafenone label: 'Concomitant use of propafenone and digoxin increased steady-state serum digoxin exposure (AUC) in patients by 60 to 270%, and decreased the clearance of digoxin by 31 to 67%.' (dose used in this DDI study is not known).
- Concentration used in the colchicine DDI study: 225 mg BID for 5 days
- Plasma concentration of propafenone at 225 mg bid (< 0.64 microM), may be insufficient to block P-gp activity
  - IC50 for P-gp inhibition of digoxin in vitro: 6.8 microM in Caco-2 cells\*
  - $I_1/IC_{50} (219/341)/6.8 = 0.094$ ;  $I_2/IC_{50} = (300/341)/250 * 1000000 = 0.0035/6.8 = 517$
  - Cmax with a 300 mg tablet: 219 ng/mL = 0.64 microM\*\*
- Sponsor's rationale for not observing an interaction with propafenone is that propafenone and colchicine may 'bind to different domains of P-gp'
  - No data to support this rationale is provided

\*Naunyn Schmiedebergs Arch Pharmacol. 2005 Mar;371(3):195-201. Epub 2005 Apr 15.

\*\*<http://www.ualberta.ca/~csps/JPPS1%282%29/Y.Tsang/Tsang.pdf>

## Summary: Choice of probes employed in West-ward's DDI studies

- West-Ward purposely used this particular set of inhibitors to avoid any overlap in data with Colcrys
  - West-Ward stated its intention to not rely on Colcrys as a listed drug or on published literature describing studies of Colcrys
- West-Ward and Mutual's DDI data combined, suggests that P-gp inhibition may play a more dominant role than CYP3A4 inhibition
- Lack of apparent interaction with propafenone requires explanation

## Labeling proposed by sponsor based on their DDI data (compared to Colcris)

	Caps WESTWARD	Tabs Colcris MUTUAL
<b>Dosing Regimen for Prophylaxis</b>	(1) 0.6 mg BID (2) 0.6 mg QD	(1) 0.6 mg BID (2) 0.6 mg QD
<b>Strong CYP3A4 inhibitors</b>	(b) (4)	(1) 0.3 mg QD (2) 0.3 mg every other day
<b>Moderate CYP3A4 inhibitors</b>		(1) 0.3 mg BID or 0.6 mg QD (2) 0.3 mg QD
<b>P-gp inhibitors</b>		(1) 0.3 mg QD (2) 0.3 mg every other day

**Proposed dosing changes not supported by data**

## Summary of Colchicine DDI Data

- Mutual's data with Colcryls represents the worst-case scenario, i.e., when both P-gp and CYP3A4 are inhibited simultaneously
- Generally, if interaction with a dual CYP3A4+P-gp inhibitor is positive, then one should continue evaluation with inhibitors that are specific for one pathway
  - Mutual did not evaluate colchicine DDI with more 'pure' CYP3A4 or P-gp inhibitors
- West-Ward used more 'pure' CYP3A4 and P-gp inhibitors, however did not observe any interactions
- Overall, Westward's data raise the question of whether CYP3A4 or P-gp interactions alone would present a DDI risk with colchicine
  - Note that interacting drugs of significance inhibit both pathways

## Additional data to clarify observed differences

<b>Ideal</b>	<b>Necessary</b>
In vitro metabolism data for colchicine: CYP contribution? UGT contribution?	In vivo study with a potent P-gp inhibitor (could be a dual CYP3A4+P-gp inhibitor)
In vivo ADME study or metabolite profiling: how is colchicine metabolized and excreted in humans?	In vitro, address metabolism pathways of colchicine to enable labeling with respect to negative interactions
Each sponsor can selectively confirm the other's results	
Each company can employ the other's as control	



# Consideration of Next Steps

Dr. Sarah Yim

## Considerations on Next Steps

- We do not have a clear understanding of reason(s) why West-Ward's DDI data are not consistent with other data with colchicine
- The West-Ward DDI data suggest potentially new insights into colchicine drug interactions but are not conclusive
  - Is inhibition of both CYP3A4 and P-gp required for significant interaction?
  - Or is the interaction predominantly due to P-gp, and the apparent lack of interaction with propafenone due to some other factor?
- Knowledge gap makes it difficult to know how to label the product

## Considerations on Next Steps

- Alternatives to Colcrlys are strongly being called for by the medical and patient communities
- Colchicine-Probenecid combination product has not yet been labeled with colchicine drug drug interaction information
  - Old, low-usage drug; no DDI information available specific to the combination product
  - Both the Colcrlys and West-Ward 505(b)(2) NDAs rely on Col-Probenecid
  - 505(b)(2) NDA must include adequate data to support S+E of any aspects of the proposed product that differ from the listed drug
  - Generally do not require data from a 505(b)(2) applicant that would not also be required for the marketed listed drug because 505(b)(2) applicant relies on FDA's finding of S+E for the listed drug
- FDA's response to Mutual's Citizen Petition agrees with need to include adequate DDI and dose modification information in the labeling of single-ingredient oral colchicine products

# Possible Action Scenarios

NDA 204820: DDI Study Results Discrepant with Historical Knowledge

Complete Response

Additional DDI Study(ies)

Pros:  
Scientifically justified

Cons:  
Public's need to have alternative colchicine products available

Approval

With label that has literature-based general cautionary language

Pros:  
Consistent with decades of clinical use

Cons:  
Does not account for NDA's DDI data

With label that has current data from West-Ward DDI program

Pros:  
Supported by NDA data

Cons:  
May be misconstrued as no DDI concern



# Discussion of Questions

Dr. Sarah Yim

## Discussion Question 1

- Do the unexpected drug-drug interaction results for West-Ward's colchicine 0.6 capsules justify a complete response action?
  - If so, what response should be required to address the deficiency?
  - Please comment on why you believe West-Ward's proposal to label based on the literature and conduct clarifying studies post-approval is not acceptable

## Discussion Question 2

- If you believe the application should be approved:
  - How should the product be labeled pending clarifying DDI study(ies)?
  - What issues does the panel see with having different labeling for the two different single-ingredient colchicine products and how should these be addressed?

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May 31, 2013

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*LaVeng, Lisa*

*Leo J. Wang*

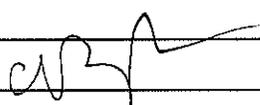
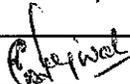
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DCP<sup>2</sup>/DCP/OTS

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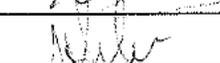
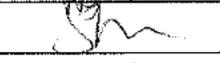
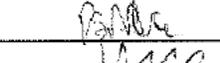
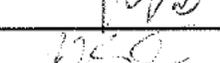
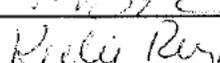
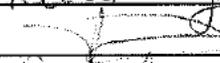
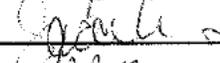
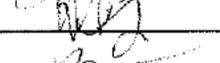
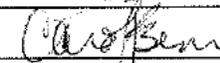
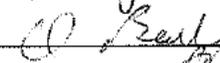
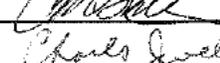
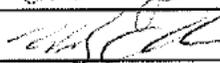
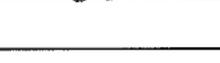
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Jeffy Florin	<i>[Signature]</i>	OCP / OPM
Marysue Givish GHOSE	<i>[Signature]</i>	DAP / DAP
Joann Lee	<i>[Signature]</i>	DSE / DAV
LAURA MUSSE	<i>[Signature]</i>	ODE / DPARP
Salma Lemtouni	<i>[Signature]</i>	OCD / SUI

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/s/  
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MICHELLE Y JORDAN GARNER  
09/19/2014

**From:** [Jordan Garner, Michelle](#)  
**To:** [Susan Neufang-Todd](#)  
**Cc:** [Jordan Garner, Michelle](#)  
**Subject:** RE: NDA 204820: Mitigare (Colchicine) Capsules 0.6mg - LABELING  
**Date:** Wednesday, September 17, 2014 4:19:07 PM

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Hi Susan,

Please proceed with making Section 12.3 match Sections 8.6 and 10. Also, delete “(b) (4)” in Section 11, and submit as the final agreed upon labeling. Let me know if you have any questions/concerns.

