

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-620

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-620	Efficacy Supplement Type -	Supplement Number
Drug: Mucinex DM (guaifenesin and dextromethorphan) Tablets		Applicant: Adams Laboratories
RPM: Colette Jackson	HFD-570	Phone # 301-827-9388
Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	Reference Listed Drug (NDA #, Drug name): 21-282 Mucinex	
❖ Application Classifications:		
• Review priority	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
• Chem class (NDAs only)		
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		
		April 30, 2004
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee	<input checked="" type="checkbox"/> Paid	
• User Fee waiver	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other	
• User Fee exception	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other	
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		
		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted	<input checked="" type="checkbox"/> Verified	
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)	
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	<input type="checkbox"/> Verified	

❖ Exclusivity (approvals only)	
• Exclusivity summary	4/30/04
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (x) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A
General Information	
❖ Actions	
• Proposed action	(x) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(x) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (x) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	3/1/04
• Applicant proposed	6/30/03 and 3/12/04
• Reviews	OTC on 2/17/04 and 3/23/04
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	9/4/03, 9/8/03, 2/2/04, 2/20/04 3/1/04 and 3/25/04
❖ Memoranda and Telecons	8/21/03
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	None
• Pre-NDA meeting (indicate date)	None
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

❖ Advisory Committee Meeting	No meeting held
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary/ Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Team Leader 4/19/04 Division Director 4/30/04,
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	8/29/03, and 4/19/04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	In 4/19/04 review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	4/30/04
❖ Statistical review(s) (indicate date for each review)	None needed
❖ Biopharmaceutical review(s) (indicate date for each review)	8/26/03 and 3/10/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	9/16/03
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	3/1/04
CMC Information	
❖ CMC review(s) (indicate date for each review)	8/26/03 and 4/15/04
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	8/26/03
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	Not needed
❖ Facilities inspection (provide EER report)	Date completed: 9/12/03 (x) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (x) Not yet requested
Preclinical/Pharm Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	1/14/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

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❖ Pediatric Page(separate page for each indication addressing status of all age groups)	4/30/04
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• Review & Environmental Impact Statement (indicate date of each review)	
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	Not needed
❖ Facilities inspection (provide EER report)	Date completed: 9/12/03 (x) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (x) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	1/14/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

13.0 PATENT INFORMATION

Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53

for

NDA #21-620

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Mucinex® DM Extended-Release Tablets
 - Active Ingredient(s): guaifenesin, dextromethorphan HBr
 - Strength(s): 600mg/30mg & 1200mg/60mg
 - Dosage Form: Extended-Release Tablet
 - Approval Date:
-

A. This information should be provided for each individual patent submitted.

U.S. Patent Number: 6,372,252 B1

Expiration Date: April 28, 2020

Type of Patent--Indicate all that apply:

1. Drug Substance (Active Ingredient) ___Y X N
2. Drug Product (Composition/Formulation) X Y ___N
3. Method of Use ___Y X N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: _____

Name of Patent Owner: Adams Laboratories, Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): Not Applicable

B. The following declaration statement is required by 21CFR 314.53. If any of the submitted patents have Composition/Formulation or Method of Use claims, it should be submitted for each patent that contains composition/formulation or method of use claims.

The undersigned declares that the above stated United States Patent Number 6,372,252 B1 covers the composition, formulation and/or method of use of Mucinex[®] products (Mucinex[®] DM) Extended-Release Tablets. This product is:

- currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

OR

- the subject of this application for which approval is being sought.)

Signed:



Date:

06/2/2003

Title:

Vice President, Development and Regulatory Affairs

Telephone Number: 817-786-1243

14.0 PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

Adams Laboratories, Inc. certifies to the best of their knowledge, there are no patents other than US 6,372,252B1 and four pending that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Adams Laboratories, Inc. currently has a patent pending on guaifenesin and dextromethorphan HBr for which patent information must be submitted according to 21 CFR314.53. Within 30 days of the date of issuance of the patent, Adams Laboratories, Inc. will submit to the FDA the required patent information.

 _____ Date 5/16/03
D. Jeffrey Keyser
Vice President,
Development and Regulatory Affairs

EXCLUSIVITY SUMMARY FOR NDA # 21-620 SUPPL # _____

Trade Name Mucinex DM (Extended Release Tablets)

Generic Name guaifenesin and dextromethorphan

Applicant Name Adams Respiratory Therapeutics (formerly Adams Laboratories) HFD # 570

Approval Date If Known April 29, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES / X / NO / ___ /

b) Is it an effectiveness supplement?
YES / ___ / NO / X /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / ___ / NO / X /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The application is based on the bioequivalence between Mucinex DM and reference guaifenesin and dextromethorphan drug products based on criteria established by the OTC monograph.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

_____ expires _____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X_/

If yes, NDA #_ . Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product. Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this

particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__ / NO /__ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / X / NO /__ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-282 Mucinex (quaifenesin) ER tablets

NDA# 18-658 Delsym (extended release suspension of dextromethorphan)

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant."

This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any

reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/! NO /___/ Explain: _____

Signature of Office/
Division Director

Date

Form OGD-011347 Revised 10/13/98

cc: Original NDA
Holovac

Division File

HFD-610 Mary Ann

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

/s/

Badrul Chowdhury
5/4/04 11:48:35 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # 21-620 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: June 30, 2003 Action Date: April 30, 2004

HFD 570 Trade and generic names/dosage form: Mucinex DM (guaifenesin and dextromethorphan)

Applicant: Adams Respiratory Therapeutics Therapeutic Class: 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Expectorant

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. 0 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. <12 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns for use of the extended release in ages <12.
- Adult studies ready for approval
- Formulation needed
- Other: There are liquid immediate-release formulations labeled for use in ≥ 2 years of age and for ages <2 the labeling recommends consulting a physician.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max Adult kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Antitussive

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. 0 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. <12 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns for use of the extended release in ages <12.
- Adult studies ready for approval
- Formulation needed
- Other: There are liquid immediate-release formulations labeled for use in ≥ 2 years of age and for ages <2 the labeling recommends consulting a physician.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max Adult kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 20-784
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

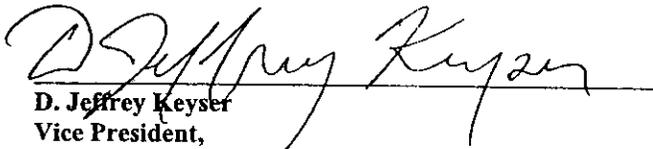
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Colette Jackson
4/28/04 02:30:03 PM

16.0 DEBARMENT CERTIFICATION

Adams Laboratories, Inc. certifies that it did not and will not use in any capacity the services of any person debarred under subsection 306(a) and 306(b) of the Federal Food, Drug and Cosmetic Act (21 USC 335a and 335b) in connection with this New Drug Application.



D. Jeffrey Keyser
Vice President,
Development and Regulatory Affairs

5/16/03

Date

19. FINANCIAL INFORMATION

In accordance with 21CFR, Part 54, Financial disclosure was collected for principal and subinvestigators listed on the signed FDA Form 1572 for all studies conducted in support of this New Drug Application.

List of investigators:

Dennis N. Morrison, D.O. – Principal Investigator

Subinvestigators:



Form FDA 3454 follows this cover page.

