

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-353

CHEMISTRY REVIEW(S)

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

DATE: 28-JUL-2009
TO: N22-353 File
FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II



THROUGH: Ali Al-Hakim, Ph.D.
Branch Chief
ONDQA, Division I, Branch II

SUBJECT: Review of CMC section of N22-353; EES Status

SUPPORTING DOCUMENTS REVIEWED (FDA Form 356h dates): 25-NOV-2008
(original); 11-DEC-2008; 12-FEB-2009; 25-MAR-2009; 07-APR-2009; 22-MAY-2009

Cross Reference of N22-353 CMC section to N22-351 and N22-352

EVALUATION: The module 3 section of original supporting document for N22-353 included the following (reproduced from application):

“Notes to the Reviewer:

This NDA (prevention of gout flares) is the last of the 3-series NDAs undertaken by Mutual. The two preceding submissions are NDA 22-351 (Gout flares) and NDA 22-352 (FMF), both of which are currently under review by the Division. All of the CMC information contained in this NDA has already been submitted by Mutual in the preceding original NDAs and/or follow-up amendments and responses to FDA’s requests. The CMC sections are nevertheless included in this NDA, regardless of the redundancy, because of the difficulty, at this time of using the cross-referencing option in an eCTD submission.”

The amendments to the CMC section of the application that were provided in the remaining supporting documents listed above, were already reviewed for related N22-352 and/or N22-351. As the recommendation for action, from the CMC perspective, is “approval” for both N22-352 and N22-351, the same recommendation is made for N22-353.

EES Status

The office of compliance has provided a recommendation of “acceptable” for the application on 28-MAY-2009.

CONCLUSION: The application N22-353 is recommended for approval.

Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:

DAARP/MTossa

ONDQA/DIV 1/CBertha

ONDQA/DIV 1/DChristodoulou

ONDQA/DIV 1/AAI-Hakim

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22353	ORIG 1	MUTUAL PHARMACEUTICA L CO INC	COLCHICINE TABLETS USP 0.6MG

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/s/

CRAIG M BERTHA
07/28/2009

ALI H AL HAKIM
07/28/2009

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

DATE: 10-FEB-2009
TO: N22-352 File
FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II
THROUGH: Ali Al-Hakim, Ph.D.
Branch Chief
ONDQA, Division I, Branch II



SUBJECT: Update to Chemistry Review #3 regarding stability data

The third review of N22-352 had included a comment to be included in the action letter indicating that the applicant's proposal for a _____ expiration dating period for the _____ product was not acceptable, but that an _____ expiry could be given. This comment is reproduced below:

b(4)

b(4)

The drug product stability batches for N22-352 are the same as those presented in the related applications from the applicant for treatment and prevention of gout (N22-351 and N22-353). The applicant provided updated stability data in the 03-FEB-2009, amendment to N22-351, which supported their proposal for a _____ product. Thus, it is no longer necessary to include the comment to the applicant in the forthcoming action letter for N22-352 regarding the expiry period for the _____ product.

b(4)

ACTION ITEM: NAI

Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

N22-352

Stability Data Update

p. 2

cc:

DAARP/MTossa

ONDQA/DIV 1/CBertha

ONDQA/DIV 1/DChristodoulou

ONDQA/DIV 1/AAI-Hakim_____

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/s/

Craig Bertha
2/10/2009 09:03:14 AM
CHEMIST

Ali Al-Hakim
2/10/2009 12:59:14 PM
CHEMIST



CHEMISTRY REVIEW



NDA 22-351

Colchicine Tablets USP

Mutual Pharmaceutical Company, Inc.

**Craig M. Bertha, Ph.D.
ONDQA/DIV I for DAARP**



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Chemistry Review Data Sheet

1. NDA 22-351
2. REVIEW #: 1
3. REVIEW DATE: 10-FEB-2009
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedOriginal
AmendmentDocument Date30-SEP-2008
03-FEB-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Mutual Pharmaceutical Company, Inc.
Address:	1100 Orthodox Street
Representative:	Philadelphia, PA 19124
Telephone:	(215) 288-6500

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Colstat™
- b) Non-Proprietary Name (USAN): Colchicine
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDQA only): N/A



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- Chem. Type: 7
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: For treatment of Gout flare (Familial Mediterranean Fever or FMF under NDA 22-352; prevention of Gout flare under NDA 22-353)