*Michelle J Garner*

Michelle Jordan Garner, MS, OTR/L  
CDR, U.S. Public Health Service  
Sr. Regulatory Management Officer  
Food and Drug Administration  
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Division of Pulmonary, Allergy, and Rheumatology Products  
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✉ [michellejordan@fda.hhs.gov](mailto:michellejordan@fda.hhs.gov)

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**From:** Susan Neufang-Todd [mailto:[stodd@west-ward.net](mailto:stodd@west-ward.net)]  
**Sent:** Tuesday, September 16, 2014 8:43 AM  
**To:** Jordan Garner, Michelle  
**Cc:** Susan Neufang-Todd  
**Subject:** NDA 204820: Mitigare (Colchicine) Capsules 0.6mg - LABELING  
**Importance:** High

Michelle,

In re-reviewing the outsert to prepare the AG, we have noticed the following, attachment is provided, highlighted in yellow:

**Section 8.6**

(b) (4)

**Section 10**

(b) (4)

**Section 12.3**

(b) (4)

Can you please clarify which statement is correct? We would need to update the Mitigare outsert if you feel that a change is needed.

Thanks!  
Susan

---

**From:** Jordan Garner, Michelle [<mailto:Michelle.Jordan@fda.hhs.gov>]  
**Sent:** Monday, September 15, 2014 11:55 AM  
**To:** Susan Neufang-Todd  
**Subject:** RE: NDA 204820: Mitigare (Colchicine) Capsules 0.6mg

Hi Susan. Hope you enjoyed your vacation. The NDA is still under review. Please remind 'management' that the PDUFA goal date is September 28, 2014. ☺

*Michelle J Garner*

Michelle Jordan Garner, MS, OTR/L  
CDR, U.S. Public Health Service  
Sr. Regulatory Management Officer  
Food and Drug Administration  
Center for Drug Evaluation and Research/ODEII  
Division of Pulmonary, Allergy, and Rheumatology Products  
10903 New Hampshire Ave., Bldg 22, Room 3200  
Silver Spring, MD 20993  
☎ 301-796-4786  
☎ 301-796-9728  
✉ [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov)

---

**From:** Susan Neufang-Todd [<mailto:stodd@west-ward.net>]  
**Sent:** Monday, September 15, 2014 11:53 AM  
**To:** Jordan Garner, Michelle  
**Cc:** Susan Neufang-Todd  
**Subject:** NDA 204820: Mitigare (Colchicine) Capsules 0.6mg

Hi Michelle,

I am back from vacation and back to the grind ☺ ! Hope that you are doing well.

Just a quick question – from management – do you believe that the label review process has been completed?

Thank you, so sorry to bother you!!!!  
Susan

**Susan Todd**

Senior Manager, Regulatory Affairs  
West-Ward Pharmaceutical Corp.  
Tel: 732.542.1191 Ext. 2871  
Fax: 732.542.6150  
435 Industrial Way West  
Eatontown, NJ 07724  
[www.west-ward.com](http://www.west-ward.com)

Part of the Hikma Group

[www.hikma.com](http://www.hikma.com)

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/s/  
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MICHELLE Y JORDAN GARNER  
09/17/2014

**From:** Jordan Garner, Michelle  
**To:** [Elizabeth A. Marro \(EMarro@west-ward.net\)](mailto:EMarro@west-ward.net)  
**Cc:** [Jordan, Michelle \(Michelle.Jordan@fda.hhs.gov\)](mailto:Michelle.Jordan@fda.hhs.gov)  
**Subject:** Follow Up on questions to proposed MITIGARE label: NDA 204820  
**Date:** Thursday, September 11, 2014 12:12:00 PM

---

Hi Liz,

Per our phone conversation today (9/11/14), I wanted to reiterate the following:

MedGuide – Eliminating 2<sup>nd</sup> bullet - (b) (4) ” from the “**What is Mitigare**” section: (b) (4) The reason we included acute treatment of gout flares during prophylaxis is that if Mitigare is being used for prophylaxis, it may be natural for the provider to use it for acute treatment as well. (b) (4)

Putting “TM” next to tradename: With regard to putting a “TM” with your tradename, we believe that is acceptable, but only for Word and Adobe versions of the label. Note that the “TM” will **not** appear in the SPL version, due to style sheet restrictions. Therefore, when you make our requested changes to the MedGuide and the PI, you may also include in the Word and Adobe versions.

Let me know if you have additional questions/concerns.

*Michelle J Garner*

Michelle Jordan Garner, MS, OTR/L  
CDR, U.S. Public Health Service  
Sr. Regulatory Management Officer  
Food and Drug Administration  
Center for Drug Evaluation and Research/ODEII  
Division of Pulmonary, Allergy, and Rheumatology Products  
10903 New Hampshire Ave., Bldg 22, Room 3200  
Silver Spring, MD 20993  
☎ 301-796-4786  
☎ 301-796-9728  
✉ michelle.jordan@fda.hhs.gov

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MICHELLE Y JORDAN GARNER  
09/12/2014

**From:** [Yim, Sarah](#)  
**To:** [Adeleye, Adewale](#); [Jordan Garner, Michelle](#); [Weiner, Janice](#); [Nikolov, Nikolay](#); [Hull, Keith](#)  
**Cc:** [Dettelbach, Kim](#); [Robison, Timothy W](#); [Whittaker, Matthew](#); [Brar, Satjit S.](#); [Agarwal, Sheetal](#); [Bertha, Craig M](#); [Szydlo, Roberta](#)  
**Subject:** RE: WestWard's questions regarding labeling: colchicine/Hikma/NDA 204820  
**Date:** Thursday, September 11, 2014 10:40:35 AM

---

Hi Michelle,

- 1) As Wale said, the main issue with the MedGuide is that it doesn't match the PI. Regarding the PI, (b) (4)  
[Redacted]
- 2) I think putting a "TM" in with their tradename is fine. I'd heard previously that SEALD had a preference for it being used once but not each time in the label, but I can't find this in the labeling review tool. The labeling review tool says it can be included in Word and Adobe versions of the label but will not appear in the SPL due to style sheet restrictions. So I think this is OK.

Thanks,

Sarah

---

**From:** Adeleye, Adewale  
**Sent:** Thursday, September 11, 2014 10:33 AM  
**To:** Jordan Garner, Michelle; Yim, Sarah; Weiner, Janice; Nikolov, Nikolay; Hull, Keith  
**Cc:** Dettelbach, Kim; Robison, Timothy W; Whittaker, Matthew; Brar, Satjit S.; Agarwal, Sheetal; Bertha, Craig M; Szydlo, Roberta  
**Subject:** RE: WestWard's questions regarding labeling: colchicine/Hikma/NDA 204820

Hi Michelle,

OPDP's concern about adding (b) (4) " to the MG is that this information is not included in the full PI. The information in the MG must be supported by the information in the PI. If the sponsor can add this information to the full PI for Mitigare, we will be okay with it appearing in the MG.

Please let me know if you have additional questions or concerns.

Thanks,  
Wale

---

**From:** Jordan Garner, Michelle  
**Sent:** Thursday, September 11, 2014 10:07 AM  
**To:** Yim, Sarah; Adeleye, Adewale; Weiner, Janice; Nikolov, Nikolay; Hull, Keith  
**Cc:** Dettelbach, Kim; Robison, Timothy W; Whittaker, Matthew; Brar, Satjit S.; Agarwal, Sheetal; Bertha, Craig M; Jordan Garner, Michelle  
**Subject:** WestWard's questions regarding labeling: colchicine/Hikma/NDA 204820

All,

WestWard is preparing to respond to our labeling changes, and have concern about the following:

- 1) MG – Eliminating 2<sup>nd</sup> bullet - “ (b) (4) ” from the “**What is Mitigare**” section. (b) (4)  
 (b) (4)  
 (b) (4)  
 (b) (4). **(Please advise how you would like to respond to them)**
- 2) PI/MG – They realized that **they** did not add the “**TM**” next to “MITIGARE” throughout the PI, and didn’t capitalize “Mitigare” in the MG. Therefore, they would like to also make that change when they submit their revised PI/MG. **(Please confirm if this is acceptable).**

I’ve requested that they respond to our labeling changes by 3pm today. However, they are awaiting our feedback. Please advise ASAP. Thanks, and let me know if you have any questions/concerns.