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

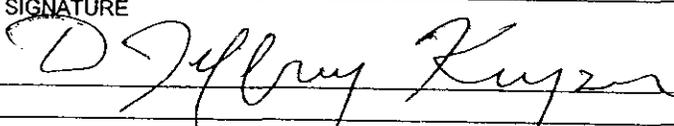
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Dennis N. Morrison, D.O.	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME D. Jeffrey Keyser	TITLE Vice President Development and Regulatory Affairs
FIRM / ORGANIZATION Adams Laboratories, Inc.	
SIGNATURE 	DATE 5/16/03

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DIVISION DIRECTOR'S MEMORANDUM

Date: April 28, 2004

To: NDA 21-620

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Mucinex DM (1200 mg guaifenesin and 60 mg dextromethorphan HBr, or 600 mg guaifenesin and 30 mg dextromethorphan HBr) extended-release bi-layer tablets

Applicant: Adams Respiratory Therapeutics

Administrative and Introduction

Adams Respiratory Therapeutics (previously called Adams Laboratories) submitted NDA 21-620 for Mucinex DM (guaifenesin and dextromethorphan HBr) extended-release bi-layer tablets as a 505(b)(2) application on June 30, 2003. The NDA was received by the Agency on June 30, 2003. The PDUFA due date on this application is April 30, 2004. The applicant requested approval of two dosage strengths: 1200 mg guaifenesin and 60 mg dextromethorphan HBr, and 600 mg guaifenesin and 30 dextromethorphan HBr. The product is intended to be marketed over-the-counter as an expectorant and cough suppressant for patients 12 years of age and older at a dose of one tablet (for higher strength tablets) or two tablets (for lower strength tablets) twice daily. Adams Respiratory Therapeutics has one related product approved for marketing in the United States. The product is Mucinex (guaifenesin) extended-release tablets (NDA 21-282). Mucinex and Mucinex DM have same dosages of guaifenesin in extended release formulations. Mucinex DM has the added ingredient dextromethorphan. Both guaifenesin and dextromethorphan are listed in the OTC monograph for cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter human use (21 CFR 341). The total daily doses of guaifenesin and dextromethorphan in the Mucinex DM tablets are within the total daily doses approved in the OTC monograph for ages 12 years and above (21 CFR 341.78 and 341.74). Therefore, no clinical efficacy or safety studies were required. The clinical program for this application consists of bioequivalence studies with supported safety data. The submitted data support approval of this application. There are no outstanding issues from any disciplines.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug product Mucinex DM contains active drug substances guaifenesin and dextromethorphan and a number of commonly used excipients. The DMFs associated with the manufacture of drug substances are adequate. The drug product is a bi-layer tablet, with a white immediate release layer and a colored modified release layer. The color of the modified release layer is light blue for the higher strength tablets and yellow

for the lower strength tablets. Both layers contain guaifenesin and dextromethorphan. The components of both strength tablets are identical and compositionally proportional. Mucinex DM will be packaged in _____ bottles containing 2 tablets to be distributed as physician samples or containing _____ for commercial sale. The drug product is manufactured at the Adams Laboratories manufacturing facility in Waco, Texas. All manufacturing sites related to this application have acceptable evaluation status.

There were some CMC issues particularly around friability of the tablet that were resolved during review of the application. There are also some minor deficiencies that will not impact the safety or efficacy of the drug product, which the applicant has agreed to resolve post-approval. These are discussed in detail in Dr. Place's excellent review. The CMC team has recommended an approval action on this application, and I concur with that recommendation.

Clinical Pharmacology and Biopharmaceutics, and Clinical

The applicant submitted results of six clinical pharmacology studies and a summary of safety data. Of the six clinical pharmacology studies four were conducted with the to-be-marketed formulation and were considered relevant to this NDA. The four clinical pharmacology studies were conducted in healthy male and female volunteers between the ages of 18 and 55 years. The studies were designed to show bioequivalence of Mucinex DM to the reference products after a single dose (Study 2002-08) and at steady state (Study 2002-10), to assess the effect of high fat high calorie diet on the absorption of guaifenesin and dextromethorphan from Mucinex DM tablets (Study 2002-12), and to assess the interaction between guaifenesin and dextromethorphan when administered as Mucinex DM tablets (Study 2001-15). Reference products used in the clinical pharmacology studies were extended release guaifenesin tablets (Mucinex) and immediate release dextromethorphan (Vicks 44 Cough Relief) in Studies 2002-08 and 2002-10, and immediate release dextromethorphan syrup (Benylin) in Study 2002-15. The higher dosage strength of Mucinex DM was used in all clinical pharmacology studies. The lower dosage strength was supported by in vitro dissolution profiles. The clinical pharmacology studies were reviewed in depth by the Office of Clinical Pharmacology and Biopharmaceutics (OCBP) Reviewer Dr. Kim, and all submitted studies and additional safety data were reviewed by Medical Officer Dr. Szema. The OCBP team concluded that the pharmacokinetic profile of Mucinex DM is sufficiently similar to the reference listed drugs to support approval, and I concur with that conclusion.

The C_{max} and AUC data from the four relevant studies are shown in Table 1. For the single dose and multiple dose bioequivalence studies the 90% CI were mostly within the accepted 80% to 125% bioequivalence limit. Values outside the 80% to 125% CI were for dextromethorphan, which is known to have high variability. The point estimates for these were generally close to unity and the differences were not large and not clinically relevant. The food effect study has shown that there was no effect of high fat high calorie meal on the absorption of guaifenesin and dextromethorphan from Mucinex DM tablets. The drug interaction study has shown that there was no interaction between guaifenesin and dextromethorphan when administered as Mucinex DM tablets.

Table 1. Ratio between test and reference products (test/reference) for log-transformed values of guaifenesin and dextromethorphan from various studies

	PK parameter	Guaifenesin		Dextromethorphan	
		Point estimate	90% CI	Point estimate	90% CI
Study 2002-08 (Single dose) *					
	Cmax	100	91.4-111	95.4	77.4-118
	AUC inf	92.5	97.9-97.5	87.8	76.3-101
Study 2002-10 (Steady state) *					
	Cmax	93	85.3-100	104	90.2-121
	AUC inf	96	91.1-101	101	87.6-116
Study 2002-12 (Food effect)					
	Cmax	96	82.2-100	121	107-136
	AUC inf	87	85-94.5	107	96.4-120
Study 2002-15 (Drug interaction) †					
	Cmax	97.3	88.7-107	97.6	110-153
	AUC inf	97	90.1-104	102	88.2-119
* Reference drugs: Mucinex (guaifenesin), Vicks (dextromethorphan) at 30 mg every 6 hours					
† Reference drugs: Mucinex (guaifenesin), Benylin (dextromethorphan) 30 mg every 6 hours					

Review of the safety data in the clinical pharmacology studies did not reveal any safety signal. Review of the literature and US AERS database do not raise any safety concerns.

The clinical pharmacology studies were conducted in subjects down to the age of 18 years, but the applicant is seeking approval down to the age of 12 years. This is acceptable because the pharmacokinetic parameter is not expected to be different in children between the ages of 12 and 18 years to that of subjects over 18 years. The safety is also not expected to be different in the 12 to 18 years age group.

