CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-585

PHARMACOLOGY REVIEW

PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA #: 21-585

Drug Name: Mucinex™ D (guaifenesin and pseudoephedrine HCl)

Sponsor: Adams Laboratories, Inc.

Indication: Expectorant and Nasal Decongestant

Division: Pulmonary and Allergy Drug Products

Reviewer: Gary P. Bond, Ph.D., DABT

Regulatory recommendation: Approvable from Preclinical Perspective

Date: September 15, 2003

TABLE OF CONTENTS

EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability:

This drug is approvable from a preclinical perspective.

1.2 Recommendation for nonclinical studies: None.

1.3 Recommendations on labeling: None, since this is an over the counter product (OTC) which requires no preclinical data in the label.

2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings:

Changes in righting reflex, respiratory depression and chronic pulmonary edema were observed. Increases in respiratory tract secretions were reported in animals who received doses larger than those used clinically.

In animal studies, pseudoephedrine reduced average weight, length, and rate of skeletal ossification in animal fetus (USP Convention. USPDI – Drug Information for the Health Care Professional. 16th edition Volume I, Rockville, MD: U.S. Pharmaceutical Convention, Inc. 1996 (Plus updates), pg. 2509.).

2.2 Pharmacological activity:

For guaifenesin, nonnarcotic antitussive agent, it is claimed to act by stimulating receptors in gastric mucosa, thereby initiating reflex secretion of respiratory tract fluid that increases volume and decreases viscosity of bronchial secretions; mechanism of action of most nonnarcotic antitussive agent has not been adequately studied, but their primary action appears to be depression of central cough mechanism.

For pseudoephedrine, these agents act on beta-2 receptors to relax bronchial smooth muscle and peripheral vasculature, apparently by stimulation production of cAMP. Pseudoephedrine acts on alpha-adrenergic receptors in the mucosa of the respiratory tract, producing vasoconstriction. The medication shrinks swollen nasal mucous membranes; reduces tissue hyperemia, edema, and nasal congestion; and increases nasal airway patency. Also, drainage of sinus secretions may be increased and obstructed eustachian ostia may be opened.

2.3 Nonclinical safety issues relevant to clinical use: none

PHARMACOLOGY/TOXICOLOGY REVIEW

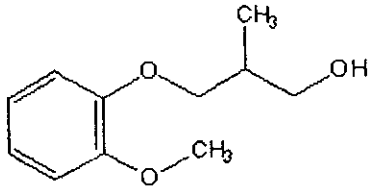
3.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-585
Review number: 1
Sequence number/date/type of submission: 000/January 31, 2003/Original
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth Texas, 76155-2645
Manufacturer for drug substance: Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth Texas, 76155-2645

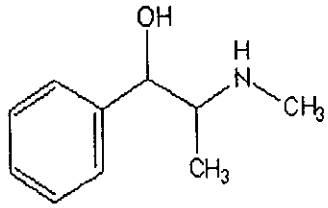
Reviewer: Gary P. Bond, Ph.D., DABT
Division: Pulmonary and Allergy Drug Products
HFD #: 570
Review completion date: September 11, 2003

Drug:

Trade name: Mucinex D Extended Release Tablets
Generic name (list alphabetically): guaifenesin and pseudoephedrine HCl
Code name: NA
Chemical name: 1,2-propanediol,3-(2methoxyphenoxy) and [S-(R*, R*)]
-α-[1-Methylamnino)ethyl]benezenemethanol hydrochloride
CAS registry number: 93-14-1 & 345-78-8
Mole file number: not reported
Molecular formula: C10-H14-O4 & C10-H15-N-O.Cl-H
Molecular weight: 198.24 & 201.72
Structure:



guaifenesin



pseudoephedrine (OH = OClH for hydrochloride)

Relevant INDs/NDAs/DMFs: NDA 21-282 (guaifenesin extended release tablets – Mucinex™)
NDA 17,941 (pseudoephedrine HCl)
IND 60,923 (guaifenesin/pseudoephedrine HCl)

Drug class: guaifenesin – a glyceryl guaicolate]

pseudoephedrine hydrochloride - an alkaloid obtained from —— spp.