*Michelle J Garner*

Michelle Jordan Garner, MS, OTR/L  
CDR, U.S. Public Health Service  
Sr. Regulatory Management Officer  
Food and Drug Administration  
Center for Drug Evaluation and Research/ODEII  
Division of Pulmonary, Allergy, and Rheumatology Products  
10903 New Hampshire Ave., Bldg 22, Room 3200  
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☎ 301-796-4786  
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/s/  
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MICHELLE Y JORDAN GARNER  
09/12/2014



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: September 10, 2014**

<b>To:</b> Susan Todd	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> West-Ward Pharmaceuticals, US Agent for Hikma Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 732-542-6150	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 732-720-2871	<b>Phone number:</b> 301-796-4786

**Subject:** Labeling Comments #2 (Mitigare) NDA 204820 (Resubmission)

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**Total no. of pages including  
cover: 20**

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**Comments:**

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Thank you.**

NDA 204820

We are currently reviewing your NDA for Mitigare (colchicine capsules), resubmitted March 28, 2014. Submit revised labeling incorporating changes shown in the attached marked up PI and MedGuide. Additional labeling changes may be forthcoming as we continue our review.

Submit your response to me via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov) by 3p.m. September 11, 2014. Your response will subsequently need to be submitted officially to the NDA. If you have any questions, please contact me at 301-796-4786.

NDA 204820

Drafted by: MichelleJG 9/10/14

Cleared by: SandyB 9/10/14

Finalized by:MichelleJG 9/10/14

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

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MICHELLE Y JORDAN GARNER  
09/10/2014



**Food and Drug Administration  
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**DATE:** August 25, 2014

<b>To:</b> Susan Todd	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> West-Ward Pharmaceuticals, US Agent for Hikma Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 732-542-6150	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 732-720-2871	<b>Phone number:</b> 301-796-4786

**Subject:** Labeling Comments #1 (Mitigare) NDA 204820 (Resubmission)

**Total no. of pages including  
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in error, please notify us immediately by telephone at (301) 796-2300.  
Thank you.**

We are currently reviewing your NDA for Mitigare (colchicine capsules), resubmitted March 28, 2014. Submit revised labeling incorporating changes shown in the attached marked up PI, MedGuide, and comments to the carton and container labeling below. Additional labeling changes may be provided as we continue our review.

- 1) We remind you of your requirement to comply with 21 CFR 208.24. We acknowledge the use of a Medication Guide statement. Please ensure that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose.
- 2) We note the phrase “(b) (4)” in the proposed Medication Guide statement is confusing. Clearly identify how the Medication Guide will be provided based upon whether the Medication Guide accompanies the product or is enclosed in a carton [see 21 CFR 208.24(d)]. Consider using one of the following statements:
  - a. “Dispense the enclosed Medication Guide to each patient.” Or
  - b. “Dispense the accompanying Medication Guide to each patient.”

In addition we recommend presenting the statement in title case instead of all cases to improve the readability of the statement.

Submit your response to me via fax at 301-796-9728 or via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov) by noon Monday September 1, 2014. Your response will subsequently need to be submitted officially to the NDA. If you have any questions, please contact me at 301-796-4786.

NDA 204820

Drafted by: MichelleJG 8/25/14

Cleared by: SandyB 8/25/14

Finalized by:MichelleJG 8/25/14

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

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MICHELLE Y JORDAN GARNER  
08/25/2014



NDA 204820

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Hikma Pharmaceuticals LLC  
c/o West-Ward Pharmaceutical Corp.  
200 401 435 465 Industrial Way West  
Eatontown, NJ 07724

ATTENTION: Susan Todd  
Senior Manager Regulatory Affairs

Dear Ms. Todd:

Please refer to your New Drug Application (NDA) dated and received March 28, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Colchicine Capsules, 0.6 mg.

We also refer to your correspondence, dated and received, April 15, 2014, requesting review of your proposed proprietary name, Mitigare.

We have completed our review of the proposed proprietary name, Mitigare and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your April 15, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Harris, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4774. For any other information regarding this application, contact Michelle Jordan Garner, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4786.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
06/20/2014



NDA 204820

**ACKNOWLEDGE –  
CLASS 2 RESUBMISSION**

Hikma Pharmaceuticals LLC  
c/o West-Ward Pharmaceutical Corp.  
200/401/435/465 Industrial Way West  
Eatontown, NJ 07724

Attention: Susan Todd  
Senior Manager, Regulatory Affairs

Dear Ms. Todd:

We acknowledge receipt on March 28, 2014, of your March 28, 2014, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Mitigare (colchicine) capsule, 0.6 mg.

We consider this a complete, class 2 response to our August 5, 2013 action letter. Therefore, the user fee goal date is September 28, 2014.

If you have any questions, call me, at (301) 796-4786.

Sincerely,

*{See appended electronic signature page}*

Michelle Jordan Garner, MS, OTR/L  
Senior Regulatory Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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MICHELLE Y JORDAN GARNER  
04/11/2014



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** April 4, 2014

<b>To:</b> Susan Todd	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> West-Ward Pharmaceuticals, US Agent for Hikma Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 732-542-6150	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 732-720-2871	<b>Phone number:</b> 301-796-4786

**Subject:** CMC Information Request (colchicine) NDA 204820

**Total no. of pages including  
cover:** 3

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Thank you.**

NDA 204820

We are currently reviewing Hikma Pharmaceutical's resubmitted NDA, submitted March 28, 2014. Provide a specific list of changes that have been made to the various sections/subsections of module 3 in this resubmission, relative to what was submitted at the time the complete response letter issued. Such a list will greatly expedite our review of the CMC section of your resubmission, and allow us to avoid review of material that was previously evaluated in your original application.

Submit this information, via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov) by **12:00 PM Friday April 11, 2014**. Your response will subsequently need to be submitted officially to the NDA.

NDA 204820

Drafted by: MichelleJG 4/4/14

Cleared by: SandyB 4/4/14

Finalized by:MichelleJG 4/4/14

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MICHELLE Y JORDAN GARNER  
04/04/2014

## Liu, Youbang

---

**From:** Liu, Youbang  
**Sent:** Monday, June 10, 2013 3:16 PM  
**To:** 'stodd@west-ward.net'  
**Subject:** Information Request for NDA 204820

Hikma Pharmaceuticals LLC  
Attention: Susan Todd  
Senior Manager, Regulatory Affairs  
200/401/435/465 Industrial Way West  
Eatontown, NJ 07724

Dear Ms. Todd:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 204820 (Colchicine Capsules, 0.6mg) received October 5, 2012. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission:

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

Please acknowledge the receipt of this email and provide your response by June 21, 2013.

Sincerely,

*Youbang Liu, Ph.D.*  
Regulatory Project Manager  
Division III, ONDQA/OPS/CDER/FDA  
10903 New Hampshire Avenue  
Building 21, Room 2525  
Silver Spring, MD 20993  
Phone: (301) 796-1926

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/s/

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YOUBANG LIU  
06/10/2013



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: April 25, 2013**

<b>To:</b> Susan Todd	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> West-Ward Pharmaceuticals, US Agent for Hikma Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 732-542-6150	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 732-720-2871	<b>Phone number:</b> 301-796-4786