One concern with Mucinex DM is the potential for dextromethorphan abuse since this drug product contains a large amount of dextromethorphan. This concern was considered during the review and consults were obtained from Controlled Substance Staff (HFD-009) and the Division of Drug Risk Assessment of the Office of Drug Safety (HFD-430). This Division and the consulting Divisions concluded that the concerns were not high enough to preclude approval. The total amount of dextromethorphan in Mucinex DM is not outside the range of already approved over-the-counter drugs. Both the immediate release and sustained release layers contain dextromethorphan and guaifenesin and the potential abuser cannot separate the two active ingredients. Furthermore, the formulation makes it likely that abusers will ingest sufficient amount of guaifenesin to cause stomach irritation prior to ingesting sufficient amount of dextromethorphan to cause the desired abuse effect. Nevertheless, the applicant agreed to monitor MedWatch for any potential signals of abuse. If a signal is detected the applicant will consider moving the drug product behind the pharmacy counter to deter individuals from purchasing large quantities at a single time.

Pharmacology and Toxicology

The applicant did not conduct any new preclinical studies for this application because the active components of Mucinex DM tablets are in the over-the-counter monographs.

Data Quality, Integrity, and Financial Disclosure

There was one study center and one analytical site for the four clinical pharmacology studies considered relevant to this NDA. DSI audited the study center. No serious deficiencies were noted, DSI recommended acceptance of the studies. During review of these studies no issues with data quality and integrity were noted. All studies were conducted in accordance with accepted ethical standards. No financial disclosure issues were present.

Pediatric Considerations

The applicant is proposing indication down to the age of 12 years and is not proposing to seek approval in patients below 12 years of age. This is acceptable because the fixed dose combination at the proposed dosage would not be suitable for children younger than 12 years of age. The lower age limit also conforms to the acceptable total daily doses in the OTC monograph. Immediate release formulations of both guaifenesin and dextromethorphan are available down to the youngest age group (age 2 years) recommended in the OTC monograph for these products (21 CFR 341.74 and 341.78).

Product Name

The trade name of Mucinex is approved and used by Adams Respiratory Therapeutics for the product line containing extended release formulations of guaifenesin. The suffix "DM" is acceptable addition to Mucinex that distinguish this product as containing dextromethorphan. The suffix "extended-release bi-layer tablets" is appropriate for this dosage form.

Labeling

Adam Respiratory Therapeutics submitted a product label that generally conforms to the over-the-counter product label for such products. The label has been reviewed by the Division of Over-the-Counter Drug Products and this Division. The Divisions and Adams Respiratory Therapeutics have agreed on a final labeling text.

Action

The clinical pharmacology data and clinical safety data are sufficient to support approval of both dosage strengths of Mucinex DM tablets for over-the-counter use as an expectorant and cough suppressant at a dose of one tablet (for higher strength tablets) or two tablets (for lower strength tablets) twice daily for patients down to the age of 12 years. Therefore, the action on this application will be APPROVAL.

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/s/

Badrul Chowdhury
4/28/04 10:04:24 AM
MEDICAL OFFICER

NDA 21-620

Mucinex TMDM (guaifenesin and dextromethorphan) Extended Release Tablets.

We are currently reviewing your submission dated June 30, 2003, and we have the following Chemistry, Manufacturing, and Control (CMC) comments:

The following comments relate to Chemistry, Manufacturing and Controls of the drug product.

1. Please clarify that the drug name is included on the package insert. The draft you submitted which was used for the CMC review did not list the drug name.
2. In your first annual report to this NDA, we ask that you agree to provide the following information:
 - a. Describe the composition, source and your quality controls for the _____ for both the MR and IR _____. Since it is in contact with the drug product formulations, verify that no residue or other impurities from the _____ contaminates the drug product.
 - b. At the end of the tableting of the drug product, Quality Control tests the tablets. In Table 24 (Vol. 1.2, page 57), for the friability test quantity you list "Report Average". This is not a quantity. Please modify this table entry. A rate (number of tablets per ½ hour) would be acceptable.
 - c. When you begin full scale manufacture, please report the scaled-up manufacture as outlined in the FDA Guidance entitled SUPAC-MR: Modified Release Solid Oral Dosage Forms (Released September 1997).
3. The dose uniformity specification is too broad. Although it complies with USP (905), Uniformity of Dosage Units, your data shows that you are capable of producing a more uniform product. We ask that you agree to propose a prior approval supplement within _____ to tighten your specifications accordingly to better reflect your manufacturing capability.

In order to utilize your response in this review, please respond to all issues by COB Friday April 02, 2004.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-827-9388.

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/s/

Colette Jackson
3/25/04 11:42:48 AM
CSO

sample tray labels. These final printed labels must be identical to the labels submitted on March 12, 2004.

2. Inform the sponsor that the word "NEW" must be deleted from the PDP six months after introduction into the market place.

Cazemiro R. Martin
IDS: Reg. Review Scientist

Concur: Marina Chang, R.Ph.
Team Leader

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/s/

Cazemiro Martin
3/23/04 01:39:35 PM
INTERDISCIPLINARY

Marina Chang
3/23/04 01:45:33 PM
INTERDISCIPLINARY

NDA 21-620

Mucinex TMDMD (guaifenesin and dextromethorphan) Extended Release Tablets.

We are currently reviewing your submission dated June 30, 2003, and we have the following comments:

1. For each study, specify whether the to-be-marketed product was utilized and in which treatment group.
2. In Study 2001-04, specify if the to-be-marketed formulation was used in any of the arms.
3. Clarify the following for Study 2001-15.
 - a. There is a discrepancy in the patient data listings and the study report. The demographic chart (vol 1.64, p. 488) indicates that Subject 23 was Caucasian while the study report (vol. 1.59, p. 12 and 20) states that Subject 23 was classified as "other". Clarify the ethnicity of Subject 23.
 - b. Subject 17, Period 1, Treatment B had taken dextromethorphan on the afternoon before dose day. Submit case reports for this patient to explain the circumstances for this situation.
4. Provide all data from the graph "Mean Steady-State Guaifenesin Plasma Concentration – Time Profiles", figure 3.5.1:2 (vol 1.1, p. 81)

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-827-9388.

NDA 21-620

Mucinex TMDM (guaifenesin and dextromethorphan) Extended Release Tablets.

We are currently reviewing your submission dated June 30, 2003, and we have the following comment:

Recently there were several media reports regarding the abuse of dextromethorphan (DM) by teenagers. These reports indicated that one over the counter (OTC) product in particular, Coricidin HBP Cough Cold, seems to be misused frequently. Coricidin HBP Cough Cold contains 4 mg chlorpheniramine and 30 mg DM in a tablet formulation. This product has the maximum content of DM in a tablet form and is available OTC.

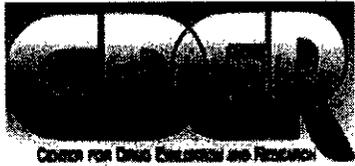
The two Mucinex DM Tablets submitted by your firm under NDA 21-620 contain 30 and 60 mg of DM, respectively. The Agency has concerns about DM abuse, especially by teenagers. The Agency wants to know whether your firm has had any concerns and/or discussions regarding the potential DM abuse of your product(s). Please state whether you have developed a risk-management plan in the event that these products are abused. If so, please submit your plans within 30 days of receipt of this correspondence.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-827-9388.