Indication: loosening of phlegm and bronchial secretions and temporary relief of nasal congestion due to the common cold, hay fever, upper respiratory allergies, and ——

Clinical formulation: The levels of all the excipients are at acceptable levels.

Ingredient	(mg/tablet)
Guaifenesin DC ——	
Hydroxypropyl methylcellulose ——	
Pseudoephredrine HCl	
Microcrystalline cellulose	——
Sodium starch glycolate	
Carbomer 934P	
Magnesium stearate	
FD&C Red # Aluminum Lake ——	
Water, purified	
Total Weight	1587.0

1 – Guaifenesin direct compression used in the manufacturing process consists of —— guaifenesin, USP and —— hydroxypropyl methylcellulose, USP —— with purified water, USP.

Route of administration: Oral (tablet)

Proposed use: Expectorant and Decongestant

Guaifenesin is considered to be generally recognized as safe and effective (GRASE) as an expectorant in the following age groups at the following oral doses [21 CFR 341.78]:

- Adults and children 12 years of age and older: 200 to 400 mg every 4 hours, not to exceed (NTE) 2400 mg in 24 hours
- Children 6 to under 12 years of age: 100 to 200 mg every 4 hours, NTE 1200 mg in 24 hours
- Children 2 to under 6 years of age: 50 to 100 mg every 4 hours, NTE 600 mg in 24 hours
- Children under 2 years of age: consult a doctor

Pseudoephedrine hydrochloride is an orally active sympathomimetic that has a decongestant effect on the nasal mucosa. It is considered to be generally recognized as safe and effective (GRASE) as an nasal decongestant in the following age groups at the following oral doses [21 CFR 341.80]:

• Adults and children 12 years of age and older: 60 mg every 4 to 6 hours, NTE 240 mg in 24 hours
• Children 6 to under 12 years of age: 30 mg every 4 hours, NTE 120 mg in 24 hours
• Children 2 to under 6 years of age: 15 mg every 4 hours, NTE 60 mg in 24 hours
• Children under 2 years of age: consult a doctor

Note: [redacted] is not supported for the 600-mg guaifenesin/60-mg PSE product based on lack of efficacy data.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: none – none submitted

Studies not reviewed within this submission: none – none submitted

3.2 PHARMACOLOGY

3.2.1 Brief summary: NA

3.2.2 Primary pharmacodynamics: NA

3.2.3 Secondary pharmacodynamics: NA

3.2.4 Safety pharmacology: NA

3.2.5 Pharmacodynamic drug interactions: NA

3.3 PHARMACOKINETICS/TOXICOKINETICS

3.3.1 Brief summary: NA

3.3.3 Absorption: NA

3.3.4 Distribution: NA

3.3.5 Metabolism: NA

3.3.6 Excretion: NA

3.3.7 Pharmacokinetic drug interactions: NA

3.3.10 Tables and figures to include comparative TK summary: NA

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary: NA

3.4.2 Single-dose toxicity: NA

3.4.3 Repeat-dose toxicity: NA

3.4.4. Genetic toxicology: NA

3.4.5. Carcinogenicity: NA

3.4.6. Reproductive and developmental toxicology: NA

3.4.7 Local tolerance: NA

3.4.8 Special toxicology studies: NA

3.5 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Both components are GRASE safe and effective. Doses and combination of the two for proposed use are approved per OTC.

Unresolved toxicology issues (if any): none

Recommendations:

> The proposed use of Mucinex™ D Extended Release Tablets is approvable from a preclinical perspective.

Suggested labeling: none

Signatures (optional):

Reviewer Signature Gary P. Bond Ph.D., DABT

Supervisor Signature_____ Concurrence Yes ___ No ___

3.7. APPENDIX/ATTACHMENTS - none

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

/s/

Gary Bond
9/15/03 06:31:24 AM
PHARMACOLOGIST

Joseph Sun
9/15/03 02:44:32 PM
PHARMACOLOGIST
I concur.