**Subject:** CMC Information Request (colchicine) NDA 204820

**Total no. of pages including cover:** 4

**Comments:**

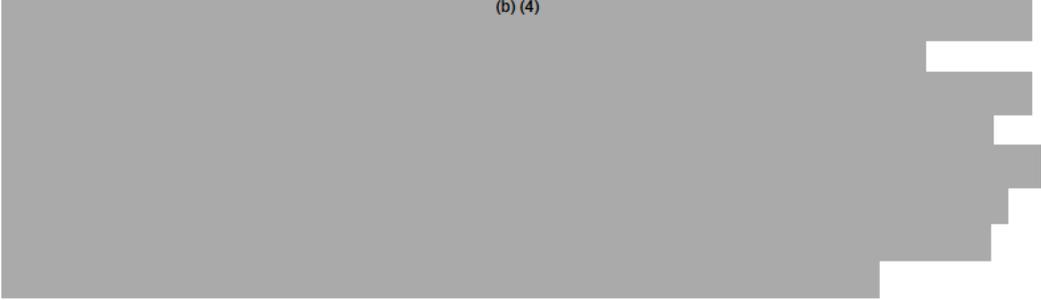
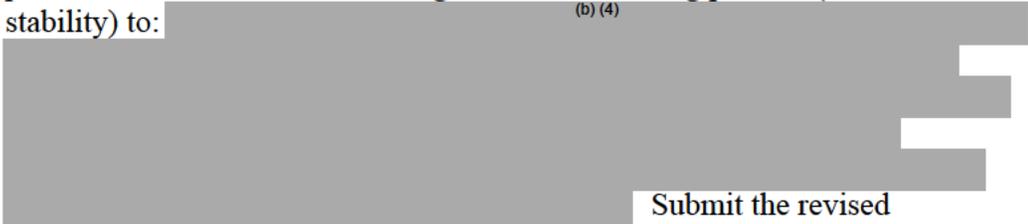
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We are currently reviewing Hikma Pharmaceutical's NDA, submitted October 5, 2012, and have the following comments and request for information:

1. You have stated in your response to the filing issues letter comment 6 that if the (b) (4)  

2. We remind you of your commitment to revise the impurity specifications parameters for the Colchicine drug substance and drug product (release and stability) to: (b) (4)  
 Submit the revised specifications in accordance with the commitment.
3. As per your commitment, provide the updated drug substance specification that includes the tightened acceptance criteria for the particle size test.
4. Considering the absence of a sufficient explanation for the apparent discrepancy between the (b) (4) and regulations [21 CFR 211.110(a)(3)], it is recommended that you test for (b) (4) routinely during manufacture of the drug product.
5. Provide the revised specification that includes the test and acceptance criterion for (b) (4) content for the drug product. Provide a time-line for when this acceptance criterion will be updated based on stability data. Provide the method and validation data, if applicable (non-compendial method), for the method used to determine the drug product (b) (4) content.
6. With regard to comment 11 of the February 4<sup>th</sup>, 2013, CMC discipline review letter, we would like to clarify that there is to be *one* regulatory specification that is applied to the drug product that must be met at both release and during shelf life. This specification should be provided in section P.5.1 of the application. Currently, P.5.1 has two distinct specifications in terms of the acceptance criteria applied for impurities (one for the Finished Product and one for Stability Testing). Revise P.5.1 such that it contains a single regulatory specification for the drug product. One way to accomplish this would be to revise the acceptance criteria for "highest unspecified impurity" and "total specified and unspecified

impurities” for the Finished Product to not more than (b) (4) respectively. If you wish to have tighter limits for these parameters applied at release than what is applied during shelf-life (stability), these can be considered in-house specification criteria, but would not be considered to be the regulatory specification criteria. If there is any confusion regarding this distinction, we recommend that you contact the Agency for further clarification. Also refer to comments 2 and 5 above.

Submit this information, via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov) by **12:00 PM Friday May 10, 2013**. Your response will subsequently need to be submitted officially to the NDA.

NDA 204820

Drafted by: MichelleJG 4/25/13  
Cleared by: SandyB 4/25/13  
Finalized by:MichelleJG 4/25/13

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/s/  
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MICHELLE Y JORDAN GARNER  
04/25/2013

**From:** Jordan, Michelle  
**To:** ["Susan Neufang-Todd"](#)  
**Cc:** [Liu, Youbang](#)  
**Subject:** RE: CMC IR - November 20, 2012- NDA 204820  
**Date:** Monday, April 15, 2013 10:51:00 AM  
**Attachments:** [CMC Discipline Review \(COR-NDAIR-03\).pdf](#)

---

Great! Also, we will need responses to the CMC discipline review (mailed to you on/around 2/1/13 – see attached); which contained another information request. I'm requesting the same date/time as my previous email (noon Wednesday 4/17/13). Thanks.

*Michelle J Garner*

Michelle Jordan Garner, MS, OTR/L  
CDR, U.S. Public Health Service  
Sr. Regulatory Management Officer  
Food and Drug Administration  
Center for Drug Evaluation and Research/ODEII  
Division of Pulmonary, Allergy, and Rheumatology Products  
10903 New Hampshire Ave., Bldg 22, Room 3200  
Silver Spring, MD 20993  
☎ 301-796-4786  
☎ 301-796-9728  
✉ [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov)

---

**From:** Susan Neufang-Todd [mailto:[stodd@west-ward.net](mailto:stodd@west-ward.net)]  
**Sent:** Monday, April 15, 2013 10:45 AM  
**To:** Jordan, Michelle  
**Cc:** Liu, Youbang  
**Subject:** RE: CMC IR - November 20, 2012- NDA 204820

Michelle, you are correct, I was under the impression that the Change Control Process was nearing approval, but it was not.

I am awaiting the Final Report from the Lab. I will have the submission to you by Wednesday at noon.

I will also send to both of you a courtesy copy of the cover letter.

Regards,  
Susan

---

**From:** Jordan, Michelle [<mailto:Michelle.Jordan@fda.hhs.gov>]  
**Sent:** Monday, April 15, 2013 10:27 AM  
**To:** Susan Neufang-Todd  
**Cc:** Liu, Youbang; Jordan, Michelle  
**Subject:** CMC IR - November 20, 2012- NDA 204820  
**Importance:** High

Hi Susan,

Youbang Liu sent you a CMC information request email, back on November 20, 2012 (see attached). You replied, via email (11/20/12), that you received the email. Also, you stated 2/21/13, that you would be able to respond by 3/4/13. In addition, you stated (3/6/13) that the response document was going through the "Change Control Process." However, we still have not received a response from Hikma/West-Ward to date. If you have responded, please provide the date of the correspondence. If you have not, please submit by **noon Wednesday April 17, 2013**, so that we may continue our review of this application. Make sure to officially submit, Hikma's responses, to the NDA as well as send me a courtesy email of the same.

Please acknowledge receipt of this email, and let me know if you have any questions/concerns.

*Michelle J Garner*

Michelle Jordan Garner, MS, OTR/L  
CDR, U.S. Public Health Service  
Sr. Regulatory Management Officer  
Food and Drug Administration  
Center for Drug Evaluation and Research/ODEII  
Division of Pulmonary, Allergy, and Rheumatology Products  
10903 New Hampshire Ave., Bldg 22, Room 3200  
Silver Spring, MD 20993  
☎ 301-796-4786  
☎ 301-796-9728  
✉ michelle.jordan@fda.hhs.gov

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Please consider the environment before printing this e-mail.



NDA 204820

**DISCIPLINE REVIEW LETTER**

Hikma Pharmaceuticals LLC  
US Agent: West-Ward Pharmaceutical Corporation  
Attention: Susan Todd  
Senior Manager, Regulatory Affairs  
200/401/435/465 Industrial Way West  
Eatontown, NJ 07724

Dear Ms. Todd:

Please refer to your October 5, 2012 New Drug Application (NDA) submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Colchicine Capsules, 0.6 mg.

Our review of the CMC section of your submission is complete, and we have identified the following deficiencies that need your responses:

1.  (b) (4)
2. 
3. 

(b) (4)

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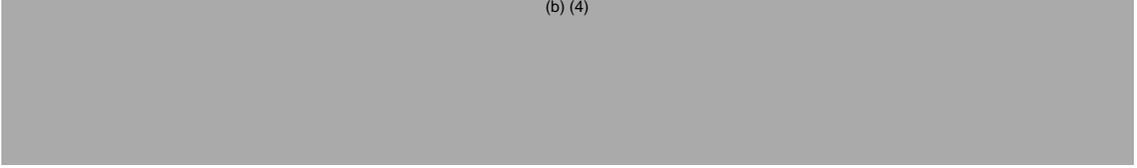
(b) (4)

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(b) (4)



We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

*{See appended electronic signature page}*

Prasad Peri, Ph.D.  
Branch Chief, Branch VIII  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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PRASAD PERI  
02/04/2013

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/s/  
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MICHELLE Y JORDAN GARNER  
04/15/2013

**From:** [Jordan, Michelle](#)  
**To:** [Susan Neufang-Todd \(stodd@west-ward.net\)](mailto:stodd@west-ward.net)  
**Cc:** [Liu, Youbang](#); [Jordan, Michelle](#)  
**Subject:** CMC IR - November 20, 2012- NDA 204820  
**Date:** Monday, April 15, 2013 10:27:00 AM  
**Attachments:** [BiopharmIRNov12.pdf](#)  
**Importance:** High

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Hi Susan,

Youbang Liu sent you a CMC information request email, back on November 20, 2012 (see attached). You replied, via email (11/20/12), that you received the email. Also, you stated 2/21/13, that you would be able to respond by 3/4/13. In addition, you stated (3/6/13) that the response document was going through the "Change Control Process." However, we still have not received a response from Hikma/West-Ward to date. If you have responded, please provide the date of the correspondence. If you have not, please submit by **noon Wednesday April 17, 2013**, so that we may continue our review of this application. Make sure to officially submit, Hikma's responses, to the NDA as well as send me a courtesy email of the same.