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/s/

Colette Jackson
2/2/04 10:00:52 AM
CSO



OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research • Food and Drug
Administration

SUBMISSION DATE(S):	June 30, 2003	RECEIVED DATE(S):	July 1, 2003
REVIEW DATE:			1/12/2004
NDA/SUBMISSION TYPE:			21-620
SPONSOR/CONTACT:			D. Jefferey Keyser Vice President Development & Regulatory Affairs Adams Laboratories, Inc. 14801 Sovereign Road Fort Worth, TX 76155-2645 (817) 786-1243
DRUG PRODUCT:			Mucinex® DM Extended-release Bi-layer Tablets
ACTIVE INGREDIENT:			Guaifenesin and dextromethorphen HBr 600/30 mg & 1200/60 mg
PHARMACOLOGICAL CATEGORY:			Expectorant and antitussive
LABELING SUBMITTED: (SKU)		Bottle labels:	600 mg/30 mg: 2, 20, 40 count 1200 mg/60 mg: 2, 10, 20 count
		Carton labels:	600 mg/30 mg: sample tray, 20, 40 count 1200 mg/60 mg: sample tray, 10, 20 count

BACKGROUND

NDA21-620 is a 505(b)(2) application that requests the regulatory approval for OTC marketing of Mucinex® DM Extended-release Bi-layer Tablets. Mucinex® DM is a combination drug product that contains two active ingredients, guaifenesin and dextromethorphen HBr (600 mg/30 mg and 1200 mg/60 mg). Guaifenesin, used as an expectorant, is under the regulation of the OTC monograph 21CFR341.18. Dextromethorphen HBr, used as an antitussive, is under the regulation of 21CFR341.14. Combination of guaifenesin and dextromethorphen is permitted in the OTC monograph 21CFR341.40(h).

Mucinex® DM builds upon the recent approval of Mucinex® (guaifenesin) 600 mg and 1200 mg extended release tablets, granted to Adams Laboratories in NDA 21-282. Mucinex® is currently the only extended release guaifenesin-containing drug product approved by the Agency.

Dextromethorphan HBr is an antitussive agent used in cough and cold medicines. It acts on the cough center in the medulla oblongata by raising the threshold for the cough reflex. The adult oral doses of dextromethorphan are 10 to 20 mg every 4 hours or 30 mg every 6 to 8 hours, not to exceed 120 mg in 24 hours. When taken in therapeutic doses, it is safe and effective.

However, abuses of dextromethorphan among teenagers and young adults have been reported in news media, magazines, journals and on the Internet. The FDA Drug Abuse Advisory Committee held two meetings in 1990 and 1992 to discuss a strategy for assessing the problem and identify possible solutions. However, no conclusive decisions were made from these meetings due to lack of sufficient data in the adverse events monitoring systems. The committee recommended that more studies were needed. Dextromethorphan abuses have also led to numerous congressional inquiries. The Agency is concerned with the abuse problem and is investigating possible mechanisms to reduce the abuse potential.

REVIEWER'S COMMENT

Reviewer comments are in italic and are bracketed. Reviewer recommended additions are identified by "redlining" and deletions are identified by "redlining and strike out."

I. Carton Label

The carton label of 600 mg/30 mg, 40-copunt product is selected for illustrative purpose. Other carton and samples tray labels should be identical with this label except dosage strength, NDC number, declaration of net quantity of contents, and "Drug Facts", where applicable, to be consistent with each individual product.

A. Principal Display Panel (PDP), Top and Side Panels (Excluding “Drug Facts” panel)

(i). 2-count sample trays

Physician Sample-Not to Be Sold

[The Agency encourages that this statement conspicuously appear on the PDP for clarity]

(ii). NEW

[This promotional flag on all SKU products must be removed from all panels six months after introduction of the products into the market place.]

(iii). Established Name

600 mg guaifenesin and 30 mg dextromethorphan HBr extended-release bi-layer tablet

[The Agency encourages the inclusion of the dosage form and the deletion of "per".]

(iv). 40 Extended-release Bi-layer Tablets

[Add “EXTENDED-RELEASE” to “BI-LAYER TABLETS” as part of the dosage form statement]

B. Drug Facts Panel

Drug Facts	
Active ingredients (in each extended-release bi-layer tablet)	Purpose
Guaifenesin 600 mg	Expectorant
Dextromethorphan HBr 30 mg	— (Cough suppressant)
<i>[There is no regulatory requirement to list both of the pharmacological categories for this ingredient. The agency encourages the use of “Cough suppressant” (i.e., the general pharmacological category or principal intended action) rather than “antitussive” (i.e., the medical term), because it is a more consumer friendly language.]</i>	
Guaifenesin 600 mg	Expectorant
<i>[According to 21CFR201.66(d)(6) the active ingredients shall be listed in alphabetical order]</i>	

Uses ■ helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs more productive

■ temporarily relieves:

- cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants
- ~~the intensity of coughing~~
- ~~to cough to help you get to sleep~~

[These changes are made to condense the statements and for clarity purpose]

■ ~~[This is not an indication statement,, therefore, should be deleted]~~

Warnings

Do not use

■ for children under 12 years of age

[This bulleted statement is not required by 21CFR341.74(c)(2) as annotated in the application. However, the reviewer suggests maintaining the statement for two reasons: (1). This statement exists in the approved Mucinex (guaifenesin) labels; (2). The size of the Mucinex DM tablets may cause choking, especially in children.]

■ if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains a MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have

- persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema
- cough accompanied by too much phlegm (mucus)

When using this product

■ do not use more than directed

■

Stop use and ask a doctor if

■ cough lasts more than ~~7~~ 7 days, come back, or occurs with a fever, rash, or persistent headache. These could be signs of a serious illness.

[These changes are consistent with the approved Mucinex (guaifenesin) labeling.]

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- do not crush, chew, or break tablet
- take with a full glass of water
- this product can be administered without regard for timing of meals
- adults and children 12 years and older: *[For the 600 mg/30 mg tablets]* one or two tablets every 12 hours; not more than 4 tablets in 24 hours
[For the 1200 mg/ 60 mg tablet] one tablet every 12 hours; not more than 2 tablets in 24 hours
- children under 12 years of age: do not use

Other information

- tamper evident: do not use if seal on bottle printed "SEALED FOR YOUR PROTECTION" is broken or missing
- store at 20-25°C (68-77°F)
- see bottom of bottle for lot code and expiration date

Inactive ingredients carbomer 934P, NF; FD&C blue #1 aluminum lake; hypromellose, USP; magnesium stearate, NF; microcrystalline cellulose, NF; sodium starch glycolate, NF

C. "Drug Facts" format and font specifications

[The format and font specifications for the "Drug Facts" label satisfy the requirements of 21 CFR 201.66 and are acceptable.]

II. Immediate Container Label**1. PDP**

600 mg guaifenesin and 30 mg dextromethorphan HBr extended-release bi-layer tablet

[The sponsor should include "Extended-release bi-layer" as part of the dosage form statement and delete the word " — "]

2. Drug Facts

[If the sponsor intends to include the Drug Facts title in the labeling of the immediate container label, the entire Drug Facts information must appear with the same standardized content and format as it appears on the outside carton label (i.e., as set forth in 21 CFR 201.66). We will reserve comments on these labels until the sponsor has an opportunity to respond to our comment. If the sponsor wants to include "Drug Facts" label, the same revisions that apply to the carton label are applicable on this immediate container labeling. In the final revision, the content and format must be identical to the carton label's "Drug Facts."]

III. Display Carton

[The sponsor should adopt all the relevant changes from the carton labels to its sample tray labels]

IV. Child-resistant Cap

[All Mucinex DM extended-release tablets will be packaged for commerce with child-resistant caps. This complies with the Consumer Product Safety Commission's regulation on child-resistant packaging for certain OTC drug products (66FR40111).]

