CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-620

PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA #: 21-620

Drug Name: Mucinex® DM Extended Release tablets

Sponsor: Adams Laboratories, Inc.

Indication: 12-hour expectorant and antitussive for treating cold, cough, and allergy patients

Division: Pulmonary and allergy drug products

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

Regulatory recommendation: Approval

Date: January 14, 2004

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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability – Recommend approval.

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

For guaifenesin, changes in righting reflex, respiratory depression and chronic pulmonary edema were observed (Pharmacological Research Communications. Academic Press, Inc., 1969, 1:413). Increases in respiratory tract secretions were reported in animals who received doses larger than those used clinically (American Medical Association, AMA Department of Drugs, AMA Drug Evaluations. 3rd ed. PSG Publishing Co., Inc., 1977, 668).

For dextromethorphan, clinical symptoms in animals treated in various lethality studies include ataxia, convulsions or effect on seizure threshold (Arzneimittel-Forschung. Drug Research. Editio Cantor Verlag, 45: 1188, 1995). , rigidity (includes catalepsy), and dyspnea. Reduced weight gain was observed in pups whose mothers were dosed prior to mating to 2 weeks after delivery (Life Sciences. Pergamon Press Inc., 69:2439, 2001).

2.2 Pharmacologic activity

Guaifenesin: 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.

Dextromethorphan: For dextromethorphan hydrobromide, a cough suppressant, it is used for the relief of non-productive cough; it has a central action on the cough centre in the medulla. It is also an antagonist of *N*-methyl-D-aspartate (NMDA) receptors. Although structurally related to morphine, dextromethorphan has no classical analgesic properties and little sedative activity.

2.3 Nonclinical safety issues relevant to clinical use - none

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-620
Review number: 1
Sequence number/date/type of submission: 0000/June 30, 2003/original
0000/July 14, 2003/BP
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: Mucinex®DM: Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth Texas, 76155-2645

guaifenesin: [redacted]

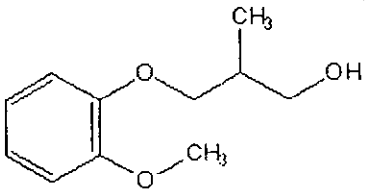
dextromethorphan HBr: [redacted]

Reviewer name: Gary P. Bond, Ph.D., DABT
Division name: Division of Allergy and Pulmonary Drug Products
HFD #: 570
Review completion date: January 14, 2004

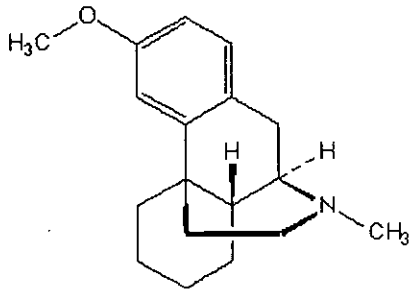
Drug:

Trade name: Mucinex® DM Extended Release Tablets
Generic name: Guaifenesin/Dextromethorphan HBr Extend Release (ER) Tablets
(600/30 mg and 1200/60 mg)
Code name: N/A
Chemical name: 1,2-propanediol,3-(2methoxyphenoxy) and morphinian, 3-methoxy-17-methyl-, (9α, 13α, 14α)-, hydrobromide, monohydrate
CAS registry number: 93-14-1 and 6700-34-1
Mole file number: not reported
Molecular formula/molecular weight: $C_{10}H_{14}O_4$ & $C_{18}H_{25}NO{\cdot}HBr{\cdot}H_2O$/198.22 and 370.32

Structure:



guaifenesin



dextromethorphan (·HBr·H2O for hydrobromide monohydrate)

Relevant ANDA/DMFs: IND 60,922 (guaifenesin/dextromethorphan HBr – 600/30 mg & 1200/60 mg)
NDA 21-282 (guaifenesin – 600 & 1200 mg)
NDA 19-801 (dextromethorphan)
[redacted] – guaifenesin
[redacted] dextromethorphan HBr

Drug class: guaifenesin - a glyceryl guaicolate

dextromethorphan HBr - a methyl morphine

Indication: 12-hour expectorant and antitussive for treating cold, cough, and allergy patients.

Clinical formulation: 600 mg guaifenesin/30 mg dextromethorphan HBr

Ingredient	**(mg/tablet)**
Guaifenesin	600.0
Dextromethorphan HBr	30.0
Microcrystalline cellulose	
Sodium starch glycolate	
Hypromellose	
Carbomer 934P	[redacted]
Magnesium stearate	
D&C Yellow #10 Aluminum Lake [redacted]	
Water, purified	
Total Weight	**765.2**

1 – removed during processing

Clinical formulation: 1200 mg guaifenesin/60 mg dextromethorphan HBr

Ingredient	(mg/tablet)
Guaifenesin	1200.0
Dextromethorphan HBr	60.0
Microcrystalline cellulose	
Sodium starch glycolate	
Hypromellose	
Carbomer 934P	
Magnesium stearate	
FD&C Blue #1 Aluminum Lake	
Water, purified	
Total Weight	**1530.4**

1 – removed during processing

The levels of all the excipients and flavoring agents are at acceptable levels.

Route of administration: oral tablets

Proposed use:

The sponsor intended to develop a novel extended release formulation of guaifenesin combined with dextromethorphan hydrobromide and subsequently obtain approval through a 505(b)(2) application. The proposed combination formulation is to be dosed twice daily in adults. The sponsor has also developed a half strength guaifenesin 600 mg/dextromethorphan hydrobromide 30 mg extended release combination tablet.

For the expectorant guaifenesin, the proposed daily doses do not exceed the recommended maximum daily doses in adults for immediate release guaifenesin tablets, which are contained in the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use monograph. The monograph provides for immediate release guaifenesin usage as follows: adults and children, 12 years and older: 200 to 400 mg every 4 hr, not to exceed 2400 mg in 24 hr (21CFR 341.18). Dextromethorphan hydrobromide is an antitussive available OTC (21 CFR 341.14(a)(4)). The recommended dose in adults and children 12 years of age and older is 10 to 20 mg every 4 hr or 30 mg every 6 to 8 hr, not to exceed 120 mg in 24 hr, or as directed by a doctor. The monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Anti-asthmatic Combination Drug Products (21 CFR 341.40(h)) allows for combination products of guaifenesin and dextromethorphan hydrobromide, if their respective daily dosage limits are maintained.

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

Studies reviewed within this submission: none

Studies not reviewed within this submission: none

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.

Recommendation: Approval of NDA 21-620

Labeling with basis for findings: None.

Signatures (optional):

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

Supervisor Signature Ching-Long Joseph Sun, Ph.D. Concurrence Yes x No ___

3.6 APPENDIX/ATTACHMENTS - NA

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
1/14/04 01:21:31 PM
PHARMACOLOGIST

Joseph Sun
1/14/04 01:28:23 PM
PHARMACOLOGIST
I concur.