Please acknowledge receipt of this email, and let me know if you have any questions/concerns.

*Michelle J Garner*

Michelle Jordan Garner, MS, OTR/L

CDR, U.S. Public Health Service

Sr. Regulatory Management Officer

Food and Drug Administration

Center for Drug Evaluation and Research/ODEII

Division of Pulmonary, Allergy, and Rheumatology Products

10903 New Hampshire Ave., Bldg 22, Room 3200

Silver Spring, MD 20993

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7301-796-9728

✉ [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov)

## Liu, Youbang

---

**From:** Liu, Youbang  
**Sent:** Tuesday, November 20, 2012 1:42 PM  
**To:** 'stodd@west-ward.net'  
**Subject:** Information Request for NDA 204820

Hikma Pharmaceuticals LLC  
Attention: Susan Todd  
Senior Manager, Regulatory Affairs  
200/401/435/465 Industrial Way West  
Eatontown, NJ 07724

Dear Ms. Todd:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 204820 (Colchicine Capsules, 0.6mg) received October 5, 2012. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission:

1. Please provide the dissolution method development report with complete detailed information supporting the selection of this method for the evaluation of the dissolution characteristics of colchicine Capsules.

The dissolution method development report should include the following information:

- a. Solubility data for each drug substance covering the pH range;
- b. Detailed description of the dissolution test being proposed for the evaluation of the proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (*i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.*). Include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (*i.e., 15, 20, 30, 45, & 60 minutes*) and cover at least 85% of drug release of the label amount or whenever a plateau (*i.e., no increase over 3 consecutive time-points*) is reached. We recommend that at least twelve samples be used per testing variable;
- c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*). The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and
- d. Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (*i.e., method robustness, etc.*) and analytical method (*precision, accuracy, linearity, stability, etc.*).

For the setting of the dissolution acceptance criteria of your product, the following points should be considered:

- e. The dissolution profile data (*i.e., 15, 20, 30, 45, & 60 minutes*) from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your proposed drug product.
- f. The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
- g. The selection of the specification time point should be where  $Q = \frac{(b)}{(4)}\%$  dissolution occurs. However, if you have a slowly dissolving product or includes a BCS-Class 2, poor-soluble drug, a two-point

specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (i.e., 15-20 minutes) and the second time point should be where  $Q = \text{(b)}_{(4)}\%$  dissolution occurs.

- h. The dissolution acceptance criterion should be based on average dissolution data (n=12).

Note that the final determination on the acceptability of the proposed acceptance criterion for your proposed product will be made during NDA review process based on the provided data.

- 2. The dissolution data that you collect during your stability study should cover the complete dissolution profile (i.e., 15, 20, 30, 45, & 60 minutes). Please provide these data. If you have not collected these dissolution data at all appropriate time points, you should start collecting these data and submit to the NDA.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Regards,

Youbang Liu  
Regulatory Project Manager  
ONDQA/OPS/CDER/FDA  
Division III of New Drug Quality Assessment  
Phone: (301) 796-1926  
Fax: (301) 796-9748

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/s/  
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YOUBANG LIU  
11/20/2012

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/s/  
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MICHELLE Y JORDAN GARNER  
04/15/2013



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: April 11, 2013**

<b>To:</b> Susan Todd	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> West-Ward Pharmaceuticals, (US Agent for Hikma)	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 732-542-6150	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 732-720-2871	<b>Phone number:</b> 301-796-4786

**Subject:** CP Feedback Mitigare- (colchicine) NDA 204820

**Total no. of pages including cover:** 3

**Comments:**

Please acknowledge receipt.

**Document to be mailed:**       YES       NO

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We are currently reviewing Hikma Pharmaceutical's NDA, submitted October 5, 2012. In your submission dated March 25, 2013, you propose to conduct a DDI study with cyclosporine employing Colcris as a control. (b) (4)

(b) (4) We have the following comments and general thoughts related to your proposal:

(b) (4)

NDA 204820

Drafted by: SheetalA 4/10/13; MichelleJG 4/11/13

Concurred by: SheetalA4/11/13

SureshD4/11/13

SarahY4/11/13

SandyB 4/11/13

Finalized by: MichelleJG 4/11/13

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/s/  
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MICHELLE Y JORDAN GARNER  
04/11/2013

**From:** [Jordan, Michelle](#)  
**To:** [Susan Neufang-Todd \(stodd@west-ward.net\)](mailto:stodd@west-ward.net)  
**Cc:** [Jordan, Michelle](#)  
**Subject:** Additional Information Needed  
**Date:** Monday, March 18, 2013 1:17:49 PM

---

Hi Susan,

In response to our filing comments, you submitted (2/12/13) several proposed changes to drug-drug interaction related dosing in section 2.2 of the package insert. However, you have not officially re-submitted the annotated package insert with the new proposed changes. Therefore, submit the annotated package insert, incorporating any additional changes as proposed in your response submitted on 2/12/2013. If you prefer, you may submit this annotated package insert, with your response to the 2nd CP related IR dated 3/7/2013 (sent 3/14/13). Let me know if you have any questions/concerns.

*Michelle J Garner*

Michelle Jordan Garner, MS, OTR/L

CDR, U.S. Public Health Service

Sr. Regulatory Management Officer

Food and Drug Administration

Center for Drug Evaluation and Research/ODEII

Division of Pulmonary, Allergy, and Rheumatology Products

10903 New Hampshire Ave., Bldg 22, Room 3200

Silver Spring, MD 20993

☎ 301-796-4786

7301-796-9728

✉ [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov)

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/s/  
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MICHELLE Y JORDAN GARNER  
03/18/2013



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: March 7, 2013**

<b>To:</b> Susan Todd	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> West-Ward Pharmaceuticals agent for Hikma Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 732-542-6150	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 732-720-2871	<b>Phone number:</b> 301-796-4786

**Subject:** Clinical Pharmacology Information Request (colchicine) NDA 204820

**Total no. of pages including cover:** 3

**Comments:**

Please acknowledge receipt.

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**Document to be mailed:**       YES                       NO

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We are currently reviewing Hikma Pharmaceutical's NDA, submitted October 5, 2012. Related to dosing in renal impairment patients, you propose a dosing regimen of (b) (4)

It is not clear if these recommendations were based on literature information alone or pharmacokinetic simulations combined with literature information. If the recommendations did not rely on pharmacokinetic simulations, we suggest that you use modeling and simulations to explore the different dosing scenarios possible with your product in these populations and submit the analysis in support of the final recommendations.

Submit clarification, specifying the basis for your proposed dosing regimen for severe renal impaired patients, via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov) by **12:00 PM Thursday March 14, 2013**. Your response will subsequently need to be submitted officially to the NDA.

NDA 204820

Drafted by: MichelleJG 3/7/13

Concurrence by: SandyB 3/7/13

Finalized by: MichelleJG 3/7/13

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/s/  
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MICHELLE Y JORDAN GARNER  
03/07/2013



NDA 204820

**DISCIPLINE REVIEW LETTER**

Hikma Pharmaceuticals LLC  
US Agent: West-Ward Pharmaceutical Corporation  
Attention: Susan Todd  
Senior Manager, Regulatory Affairs  
200/401/435/465 Industrial Way West  
Eatontown, NJ 07724

Dear Ms. Todd:

Please refer to your October 5, 2012 New Drug Application (NDA) submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Colchicine Capsules, 0.6 mg.