RECOMMENDATIONS

1. Inform the sponsor to revise the carton and sample tray labels for the Mucinex DM products as follows and resubmit, prior to the PDUFA due date, for our review and comment:

- Principal display panel and other side panels:
 - Add "Extended-release bi-layer tablets" as part of the established name and delete the word ' _____'
 - Use "EXTENDED-RELEASE BI-LAYER TABLETS" instead of _____ to the declaration of net quantity of contents statement
- Revise the "Drug Facts" label per attached prototype.

2. Inform the sponsor to revise the immediate container labels for the 600 mg/30 mg (20 and 40-count) and 1200 mg/60 mg (10 and 20-count) extended-release bi-layer tablets as follows: If the "Drug Facts" label appears on the outside container or wrapper as required in 21 CFR 201.66, this information does not need to also appear on the immediate container label. However, if the sponsor chooses to use the "Drug Facts" label, the content, format, and graphical specifications must be in accordance with 21 CFR 201.66. In addition, revisions for the PDP on the carton labels apply to the container labels.

3. Inform the sponsor that the "New" flag on the principal display panel on all carton and container labels must be deleted six months after introduction into market-place.

4. **Project manager:** Please enclose the attached prototype "Drug Facts" label when providing labeling comments to the sponsor.

Jianming Li, PhD, MBA
Interdisciplinary Scientist

Marina Y. Chang, R.Ph
Team Leader concurrence

Attachment: Prototype "Drug Facts" Label

Prototype "Drug Facts" Label

Drug Facts

<i>Active ingredients (in each extended-release bi-layer tablet)</i>	<i>Purpose</i>
Dextromethorphan HBr 60 mg	Cough suppressant
Guaifenesin 1200 mg	Expectorant

Uses ■ helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs more productive

- temporarily relieves:
 - cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants
 - the intensity of coughing
 - the impulse to cough to help you get to sleep

Warnings

Do not use ■ for children under 12 years of age

- if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains a MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have

- persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema
- cough accompanied by too much phlegm (mucus)

When using this product

- do not use more than directed

Stop use and ask a doctor if

- cough last more than 7 days, come back, or occurs with fever, rash, or persistent headache. These could be signs of a serious illness.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- do not crush, chew, or break tablet
- take with a full glass of water
- this product can be administered without regard for timing of meals
- adults and children 12 years and older: [*For the 600 mg/30 mg tablets*] one or two tablets every 12 hours; not more than 4 tablets in 24 hours
[*For the 1200 mg/ 60 mg tablet*], one tablet every 12 hours; not more than 2 tablets in 24 hours
- children under 12 years of age: do not use

Other information

- tamper evident: do not use if seal on bottle printed "SEALED FOR YOUR PROTECTION" is broken or missing
- store at 20-25°C (68-77°F)
- see bottom of bottle for lot code and expiration date

Inactive ingredients carbomer 934P, NF; FD&C blue #1 aluminum lake; hypromellose, USP; magnesium stearate, NF; microcrystalline cellulose, NF; sodium starch glycolate, NF

*The sponsor should follow this Drug Facts label **in content only**. The font sizes for title, headings, subheadings, condensed text and other graphic features must be in accordance as set forth in 21 CFR 201.66.

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/s/

Jianming Li
2/17/04 03:25:54 PM
INTERDISCIPLINARY

Marina Chang
2/17/04 03:31:56 PM
INTERDISCIPLINARY

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		ODS POSTMARKETING SAFETY REVIEW	
TO: Charles Ganley, M.D., Director Division of Over-The-Counter Drug Products (HFD-560)		FROM: Lauren Lee, Pharm. D., Safety Evaluator Division of Drug Risk Evaluation (HFD-430)	ODS PID # D030502 November 10, 2003
DRUG (Est): Dextromethorphan		THERAPEUTIC CLASSIFICATION: OTC Cough and Cold	
<p>CONSULT REQUEST: Conduct a safety review update of dextromethorphan-containing products since November 13, 2000. The Office of Drug Safety conducted two safety reviews of dextromethorphan in 2000 for the Federal Bureau of Investigation that covered the time period from 1969 through November 13, 2000. The last review identified 103 unduplicated cases of drug abuse, dependence, addiction, non-accidental overdose, withdrawal syndrome, and tolerance. An updated safety review of dextromethorphan is being requested because Mucinex DM (NDA 21-620) is a product currently under review by DPADP (HFD-570) and DOTCDP (HFD-560), and contains dextromethorphan and guaifenesin.</p> <p>BACKGROUND: Another product containing dextromethorphan, Coricidin HBP, was the subject of a congressional inquiry in the past; on June 25, 2000, the Controlled Substance Staff found evidence that teenagers abused this drug.</p>			
<p>EXECUTIVE SUMMARY:</p> <p>In response to the request from the Division of Over-The-Counter Drug Products for information regarding dextromethorphan, the Adverse Event Reporting System (AERS) database was searched for reports submitted to the FDA since November 13, 2000, and the searches revealed a total of 1886 reports as of October 17, 2003. Nervous system disorders were reported in 1621 of 1886 reports, and psychiatric disorders were reported in 548 reports. Included in these reports were 71 unduplicated cases of drug abuse, overdose, and/or suicides; all were domestic cases.</p> <p>Drug overdose was reported in 67 of 71 cases, 18 of which were accidental overdoses (none involving children \leq 17 years). Abuse was explicitly mentioned in 42 cases, 13 of which mention that the abuser used the drug for euphoric effects [Coricidin (12), Robitussin (1)]. Five (5) cases reported suicide by ingestion of multiple drugs including dextromethorphan-containing products. Twenty-one (21) of 71 cases involved individuals under the age of 17, and the reported events were abuse (17), suicide (1), and overdose with intent unknown (3).</p> <p>In 22 of 71 cases reviewed, a dextromethorphan-containing product was listed as a single suspect drug. In the remaining 49 cases, dextromethorphan-containing products were reported as co-suspect drugs. Coricidin (dextromethorphan/chlorpheniramine) was the most commonly reported brand product (35 of 71) containing dextromethorphan, either taken alone or in conjunction with other drugs. Twenty-eight (28) cases reported concomitant use of oxycodone. In cases of multiple drug use and overdoses, the precise role of dextromethorphan was uncertain.</p> <p>Death was reported in 33 of 71 cases, 2 of which were not directly drug-related. Thirty-one (31) deaths involved multiple drug overdoses. Other significant outcomes included hospitalizations (8) and emergency room visits (6). Three deaths involved 13, 14, and 15 year-olds; fatalities caused by a gun wound, car accident, and multiple drug overdose, respectively.</p> <p>The findings of this review are consistent with the two previous ODS consults (PID#s D 000470/D000694). The above cases indicate that dextromethorphan-containing products continue to be used improperly by both children and adults. These products have been abused alone or in combination with other drugs, leading to serious outcomes.</p>			
<p>Relevant Product Labeling: The usual adult oral doses are 10 to 30 mg every 4 to 8 h to a maximum of 120 mg/day; pediatric oral doses are age-dependent and are 5 to 15 mg every 4 to 8 h for children aged 6 to 12 years to a maximum of 60 mg/day, and 2.5 to 7.5 mg every 4 to 8 h to a maximum of 30 mg for children aged 2 to 6 years.</p> <p>Other Drug Information: Dextromethorphan is the methylated dextro-rotatory analogue of levorphanol. It acts on the cough center in the medulla oblongata, raising the threshold for the cough reflex. Dextromethorphan is rapidly metabolized to an active metabolite, dextroprophan, which blocks the N-methyl-D-aspartate receptor similar to phencyclidine. Massive overdosage with dextromethorphan may result in respiratory depression, excitation, confusion, toxic psychosis, and hallucinations.¹</p>			
Search Date: 10/17/03		Search Type(s): AERS database	
<p>Search Criteria:</p> <p>Drug names: dextromethorphan (generic-active ingredient), Coricidin (brand), Mucinex (brand)</p> <p>Adverse Events:</p> <ol style="list-style-type: none"> All adverse event reports in the database linked to dextromethorphan as of 10/17/03. All adverse event reports linked to dextromethorphan received between 11/13/00 and 10/17/03. Reports involving drug dependence, addiction, abuse, and overdoses. <p>specific search terms include: addiction (PT), drug and chemical abuse (HLT), drug dependence (PT), drug tolerance (PT), drug tolerance increased (PT), drug withdrawal convulsions (PT), drug withdrawal headache (PT), drug withdrawal syndrome (PT), drug withdrawal syndrome neonatal (PT), overdoses (HLT), polysubstance abuse (PT), polysubstance dependence (PT), prescribed overdose (PT), tachyphylaxis (PT), and withdrawal arrhythmia (PT)].</p>			

