CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-351

CHEMISTRY REVIEW(S)

NDA 22-351

Colchicine Tabets, USP

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124

Indication: Treatment of gout flare

Presentation: 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. [redacted] b(4)

EER Status: Pending

Consults:

EA –	Categorical exclusion provided
Statistics –	N/A
Methods Validation –	Not recommended
Biopharm–	N/A
Microbiology –	N/A
Pharm/toxicology –	Completed

Original Submission: 30-Sept-2008
Re-submissions: N/A
Post-Approval CMC Agreements: None beyond the typical stability commitment. However, the pharm/tox agreement for NDA 22-352 has involved CMC since they will be trying to develop a method to quantify the level of the impurity, lumicolchicine, under the qualification threshold, otherwise they will need to do a carcinogenicity study.

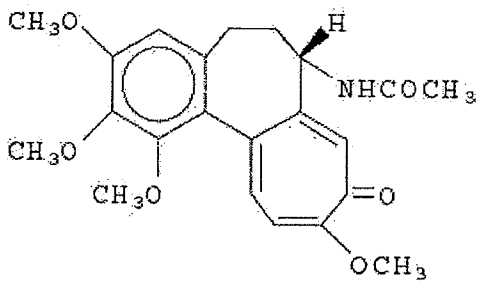
Background:
The drug product is Colchicine Tablets; each immediate release tablet contains 0.6 mg of colchicine. The maximum dose for the Colchicine product for treatment of gout flare is to be 1.8 mg in 1 hour (3 tablets). Colchicine is indicated for the treatment of Familial Mediterranean Fever (FMF; N22-352) and for treatment (N22-351) and prevention (N22-353) of gout flares. The drug product is packaged in high density polyethylene bottles [redacted]. b(4)

There is a Colchicine Tablets monograph in the current edition of the USP.
The applicant reported that there are multiple unapproved colchicine products available in the marketplace which are being used by patients.

Drug Substance:
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 part of the manufacturing process; therefore the ———— is the most likely ———— 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 two 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. **The above DMF was reviewed and found acceptable.**

b(4)

Chemical name, structural formula, molecular formula and molecular weight



Chemical name: (*S*)-*N*-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[α]heptalen-7-yl)acetamide
Molecular formula: $C_{22}H_{25}NO_6$
Molecular weight: 399.44g/mole

Conclusion: Drug substance is acceptable.

Drug Product:
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 substance is

———————————————————————

b(4)

———————————————————————

[redacted] . 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. b(4)

Specifications include all tests as described in the USP monograph. These tests include physical appearance, specific rotation, water, heavy metals, differential scanning calorimetry, organic volatile impurities, residual solvents, ethyl acetate, assay and related substances.

The applicant provided 24 months of real time data for the HDPE bottled product [redacted] b(4)

Based on the stability data, the proposed expiry dating is acceptable.

Conclusion: Drug product is satisfactory.

Additional Items: All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion: From a CMC perspective, the application is approvable pending an acceptable recommendation from the Office of Compliance regarding cGMP inspection. Currently, the recommendation is PENDING.

Ali Al-Hakim, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Ali Al-Hakim
4/14/2009 01:51:46 PM
CHEMIST

NDA 22-351

Colchicine Tablets USP

Mutual Pharmaceutical Company, Inc.

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

Table of Contents

b(4)

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	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	30-SEP-2008
Amendment	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

- 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: _X__Rx ___OTC

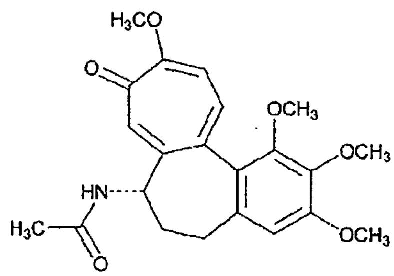
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__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 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	—	—	3	Adequate	19-NOV-2007	
—	3	—	—	1	Adequate	29-JUL-2008 01-OCT-2008	
—	4	—	—	1	Adequate	23-SEP-2008	

b(4)

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 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 ——— when the compound is ——— ——— 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)

substance is [redacted]. 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(4)

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. [redacted] 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
2/10/2009 09:00:05 AM
CHEMIST

Ali Al-Hakim
2/10/2009 04:03:24 PM
CHEMIST

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 ——————————————— b(4)
——————————————— This comment is reproduced below:

Comment: *Our evaluation of your submitted stability data as per ICH Q1E, in conjunction with your updated drug product specifications leads to the conclusion that* ——————— b(4)
——————————————— *You may extend the expiration dating period as per 21 CFR 314.70(d)(2)(vi).*

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 ——————————————— b(4)
——————— product. Thus, it is no longer necessary to include the comment to the applicant in the forthcoming action letter for N22-352 regarding the ——————————— product.

ACTION ITEM: NAI

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

cc:
DAARP/MTossa
ONDQA/DIV 1/CBertha
ONDQA/DIV 1/DChristodoulou
ONDQA/DIV 1/AAl-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