Our review of the CMC section of your submission is complete, and we have identified the following deficiencies that need your responses:

1.

(b) (4)

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(b) (4)

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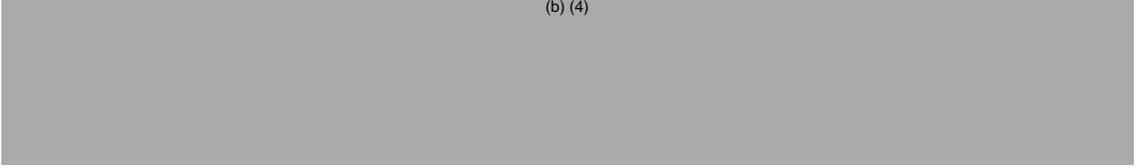
(b) (4)

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(b) (4)



We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

*{See appended electronic signature page}*

Prasad Peri, Ph.D.  
Branch Chief, Branch VIII  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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PRASAD PERI  
02/04/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 78601

MEETING MINUTES

West-Ward Pharmaceutical Corporation  
200/401/435/465 Industrial Way West  
Eatontown, NJ 07724

Attention: Susan Todd  
Senior Manager, Regulatory Affairs

Dear Ms. Todd:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for colchicine tablets.

We also refer to the meeting between representatives of your firm and the FDA on November 30, 2011. The purpose of the meeting was to discuss West-Ward's proposed 505(b)(2) development program for colchicine.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4786.

Sincerely,

*{See appended electronic signature page}*

Michelle Jordan Garner, MS, OTR/L  
Senior Regulatory Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** November 30, 2011; 12:30pm – 1:30pm  
**Meeting Location:** FDA WO Bldg 22, Room 1315

**Application Number:** IND 78601  
**Product Name:** Colchicine  
**Indication:** Treatment of Gout  
**Sponsor/Applicant Name:** West-Ward Pharmaceutical Corporation

**Meeting Chair:** Badrul A. Chowdhury, MD, PhD  
**Meeting Recorder:** Michelle Jordan Garner, MS, OTR/L

**FDA ATTENDEES**

Division of Pulmonary, Allergy, and Rheumatology Products

Badrul A. Chowdhury, MD, PhD	Director
Sarah Yim, MD	Clinical Team Leader
Keith Hull, MD	Clinical Reviewer
Molly Topper	Pharmacology/Toxicology Supervisor
Lawrence Leshin	Pharmacology/Toxicology Reviewer
Michelle Jordan Garner, MS, OTR/L	Senior Regulatory Management Officer

Office of Drug Evaluation II

Leah Ripper	ADRA
-------------	------

Division of Clinical Pharmacology 2

Suresh Doddapaneni, PhD	Deputy Director, Division of Clinical Pharmacology 2, Office of Clinical Pharmacology
Elizabeth Shang, PhD	Clinical Pharmacology Reviewer

Division of New Drug Quality Assessment III

Craig Bertha, PhD	Product Quality Reviewer
-------------------	--------------------------

Division of Biometrics

Kiya Hamilton, PhD	Biostatistics Reviewer
--------------------	------------------------

Office of Regulatory Policy  
Janice Weiner, J.D., M.P.H.

Regulatory Counsel

Office of Compliance  
Pamela Lee

Senior Regulatory Operations Officer

**WEST-WARD ATTENDEES**

Michael Raya, President and CEO

Elizabeth Marro, VP Quality Unit

(b) (4), PharmD, Consultant (b) (4)

(b) (4) MD, Consultant, (b) (4)

Clark Sullivan, Attorney at Law, Arnall Golden Gregory

Henry Knowles, General Counsel, Hikma PLC

## 1.0 BACKGROUND

West-Ward Pharmaceutical Corporation submitted a Type B meeting request dated August 18, 2011, to discuss West-Ward's proposed 505(b)(2) development program for colchicine.

Any discussion that took place at the meeting is captured directly under the original response. West-Ward's questions are in *italics*; the Agency's response is in **bold**; and the discussion is in normal font.

## 2.0 DISCUSSION

### Question 1:

*Does the labeling proposed by Dr. Hansten sufficiently address the potential for drug-drug interactions when patients take West-Ward's product with interacting drugs?*

### Response:

**Although your proposals appear to contain reasonable clinical practice recommendations, we are concerned that disparate recommendations in the labeling for Colcris (colchicine) and the proposed labeling for your product (a similar single-ingredient colchicine product seeking approval for one of the same indications as Colcris (i.e., prophylaxis of gout flares)) may cause patient and prescriber confusion with respect to drug-drug interactions. However, it may be possible for you to address this concern by providing data to demonstrate that following the clinical practice recommendations that you propose for drug-drug interactions is as safe as, or safer than, following the dose modification recommendations currently approved for Colcris. In addition, it is not clear how you derived your dose modification recommendations (e.g., (b) (4)).**

**You also may consider conducting drug-drug interaction studies to form the basis of recommendations for a West-Ward colchicine label. A limited number of studies would be needed, i.e., a study of your product with a weak CYP3A4 inhibitor, a moderate CYP3A4 inhibitor, a strong CYP3A4 inhibitor, and a P-gp inhibitor. The label for your proposed product must contain adequate information for safe and effective use of your proposed product under the conditions of use for which you are requesting approval.**

### Discussion:

West-Ward stated that they wanted to discuss the issue of drug-drug interaction studies, as earlier FDA comments did not specify these studies as a requirement. FDA noted that the issue of drug-drug interactions (DDI) has previously been highlighted as an issue that

would need to be addressed for single-ingredient colchicine products. One possible approach to providing adequate information on drug-drug interactions, including relevant dose adjustments, would be to conduct a limited number of drug-drug interaction studies to support dose modification recommendations, as described in FDA's response.

West-Ward stated that colchicine-drug interactions are unpredictable due to large variability, and therefore, in their view, patient education was of more benefit than dose modification recommendations based on drug-drug interaction studies.

FDA stated that although avoiding use of moderate to strong inhibitors of CYP3A4 or P-gp makes sense, such a recommendation does not provide guidance on what to do if a patient must take colchicine and a CYP3A4 or a P-gp inhibitor. With respect to differences between the dose modification recommendations in Colcris labeling and the proposed labeling for West-Ward's product, FDA stated that the dose modifications in the Colcris label would not be applicable to West-Ward's proposed 0.6 mg capsule (because the capsule could not be split), and different dose modification recommendations, ideally from drug-drug interaction studies, would be needed to support West-Ward's proposed label.

West-Ward reiterated their concern regarding the variability of exposure that would be expected with real-world drug-drug interactions, and that the limited variability seen in drug-drug interaction studies would likely result in dose-modification recommendations that may not be applicable for a given individual. West-Ward continued that their recommendations take into consideration the patient who would be most at risk of colchicine toxicity. West-Ward stated that although they can appreciate FDA's regulatory considerations, they believe that their proposed drug-drug interaction labeling would result in safer use of colchicine than the approach described in the Colcris label.

FDA stated that in the absence of data (e.g., a study which demonstrated improved safety with West-Ward's approach as compared to the dose-modification approach approved for Colcris) that could be used to support labeling consistent with West-Ward's proposal, some guidance on dose modification recommendations is needed. Therefore, FDA's position remains that the label should include dose modification recommendations for the situations where co-administration of colchicine and interacting drugs cannot be avoided. FDA also noted that it considers patient variability when evaluating drug-drug interaction study data.

West-Ward asked if FDA is recommending that they conduct drug-drug interaction studies. FDA replied that, from a medical/scientific perspective, conducting a limited number of drug-drug interaction studies (i.e., the four studies noted in the above response) to support dose modification recommendations in the label would be likely to provide the necessary data. However, the Agency cannot advise West-Ward on legal implications that may be associated with this development approach.

West-Ward inquired as to what type of DDI study designs are recommended. FDA referred West-Ward to the "Draft Guidance for Industry: Drug Interaction Studies – Study

Design, Data Analysis, and Implications for Dosing and Labeling (2006).” FDA noted that this is a draft guidance and the broader principles may be useful. Generally speaking, the DDI studies should include studies of West-Ward’s proposed product with a weak CYP3A4 inhibitor, a moderate CYP3A4 inhibitor, a strong CYP3A4 inhibitor, and a P-gp inhibitor. A single dose administration of West-Ward’s proposed product and crossover design would be sufficient. FDA noted that these designs are not required to be powered to demonstrate bioequivalence but to get a quantitative estimation; about 12 subjects or so may be enough for each study to account for variability.