Search Results:

Searches in the AERS database revealed a total of 2561 adverse event reports involving dextromethorphan as of October 17, 2003. Between November 13, 2000 and October 17, 2003, 1886 (of 2561) adverse event reports were received. Nervous system disorders were described in 1621 of 1886 reports, and in 548 reports, psychiatric disorders were described. These reports may include duplicate cases. The 10 most commonly reported adverse events were as follows: CVA (1187), injury (798), neurological disorder NOS (520), myocardial infarction (464), pain (435), blood pressure increased (355), supraventricular arrhythmia (324), anxiety (307), hypertension (207), and anhedonia (177).

The AERS searches for cases involving drug abuse, dependence, addiction, overdose, withdrawal syndrome, and tolerance revealed 87 cases. These cases were individually reviewed. Sixteen (16) of 87 reports were excluded from further analysis based on the following:

- Five reports were determined to be duplicates.
- Four cases were excluded because the reported adverse events were directly related to methadone, PPA, Tylenol, and respectively.
- In three cases, the adverse event was not clearly identified.
- In two cases, dextromethorphan was not taken.
- One case involved a medication error; a "cardiac event" was reported in a 4 month-old infant after a drug overdose (Bromfed DM). A dispensing error was reported.
- In one case, the reported event was not temporally related to dextromethorphan.

Of the remaining 71 cases of drug abuse, overdose, and/or suicide, the following findings were noted:

- The ages of the individuals ranged from 12 to 65 years. The median age was 22 years. This information was not available in 8 cases. Twenty-one reports involved individuals younger than 18 years of age.
- Gender distribution was females -24, males -45, and not reported - 2.
- All were US cases.
- Abuse was explicitly mentioned in 42 cases, 13 of which mention that the abuser used the drug for euphoric effects [Coricidin (12), Robitussin (1)].
- Drug overdose was reported in 67 cases, 18 of which were accidental overdoses (none involving children). The intent of the overdose was not provided in the majority of the cases.
- Twenty-one (21) of 71 cases involved individuals under the age of 17, and the reported events were abuse (17), suicide (1), and overdose with intent unknown (3).
- In 22 of 71 cases reviewed, a dextromethorphan-containing product was listed as a single suspect drug. In the remaining 49 cases, dextromethorphan-containing products were reported as co-suspect drugs among numerous others. Coricidin (dextromethorphan/chlorpheniramine) was the most commonly reported brand product (35 of 71) containing dextromethorphan, either taken alone or in conjunction with other drugs, such as alcohol, cocaine, heroine, marijuana, opiate, Robitussin, and other unspecified drugs. In one case, Coricidin was crushed for intranasal use by a 22 year-old male. In these particular cases of abuse/overdose involving Coricidin, the reported symptoms/events included aggression, chest pain, collapse, difficulty walking/breathing, dry mouth, hallucinations, headache, increased heart rate/blood pressure, muscle spasm, mydriasis, nausea, numbness, slurred speech, and sweating. Administered doses were available in 27 of 35 cases and ranged from 150 mg to 1200 mg (5-40 tablets) with the median dose of 360 mg. Twenty-eight (28) of 71 cases reported concomitant use of oxycodone, of which many were received in response to an inquiry from _____ requesting copies of autopsy and toxicological reports on media reported deaths from medical examiners. Mucinex was not named in any of the reports. In all cases of multiple drug use and overdoses, the precise role of dextromethorphan was uncertain.
- Death was reported in 33 cases, 2 of which were not directly drug-related. The remaining 31 cases involved multiple drug overdoses. Five cases reported suicide by ingestion of multiple drugs including dextromethorphan-containing products. In these cases, the ingested doses of dextromethorphan were unknown, and therefore, its role in the outcome was uncertain. Three deaths involved 13, 14, and 15 year-olds; fatalities caused by a gun wound, car accident, and multiple drug overdose, respectively. Other significant outcomes included hospitalizations (8) and emergency room visits (6).

Discussion / Conclusions:

Dextromethorphan hydrobromide is an antitussive agent used in cough and cold preparations, many of which are OTC products. Although dextromethorphan does not cause physical addiction, strong psychological dependence is reported in literature (see references). Dextromethorphan-containing products may also contain alcohol, which may contribute to the abuse of these drugs.

Seventy-one U.S. cases reported drug abuse and/or overdoses in individuals taking dextromethorphan-containing products, either alone or in combination with other drugs. Thirteen reports explicitly mentioned abusing the drug for euphoric effects. Twenty-one cases involved individuals under the age of 17. In the majority of the cases, dextromethorphan-containing products were reported as co-suspect drugs. Coricidin (dextromethorphan/chlorpheniramine) was the most commonly reported brand product (35 of 71) containing dextromethorphan, either taken alone or in conjunction with other drugs. Twenty-eight cases reported concomitant use of oxycodone. In cases of multiple drug use and overdoses, the precise role of dextromethorphan was uncertain. Significant outcomes included 31

deaths related to multiple drug overdoses (of which 5 were suicides), 8 hospitalizations, and 6 emergency room visits.

The findings of this review are consistent with the two previous ODS consults (PID#s D000470/D000694). The above cases indicate that dextromethorphan-containing products continue to be used improperly by both children and adults. These products have been used alone or in combination with other drugs, leading to serious outcomes.

References: (not all inclusive)

1. Ben JL, Peck R. Dextromethorphan. An overview of safety issues. Drug Safety 1992 ; 7(3):190-199.
2. Buss WF, Reynolds MS. Dextromethorphan abuse potential. DRUGDEX, Drug Consults 12/95.
3. Bornstein S, Czermak M & Postel J. A case of intentional drug poisoning with dextromethorphan hydrobromide. Ann Med Psychol 1968; 1:447-451.
4. Degkwitz R: Dextromethorphan (Romilor) als rauschmittel. Nervenarzt 1964; 35:412.
5. Dodds A & Revai E: Toxic psychosis due to dextromethorphan. Med J Aust 1967; 2:231.
6. Fleming PM. Dependence on dextromethorphan hydrobromide. Br Med J 1986; 293:597.
7. Helfer J & Kim OM. Psychoactive abuse potential of Robitussin-DM (letter). Am J Psychiatry 1990; 147:672-673.
8. Isabell H & Fraser HF. Actions and addiction liabilities of dromoran derivatives in man. J Pharmacol Exp Ther 1953; 107:524-530.
9. Darboe MN. Abuse of dextromethorphan-based cough syrup as a substitute for licit and illicit drugs: A theoretical framework. Adolescence 1996; 31 (121): 239-44.
10. Darboe MN, Keenan GR, Richards TK. The abuse of dextromethorphan-based cough syrup: A pilot study of the community of Waynesboro, Pennsylvania. Adolescence 1996; 31 (123): 633-44.
11. Marsh LD, Key JD, Spratt E. Bulimia and dextromethorphan abuse. A case study. J Subst Abuse Treat 1997; 14 (4): 373-6.
12. Schultz S. Turning to anything, just to get that high. A cough syrup ingredient is a popular drug [news]. US News World Rep 2000 Jun 5; 128(22): 60.
13. Price LH, Lebel J. Dextromethorphan-induced psychosis [letter]. Am J Psychiatry 2000; 157(2): 304.

