CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-353

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-353**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**Nov 25, 2008**
PRODUCT:	**Colchicine**
INTENDED CLINICAL POPULATION:	**To prevent gout flares in susceptible patients**
SPONSOR:	**Mutual Pharmaceutical Co., Inc.**
DOCUMENTS REVIEWED:	**eCTD Module 4**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia, and Rheumatology Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**L. Steven Leshin, DVM, PhD**
PHARM/TOX SUPERVISOR:	**Adam Wasserman, PhD**
DIVISION DIRECTOR:	**Bob Rappaport, MD**
PROJECT MANAGER:	**Margarita Tossa**

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approve

B. Recommendation for nonclinical studies:

1) Conduct an evaluation of the potential carcinogenicity of colchicine in two rodent species.

2) Improve detection assays to allow reduction of the specifications for the photodegradant impurities β and γ-lumicolchicine or conduct *in vitro* genetic toxicology studies evaluating mutagenicity and clastogenicity.

The Applicant was notified of these issues in a Jan 8, 2009 Discipline Review Letter upon review of NDA 22-352 (colchicine for the treatment of Familiar Mediterranean Fever). The Applicant provided the following information on Feb 2, 2009 (NDA 22-352, N-000-BM, 02-Feb-09). The carcinogenicity studies will require an approximately 2.5 year timeline, and draft protocols will be submitted for ECAC approval prior to commencement of the studies. Their timeline indicated that the toxicity and dose-ranging studies needed to support the carcinogenicity dose proposal has already started. Impurity detection assays will be developed with greater detection sensitivity and they will work with the drug substance supplier to reduce impurity levels. They estimate this implementation may require one year from the time of approval of NDA 22-352.

C. Recommendations on labeling:
On July 20, 2009, the Applicant submitted a revised label to NDA 22-351, (colchicine for the treatment of acute gout flares) which incorporated the Reviewer's previous edits for a combined label for NDAs 22-351 and 22-352. For NDA 22-353, there are no additional revisions necessary for the nonclinical Pharmacology Toxicology supported information.

II. Summary of nonclinical findings

There were no new nonclinical studies submitted with NDA 22-353. Refer to NDA 22-352 for Review of the Pharmacology and Toxicology studies.

III. Nonclinical safety issues relevant to clinical use

General Toxicology: Findings of nonclinical toxicology closely match those known historically from clinical colchicine use. Published clinical studies submitted in support of this NDA, lacked for the most part, the toxicities of colchicine that are observed with higher doses and overdosing. These toxicities

have been described in abundance in review articles and medical databases. Colchcine has a very narrow therapeutic window, with human deaths reported at doses not much greater than therapeutic doses. Comparing human lethality with the limited nonclinical data at nonlethal doses, indicates that human deaths have been reported at doses lower than those that affect rodents, implying that NOAEL determinations may not provide a useful margin of safety. A direct NOAEL comparison could not be conducted since for the most part, nonclinical studies were not conducted to identify a NOAEL, but to identify toxicities, being conducted prior to current FDA recommended guidances.

Genetic Toxicology: Genetic toxicology studies indicate that colchicine treatment results in aneuploid cells through mitotic or meiotic non-disjunction, but colchicine is not considered mutagenic or clastogenic although results from these assays often result in positive results (a false positive finding, from different mechanism leading to a similar result). The significance of aneuploidy toward carcinogenic potential in comparison with a pure clastogenic mechanism cannot be quantitatively assessed. However, most tumors consist of aneupoid cells and both mechanism can result in tumors (Weaver et al 2007, Cancer Cell 11:25-36; Torres et al 2008, Genetics 179:737-746).

Carcinogenicity: Carcinogenicity studies were not requested due to the long history of clinical experience, although specific documentation of any relationship between colchicine use and carcinogenicity is lacking. Upon review of the available data and concern about the relationship between aneuploid cells and cancer, the Applicant was notified in the Jan 8, 2009 Discipline Review Letter that 2-year duration oral dosing carcinogenicity studies in 2 species will be necessary as postmarketing commitment if NDA 22-352 is approved. They responded on Feb 2, 2009 indicating that these studies will require 2.5 year timeline, and draft protocols will be submitted for ECAC approval prior to commencement of the studies. Their timeline indicated that the toxicity and dose-ranging studies needed to support the carcinogenicity dose proposal has already started.

Reproduction and Developmental Toxicology: GLP studies of reproductive and developmental toxicology and carcinogenicity have not been conducted. For reproductive and developmental toxicology, there is sufficient information from published literature to convey the risk in the label. Furthermore there are recent clinical epidemiology studies of pregnancies in colchicine treated women with FMF that have not found detrimental effects that could be attributed to colchicine, but there were limited number of pregnancies studied.

Reviewer Signature _____
L. S. Leshin, D.V.M., Ph.D.

Supervisor Signature _____ **Concurrence Yes** ___ **No**
A. Wasserman, Ph.D.

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

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/s/

LAWRENCE S LESHIN
07/30/2009

ADAM M WASSERMAN
07/30/2009
I concur with Dr. Leshin that the application may be approved from the nonclinical standpoint.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

SeptNDA Number: **22-353** Applicant: **Mutual Pharmaceutical Co., Inc.** Stamp Date: **Nov 25, 2008**

Drug Name: **Colchicine Cols** NDA Type: **505(b)(2)**

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?	X		
3	On its face, is the pharmacology/ toxicology section of the NDA legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	Comment
7	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		X	revision of label will be needed, but not a filing issue
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)		X	Previously agreed that the (αR,7S)-isomer will not need qualification 2 photodegradants not present in the drug product have mutagenic structural alerts will need qualification studies or specifications
11	Has the sponsor addressed any abuse potential issues in the submission?			not applicable
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			not applicable
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	X		

Any Additional Comments:

Identical PharmTox submission materials as NDA 22-352 for Familiar Mediterranean Fever and NDA 22-351 for Acute Gout Flare Treatment.

Reviewing Pharmacologist L. S. Leshin Date

Team Leader/Supervisor A. Wasserman Date

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

/s/

Lawrence Leshin
1/27/2009 01:27:25 PM
PHARMACOLOGIST

Adam Wasserman
2/11/2009 02:30:20 PM
PHARMACOLOGIST