West-Ward also asked if they could submit the study protocol to FDA for review. FDA stated that the Agency does not need to review West-Ward’s protocol in order for them to conduct the study.

Westward enquired if they need to conduct four separate studies or if they can get the information from one study. FDA noted that the number of DDI studies needed to provide data would depend on the study design. Since there will be inhibition of enzymes, there might have to be long washout periods between treatments for enzymes. West-Ward stated that they cannot do just one study to obtain the data needed. FDA agreed, stating that this would not be feasible, and to refer to the suggested consideration from response to question 1.

Question 2:

*Does the labeling proposed by Dr. Schumacher sufficiently address patients who suffer acute flares when taking colchicine prophylactically?*

**Response:**

**The proposed labeling for prophylaxis of gout flares would need to clearly state that your product should not be used for treatment of acute gout flares. The other language in Section 2.1 of Dr. Schumacher’s proposed label (i.e., “** (b) (4)

**appears reasonable.**

Discussion:

West-Ward stated that published literature supports their proposed label to include

(b) (4)  
: West-Ward asserted that their recommendations are safer than the recommendations in the Colcris label.

(b) (4)  
But

rather that product labeling may indicate that the safety and effectiveness of West-Ward's product for the treatment of acute gout flares has not been studied.

Question 3:

*Does the labeling proposed by Dr. Schumacher sufficiently address dosing in renally and hepatically impaired patients?*

**Response:**

**In general, the proposed labeling for renally and hepatically impaired patients appears to be reasonable and supported by the literature.** (b) (4)

Discussion:

West-Ward noted that their proposed dose modification was an estimate based on information available in the published literature regarding the effect of renal impairment on the pharmacokinetics of colchicine.

Question 4:

*Is the published literature, in combination with a fasted bioequivalence trial versus col-probenecid adequate to support the safety and efficacy of West-Ward's product?*

**Response:**

**See response to question 1. The primary issue is how West-Ward's product would be labeled, which might require additional data. Note that the proposed study would be considered a relative bioavailability study between your proposed single-ingredient colchicine product and Col-probenecid (colchicine and probenecid) and not a bioequivalence study.**

Discussion:

No discussion.

Question 5:

*How must the bioequivalence trial versus col-probenecid be structured? Is a two-way fasted cross-over study sufficient?*

**Response:**

**A fasted, two-way, cross-over study comparing West-Ward's product with col-probenecid would be adequate to assess relative bioavailability.**

**Discussion:**

No discussion.

**Question 6:**

(b) (4)

**Response:**

(b) (4)

**Discussion:**

FDA asked how West-Ward is making the capsule. (b) (4)

(b) (4)

(b) (4)

(b) (4)

West-Ward asked about the timeframe for review of their application if they conduct the relative BA study and DDI studies. FDA responded that a standard 10-month review clock would likely apply, and the Agency could not commit to a shorter timeframe for review.

Question 7:

(b) (4)

Response:

(b) (4)

Discussion:

No discussion.

### 3.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application

### MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

**4.0 ISSUES REQUIRING FURTHER DISCUSSION**

No issues identified

**5.0 ACTION ITEMS**

No action items identified

**6.0 ATTACHMENTS AND HANDOUTS**

No attachments or handouts

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/s/

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SARAH K YIM  
12/23/2011



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: December 20, 2012**

<b>To:</b> Susan Todd	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> West-Ward Pharmaceuticals, US Agent for Hikma Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 732-542-6150	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 732-720-2871	<b>Phone number:</b> 301-796-4786
<b>Subject:</b> CMC Information Request (colchicine) NDA 204820	

**Total no. of pages including cover:** 3

**Comments:**

Please acknowledge receipt.

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**Document to be mailed:**       YES                       NO

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NDA 204820

We are currently reviewing Hikma Pharmaceutical's NDA, submitted October 5, 2012. Provide a letter of authorization (LOA) from (b) (4) (capsule manufacturer) for a Drug Master File (DMF) containing specific information regarding the manufacture of the gelatin capsules that are used for Hikma's drug product. Also request that (b) (4) send the LOA to the DMF as well.

Submit this information, via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov) by **12:00 PM Friday December 21, 2012**. Your response will subsequently need to be submitted officially to the NDA.

NDA 204820

Drafted by: MichelleJG 12/20/12

Cleared by: SandyB 12/20/12

Finalized by:MichelleJG 12/20/12

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/s/  
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MICHELLE Y JORDAN GARNER  
12/20/2012



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: December 19, 2012**

<b>To:</b> Susan Todd	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> West-Ward Pharmaceuticals, (Hikma US Agent)	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 732-542-6150	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 732-720-2871	<b>Phone number:</b> 301-796-4786

**Subject:** Reference List (colchicine) NDA 204820

**Total no. of pages including cover:** 3

**Comments:**

Please acknowledge receipt.

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**Document to be mailed:**       YES                       NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

We are currently reviewing Hikma Pharmaceutical's NDA, submitted October 5, 2012. We mailed a "Filing Issues Identified" letter to you on December 18, 2012. The first comment listed, as a potential review issue, made reference to a list of literature references for the DDI information for colchicine. Please find this list below, as it was omitted from the letter in error:

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.

NDA 204820

Drafted by: MichelleJG 12/19/12  
Concurred by: SandyB 12/19/12  
Finalized by: MichelleJG 12/19/12

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/s/  
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MICHELLE Y JORDAN GARNER  
12/19/2012



NDA 204820

**FILING COMMUNICATION**

Hakim Pharmaceuticals LLC  
c/o West-Ward Pharmaceutical Corporation  
200/401/435/465 Industrial Way West  
Eatontown, NJ 07724

Attention: Susan Todd  
Senior Manager, Regulatory Affairs  
West-Ward Pharmaceutical Corp.

Dear Ms. Todd:

Please refer to your New Drug Application (NDA) dated October 5, 2012, received October 5, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for colchicine capsules, 0.6 mg.

We also refer to your amendments dated November 20, and 30, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is August 5, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 8, 2013.

During our filing review of your application, we identified the following potential review issues:

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 (b) (4). Please provide a justification/rationale for this discrepancy.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. The following sections of the Module 2 Summaries were indicated as “Not Applicable.” Provide information for your product as it relates to drug safety to address these topics. If there is no information available, indicate that. Also provide justification why carcinogenicity studies were not included in your application or not necessary.

Placental Transfer Studies  
Excretion in Milk  
Postnatal Development  
Carcinogenicity

2. Many of the references cited in Module 2 are missing from the publications provided in Module 4. Provide those missing publications.
3. This pertains to the (b) (4) of the drug, and the instruction in the executed batch records to “(b) (4).” Provide a description of how the (b) (4) is controlled during the manufacturing process.
4. Update section 3.2.P.3.3 to ensure that it is complete, including a detailed description of the packaging and labeling processes.

5. Your application states that the particle size of colchicine is potentially critical, yet there do not seem to be any in process controls for particle size during/after the (b) (4) process. Provide a justification for the absence of these controls.
6. Describe the bulk drug product containers used to store the bulk product, prior to its encapsulation and indicate the maximum amount of storage time (and storage conditions) for the bulk product, and provide stability data for longer term storage (e.g. 30 days or more).
7. The specification for uniformity of dosage units (USP <905>) is not complete and cannot be said to meet the USP requirement. The maximum value of (b) (4) is not indicated and there are no limits on individual values. Address this concern in your application for the specification for uniformity of dosage units.
8. Drug product specifications list (b) (4), with reference to USP (b) (4) > but specific (b) (4) and limits are not listed in the specifications. Update your specifications to include specific (b) (4) which may be potentially present.
9. The application should be complete upon submission and your proposal to provide a future amendment with additional container closure system information and stability data for a blister package should be submitted after NDA approval as a supplement.
10. Provide the West-Ware SOP describing time limits on the various phases of the drug product manufacturing process, or provide the equivalent information.
11. You have indicated that you will institute written procedures for a system of (b) (4) procedures for (b) (4) that do not conform to standards or specifications, and that such (b) (4) will conform with “all established standards, specifications and characteristics.” Provide details of this (b) (4) system (or data from (b) (4) ) in section P.3.3 of your NDA, in order for FDA to review these (b) (4) system.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have not addressed how you plan to fulfill this requirement. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication(s) proposed in this application/supplemental application.