Reviewer's Signature / Date:

Lauren Lee, Pharm.D. Signed 11-10-03

Team Leader's Signature / Date:

Claudia Karwoski, Pharm.D. Signed 11-13-03

Acting Division Director Signature / Date:

Mark Avigan, M.D.

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/s/

Lauren Lee
11/14/03 03:10:48 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
11/14/03 04:59:40 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: August 27, 2003

To: Badrul A. Chowdhury, M.D., Director
Division of Pulmonary Drug Products (HFD-570)

Through: Deborah B. Leiderman, M.D., Director
Michael Klein, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

From: James Hunter, R.Ph., Senior Program Manager
Controlled Substance Staff (HFD-009)

Subject: Consultation for NDA Filing Meeting (8-15-03):
NDA 21-620
Mucinex DM (Guaifenesin and Dextromethorphan hydrobromide)
For Management of the Symptoms of Coughs and Colds
Sponsor: Adams Laboratories, Inc.

Background

Mucinex DM (guaifenesin and dextromethorphan hydrobromide) is a noncontrolled extended-release oral tablet intended for twice daily administration for management of the symptoms of coughs and colds. Dextromethorphan, as an ingredient in an OTC drug product, is specifically excluded from scheduling as a controlled substance under 21 USC 811(g)(2) of the Controlled Substances Act.

The sponsor is seeking approval under 505 (b)(2) to market two dosage strengths, 600mg of guaifenesin with 30mg of dextromethorphan, and 1200mg of guaifenesin with 60mg of dextromethorphan. The total daily dose of guaifenesin and dextromethorphan in the highest dosage strength of Mucinex DM administered twice a day is within the dosage limits provided for in OTC monograph 21 CFR 341.40(h). There are no tablet formulations of guaifenesin with dextromethorphan currently marketed in the US. Consultation from CSS was requested regarding the abuse potential of the drug product and the adequacy of the information in the NDA for filing. CSS views were sought on the history of abuse of dextromethorphan products.

Conclusions

CSS recommended that the Sponsor provide a complete update of the information on abuse of dextromethorphan. Additionally, the Sponsor should describe how the risks of abuse of the product will be managed.

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/s/

James Hunter
9/15/03 11:33:50 AM
CSO

Michael Klein
9/15/03 12:42:01 PM
CHEMIST

Deborah Leiderman
9/16/03 03:08:21 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-620

Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth, TX 76155-2645

Attention: D. Jeffrey Keyser
V.P., Development and Regulatory Affairs

Dear Mr. Keyser

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Mucinex TMDM (guaifenesin and dextromethorphan) Extended Release Tablets

Review Priority Classification: Standard (S)

Date of Application: June 30, 2003

Date of Receipt: June 30, 2003

Our Reference Number: NDA 21-620

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 29, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 30, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/ Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-620

Page 2

If you have any questions, call Colette Jackson, Project Manager, at (301) 827-5584.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Colette Jackson
9/8/03 10:31:12 AM
Signed for S. Barnes.

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: August 27, 2003

To: Badrul A. Chowdhury, M.D., Director
Division of Pulmonary Drug Products (HFD-570)

Through: Deborah B. Leiderman, M.D., Director
Michael Klein, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

From: James Hunter, R.Ph., Senior Program Manager
Controlled Substance Staff (HFD-009)

Subject: Consultation for NDA Filing Meeting (8-15-03):
NDA 21-620
Mucinex DM (Guaifenesin and Dextromethorphan hydrobromide)
For Management of the Symptoms of Coughs and Colds
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The sponsor is seeking approval under 505 (b)(2) to market two dosage strengths, 600mg of guaifenesin with 30mg of dextromethorphan, and 1200mg of guaifenesin with 60mg of dextromethorphan. The total daily dose of guaifenesin and dextromethorphan in the highest dosage strength of Mucinex DM administered twice a day is within the dosage limits provided for in OTC monograph 21 CFR 341.40(h). There are no tablet formulations of guaifenesin with dextromethorphan currently marketed in the US. Consultation from CSS was requested regarding the abuse potential of the drug product and the adequacy of the information in the NDA for filing. CSS views were sought on the history of abuse of dextromethorphan products.

Conclusions

CSS recommended that the Sponsor provide a complete update of the information on abuse of dextromethorphan. Additionally, the Sponsor should describe how the risks of abuse of the product will be managed.



FILING REVIEW LETTER

NDA 21-620

Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth, TX 76155-2645

Attention: D. Jeffrey Keyser
V.P., Development and Regulatory Affairs

Dear Mr. Keyser:

Please refer to your June 30, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mucinex TMDM (guaifenesin and dextromethorphan) Extended Release Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 29, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. The 90% CI for C_{max} and AUC comparison for dextromethorphan in pivotal BE study (Study 2002-08) were outside the BE range of 80 to 125%.
2. The C_{min} for guaifenesin is significantly lower following administration of Mucinex DM tablets compared to Mucinex tablets.
3. The biobatch size used in Studies 2001-15, 2002-08 and 2002-10 are of commercial size (Scale Up), therefore, additional dissolution and stability data may need to be submitted when you produce the planned commercial batch of tablets.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Please include the appropriate financial disclosure forms from the primary investigator and 3 sub-investigators which were not attached in this submission.

2. You identified 19 articles pertaining to guaifenesin and 18 articles for dextromethorphan which support the prescribing precautions for these two drug products. Submit copies of these articles cited in Vol. 1.46, pages 181-182 and Vol. 1.47, pages 140-141, with the exception of the following articles:

From Volume 1.46, pages 181:

DHHS, FDA (1989) OTC monograph
Assimos et al. (1999)

From Volume 1.47, pages 140

DHHS, FDA (1989) OTC monograph
Bern et al. (19920)
Di Marco et al. (2002)
Schadel et al. (1995)

3. Summarize information regarding guaifenesin and dextromethorphan gleaned from your literature review of the above articles.
4. Provide safety information and a more detailed literature review regarding intentional abuse of dextromethorphan.
5. You have provided a listing of adverse events that you identified in the AERS database. Provide a tabular summary of the frequencies of these adverse events and a narrative analysis and conclusions based on this summary.
6. Please provide a step-by-step explanation of the friability test method (Volume 1.6, pages 94-95). This description should include a sample calculation for each dosage strength, along with a detailed description of any steps not specifically outlined in USP <1216>.
7. _____ real-time stability data should be submitted when the data are available.
8. Provide a brief description of the preparation, composition, and properties of the directly compressible guaifenesin (guaifenesin DC _____).
9. Describe the improvements and/or changes addressed in any ongoing optimization batches (Vol. 1.3, page 114).
10. Provide further detail regarding the _____ process leading to the clinical batches CB00-03 and CB00-04. This description should include the timing of the addition of _____ as well as the reported _____ in the modified release (MR) layer (Vol. 1.3, page 116).
11. The batch 12LB-33 is mentioned twice in the Development History Report (Appendix 4.1.3.10, pages 117 and 119). Please confirm that both mentions of 12LB-33 refer to

an identical manufacture and formulation. If any differences exist in manufacture or formulation for the two noted references, they should be clearly noted and described.