11. DOSAGE FORM: tablets (maximum recommended dose is 1.8 mg over 1 hour period for Gout flare)

12. STRENGTH/POTENCY: 0.6 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

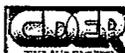
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT (reproduced from application):

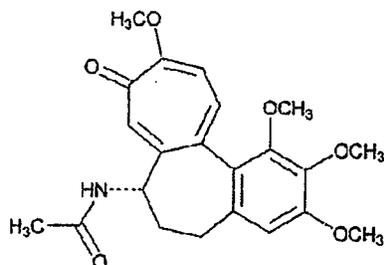
Colchicine is Acetamide, N-[5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy 9-oxobenzo[*a*]heptalen-7-yl], (S)-



CHEMISTRY REVIEW



Chemistry Review Data Sheet



Molecular formula: $C_{22}H_{25}NO_6$; Molecular weight: 399.44 g/mole

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	2		Colchicine, USP	1	Adequate	28-JUL-2008 21-OCT-2008	
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			4	N/A		Review not needed per bottle review policy for solid oral dosage forms.
	3			3	Adequate	19-NOV-2007	
	3			1	Adequate	29-JUL-2008 01-OCT-2008	
	4			1	Adequate	23-SEP-2008	

b(4)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	75,040	colchicine tablets

18. STATUS:

ONDQA:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	PAI	15-, 16- and 17- OCT-2008	Pending	Forwarded by PAL, D. Christodoulou, Ph.D.
Pharm/Tox	DS/DP impurities	Via e-mail 14-JUL- 2008	Final/L. Leshin, Ph.D.	Refer to Dr. Leshin's review for NDA 22-352
Biopharm	N/A			Refer to NDA 22-352 reviews
OSE	Labeling			Forwarded by PM
Methods Validation	N/A			See p. 77 of CR#1 of N22-352 and p. 22 of CR#2 of N22-352
EA				See p. 78 of CR#1 of N22-352
Microbiology	N/A			



The Chemistry Review for NDA 22-352

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

An **approvable** recommendation is recommended by the CMC team, as the Office of Compliance has not provided an overall recommendation as of yet.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Colchicine Tablets and each immediate release tablet contains 0.6 mg of colchicine. It is to be indicated for the treatment of Familial Mediterranean Fever (FMF; N22-352) and for treatment (N22-351) and prevention (N22-353) of gout flares. It is packaged in high density polyethylene bottles _____
_____. There is a Colchicine Tablets monograph in the current edition of the USP. **b(4)**

The drug substance has the USAN name "colchicine" and a monograph appears in the current edition of the USP. Information about the retest date for the drug substance is provided separately in the drug substance supplier's master file _____
_____. Colchicine that is provided by _____ . It was shown by the data included in the report from _____ that the _____
_____ that occurs when the _____ is the _____
_____ is part of the manufacturing process, therefore the _____ in the final drug product. It is further noted that _____ of colchicine that were revealed in the _____ were _____. Because of the unique structure of colchicine, it exists as a mixture of conformers that can interconvert relatively quickly when the compound is in solution and at ambient temperatures. The ratio of these conformers is approximately 99:1. **b(4)**

The drug product is formulated as a tablet with the following excipients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and is coated with a proprietary coating from _____
_____. The manufacturing process is summarized as follows. Colchicine drug **b(4)**



CHEMISTRY REVIEW



Executive Summary Section

substance is

b(4)

It is important to note that the primary stability/registration batch BB 374 0215 of the drug product was that used in the clinical pharmacology studies supporting the application. This batch has the same formulation and is manufactured by the same process proposed for the commercial tablets. Thus, no formulation comparability studies were necessary.

B. Description of How the Drug Product is Intended to be Used

The maximum dose for the colchicine product for treatment of gout flare is to be 1.8 mg in 1 hour (3 tablets). The marketed drug product will be packaged in HDPE bottles with internal desiccants and with the following tablet counts: 30, 60, 100, 250, 500, 1000. The current proposed expiration dating period for the bottled product of 24 months is supported by the data provided. _____ are to be given a 24 month expiration dating period and this too, is supported by the data included in the application.

b(4)

C. Basis for Approvability or Not-Approval Recommendation

Pending Office of Compliance recommendation.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./10-FEB-2009
Ali Al-Hakim, Ph.D.

C. CC Block

Margarita Tossa
Keith Hull
Lawrence (Steve) Leshin
Srikanth Nallani

12 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Craig Bertha
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