If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Pulmonary, Allergy, and Rheumatology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, call Michelle Jordan Garner, Regulatory Project Manager, at (301) 796-4786.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, MD, PhD  
Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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BADRUL A CHOWDHURY  
12/18/2012



NDA 204820

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

Hikma Pharmaceuticals LLC  
c/o West-Ward Pharmaceutical Corp.  
435 Industrial Way West  
Eatontown, NJ 07724

ATTENTION: Susan Todd  
Senior Manager Regulatory Affairs

Dear Ms. Todd:

Please refer to your New Drug Application (NDA) dated October 5, 2012, received October 5, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Colchicine Capsules, 0.6 mg.

We acknowledge receipt of your November 16, 2012, correspondence, on November 16, 2012, notifying us that you are withdrawing your request for review of the proposed proprietary name, (b) (4); and alternate proprietary name, (b) (4). These proposed proprietary name requests are considered withdrawn as of November 16, 2012.

If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nichelle Rashid, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Michelle Jordan, at (301) 796-4786.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
12/13/2012



NDA 204820

**INFORMATION REQUEST**

Hikma Pharmaceuticals LLC  
c/o West-Ward Pharmaceutical Corporation  
200/401/435/465 Industrial Way West  
Eatontown, NJ 07724

Attention: Susan Todd,  
Senior Manager, Regulatory Affairs

Dear Ms. Todd:

Your NDA 204820 submitted, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), on October 3, 2012, received October 5, 2012, for colchicine capsules 0.6mg, is currently under review. In order to continue our review, we have the following comments and requests for information:

1. This 505(b)(2) application for colchicine 0.6 mg capsules includes data from a relative bioavailability study comparing your product to an approved combination product containing colchicine and probenecid (Col-Probenecid), but does not identify ANDA 84-279 for Col-Probenecid (submitted under section 505(b) of the FD&C Act in accordance with the Drug Efficacy Study Implementation (DESI) notice of July 11, 1972) as a listed drug relied upon to support approval.
2. In order to rely on FDA's finding of safety and/or effectiveness for ANDA 84-279 for Col-Probenecid, in addition to reliance on published literature, to support your 505(b)(2) application, you need to identify the listed drug in accordance with the Agency's regulations at 21 CFR 314.54. This requires submission of an amendment to your 505(b)(2) application that includes:
  - A corrected Form FDA 356h that lists ANDA 84-279 for Col-Probenecid in section 20 as the listed drug upon which your 505(b)(2) application relies for approval.
  - An appropriate patent certification or statement for the listed drug relied upon in accordance with 21 CFR 314.50(i).
  - Any other revisions needed to clarify that the comparative bioavailability study with Col-Probenecid supports the scientific appropriateness of reliance on FDA's finding of safety and/or effectiveness for ANDA 84-279 for Col-Probenecid.

Submit your response to Michelle Garner via telephone facsimile to 301-796-9728 or email at Michelle.Jordan@fda.hhs.gov **no later than 3p.m. November 30, 2012**. Your response will subsequently need to be submitted officially to the NDA. If you have any questions, call Michelle Jordan Garner, Regulatory Project Manager, at (301) 796-4786.

Sincerely,

*{See appended electronic signature page}*

Sarah Yim, M.D.  
Supervisory Associate Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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SARAH K YIM  
11/28/2012

## Liu, Youbang

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**From:** Liu, Youbang  
**Sent:** Tuesday, November 20, 2012 1:42 PM  
**To:** 'stodd@west-ward.net'  
**Subject:** Information Request for NDA 204820

Hikma Pharmaceuticals LLC  
Attention: Susan Todd  
Senior Manager, Regulatory Affairs  
200/401/435/465 Industrial Way West  
Eatontown, NJ 07724

Dear Ms. Todd:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 204820 (Colchicine Capsules, 0.6mg) received October 5, 2012. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission:

1. Please provide the dissolution method development report with complete detailed information supporting the selection of this method for the evaluation of the dissolution characteristics of colchicine Capsules.

The dissolution method development report should include the following information:

- a. Solubility data for each drug substance covering the pH range;
- b. Detailed description of the dissolution test being proposed for the evaluation of the proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (*i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.*). Include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (*i.e., 15, 20, 30, 45, & 60 minutes*) and cover at least 85% of drug release of the label amount or whenever a plateau (*i.e., no increase over 3 consecutive time-points*) is reached. We recommend that at least twelve samples be used per testing variable;
- c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*). The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and
- d. Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (*i.e., method robustness, etc.*) and analytical method (*precision, accuracy, linearity, stability, etc.*).

For the setting of the dissolution acceptance criteria of your product, the following points should be considered:

- e. The dissolution profile data (*i.e., 15, 20, 30, 45, & 60 minutes*) from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your proposed drug product.
- f. The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
- g. The selection of the specification time point should be where  $Q = \frac{(b)}{(4)}\%$  dissolution occurs. However, if you have a slowly dissolving product or includes a BCS-Class 2, poor-soluble drug, a two-point

specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (i.e., 15-20 minutes) and the second time point should be where  $Q = \text{(b)}_{(4)}\%$  dissolution occurs.

- h. The dissolution acceptance criterion should be based on average dissolution data (n=12).

Note that the final determination on the acceptability of the proposed acceptance criterion for your proposed product will be made during NDA review process based on the provided data.

- 2. The dissolution data that you collect during your stability study should cover the complete dissolution profile (i.e., 15, 20, 30, 45, & 60 minutes). Please provide these data. If you have not collected these dissolution data at all appropriate time points, you should start collecting these data and submit to the NDA.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Regards,

Youbang Liu  
Regulatory Project Manager  
ONDQA/OPS/CDER/FDA  
Division III of New Drug Quality Assessment  
Phone: (301) 796-1926  
Fax: (301) 796-9748

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/s/  
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YOUBANG LIU  
11/20/2012

## Liu, Youbang

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**From:** Liu, Youbang  
**Sent:** Monday, November 05, 2012 9:00 AM  
**To:** 'stodd@west-ward.net'  
**Subject:** Information Request NDA 204820

Hikma Pharmaceuticals LLC  
Attention: Susan Todd  
Senior Manager, Regulatory Affairs  
200/401/435/465 Industrial Way West  
Eatontown, NJ 07724

Dear Ms. Todd:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 204820 (Colchicine Capsules, 0.6mg) received October 5, 2012. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission:

The Form FDA 356h needs to be updated in the NDA to include all facilities used for the drug product and the drug substance. See below for the information to be provided for the facilities in FDA 356h.

- Include a table of all facilities, specifically what is the function of each facility, the contact name and address, the CFN number, and the complete name and address of the facility.
- Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.

In addition, all referenced DMFs should be listed on this form.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Regards,

Youbang Liu  
Regulatory Project Manager  
ONDQA/OPS/CDER/FDA  
Division III of New Drug Quality Assessment  
Phone: (301) 796-1926  
Fax: (301) 796-9748

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/s/  
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YOUBANG LIU  
11/05/2012



NDA 204820

**NDA ACKNOWLEDGMENT**

Hakim Pharmaceuticals LLC  
c/o West-Ward Pharmaceutical Corporation  
200/401/435/465 Industrial Way West  
Eatontown, NJ 07724

Attention: Susan Todd

Dear Ms. Todd:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: colchicine capsules 0.6 mg

Date of Application: October 5, 2012

Date of Receipt: October 5, 2012

Our Reference Number: NDA 204820

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 4, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinformo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 204820** submitted on October 5, 2012, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary, Allergy, and Rheumatology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications. If you have any questions, call me, Regulatory Project Manager, at (301) 796-4786.

Sincerely,

*{See appended electronic signature page}*

Michelle Jordan Garner, MS, OTR/L  
Senior Regulatory Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHELLE Y JORDAN GARNER  
10/25/2012