12. Further detail regarding the of batches PB01-H30 and 12LB-33 is requested. A detailed description of the process for both batches, including the timing of the addition of , should be provided.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Colette Jackson, Project Manager, at (301) 827-5584.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
9/4/03 05:11:52 PM

Record of Telephone Conversation

Date: August 19, 2003

Application Number: NDA /21-620/Mucinex DM/Adams Laboratories

Between:

Name: D. Jeffrey, Keyser, V.P. Development and Regulatory Affairs
Representing: Adams Laboratories

AND

Name: Sarah Pope, Ph.D.
Office of Pharmaceutical Science
Representing: Division of New Drug Chemistry II

Akilah Green, Project Manager
Representing: Division of Pulmonary and Allergy Drug Products

SUBJECT: Request for additional information regarding the developmental history of the drug product.

Dr. Pope requested that Adams Laboratories provide the Division with the number of batches reported in the developmental history located in Appendix 4.1.3.10 in tabular form. In addition, Dr. Pope requested the following information:

1. The batch numbers for all of the batches Adams Labs is reporting.
2. The formulation for each batch. This includes the amount of each drug substance in both the modified and immediate release layers.
3. Indicate which batches were used in each reported clinical study.
4. Provide information on any variations in manufacturing with those formulations and the to be marketed formulations.
5. Specify the batches that were used in stability studies/testing. Please provide this in the tabular format mentioned above.

Mr. Keyser noted that generally there are ~~1~~ different lots of the to be marketed formulation and they are put up on stability. PB01H30A is a lot of the to be marketed formulation used in clinical trials. PB01H43A is a lot of the to be marketed formulation that is up on stability. PB01H44A is also a lot of the to be marketed formulation that is up on stability. The lot numbers are at the back end. They have packaging runs on the same bottle of ~~1~~ An A that is not followed by a number is the first run. An A

followed by a 2 is the second run on the same lot. In this instance, it has the same packaging formulation. Dr. Pope requested that Mr. Keyser include this information in his submission.

Mr. Keyser agreed to submit the requested information within one week.

Akilah Green
Regulatory Project Manager

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

/s/

Akilah Green
8/21/03 01:41:05 PM
CSO

NDA FILEABILITY CHECKLIST

NDA Number: 21-620

Applicant: Adams Laboratories, Inc.

Stamp Date: 02-JUL-2003

Drug Name: Mucinex DM Extended-Release Tablets

Guaifenesin/dextromethorphan HBr, 600/30 mg and 1200/60 mg

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	<i>Parameter</i>	<i>Yes</i>	<i>No</i>	<i>Comment</i>
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		Drug substance manufacture is referenced to DMFs (dextromethorphan) and DMF (guaifenesin).
5	Is a statement provided that all facilities are ready for GMP inspection?		√	This statement has been requested, and will be provided by the Sponsor.
6	Has an environmental assessment report or categorical exclusion been provided?	√		Reference to CFR 25.31(a) – the Sponsor has filed a claim for categorical exclusion.
7	Does the section contain controls for the drug substance?	√		See DMFs
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?		√	Additional data should be submitted when available – see filing comments.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has an investigational formulations section been provided?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?		√	Not necessary, since this is a solid oral dosage form (tablet).

Review Chemist: Sarah C. Pope, Ph.D.

Date: 25-AUG-2003

Team Leader: Guirag Poochikian, Ph.D.

Date: 25-AUG-2003

Original NDA 21-620
HFD-570/Division File
HFD-570/G. Poochikian/S. Pope
HFD-570/C. Jackson

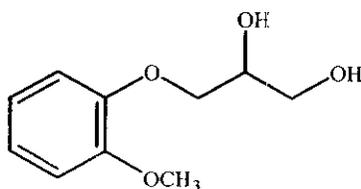
Have all DMF References been Identified?

<i>DMF Number</i>	<i>DMF Holder</i>	<i>Description</i>	<i>LOA Included</i>	<i>Status</i>
		Guafenesin	Yes	Reviewed by Dr. J. Salemme (adequate) on 20-MAY-2003
			Yes	Under review
			Yes	Under review
			Yes	Under review
			Yes	Under review
			Yes	Under review

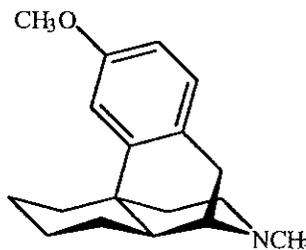
Drug Substance

Guaifenesin is a well-known expectorant, and was recently detailed in the Sponsor's NDA 21-282 for the Mucinex® (guaifenesin) extended release tablet. Structurally, guaifenesin possesses a glyceryl ether skeleton, incorporating a 1,2-propanediol chain with an o-methoxy phenoxy moiety through the ether linkage. The Sponsor has referenced DMF i. for all Chemistry, Manufacturing and Controls information for the guaifenesin drug substance. This DMF was recently reviewed by Dr. J. Salemme (20-MAY-2003), and was determined to be adequate in support of NDA 21-585.

Dextromethorphan is present as a hydrobromide salt/monohydrate (dextromethorphan HBr:H₂O), and is used as a cough suppressant. The chemical structure includes a bridged system, containing three fused six-membered rings and a methoxyphenyl moiety. DMF is referenced for all Chemistry, Manufacturing and Controls information for the dextromethorphan drug substance. This DMF is currently under review.



Guaifenesin (C₁₀H₁₄O₄)
MW = 198.22 g/mole



Dextromethorphan (C₁₈H₂₅NO)
MW = 370.32 g/mole

Drug Product

Mucinex® DM (guaifenesin/dextromethorphan HBr) extended release tablets are designed as a line extension to the recently approved Mucinex 600 mg and 1200 mg tablets (NDA 21-282, approved 12-JUL-2002). Mucinex® DM tablets are proposed in two dosage strengths, 1200/60 and 600/30 mg guaifenesin/dextromethorphan HBr.

Mucinex® DM tablets are manufactured as bi-layer tablets with both immediate and modified release layers, each containing the two drug substances. With the exception of dosage strength, the components of the immediate release layers are identical for the two dosage strengths. The modified release layers are also identical in composition based on dosage strengths, and differ only in color.

Mucinex® DM tablets will be manufactured, packaged, tested and stored for stability at the following facility:

Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth, TX 76155
USA

Alternate packaging sites are the following:

Mucinex® DM tablets may also be stored on stability at the following facility:

Photostability storage and testing may be done at the following facility:

Mucinex® DM tablets are manufactured through the compression of an immediate release layer and a modified release layer. The layers are _____ separately, and are then compressed together to produce the single tablet. The _____ and _____ are identical for both dosage strengths. The manufacturing process produces _____ tablets/batch for the higher dosage strength, and _____ tablets/batch for the lower dosage strength.

Component	Mg/tablet (1200/60 mg)	Mg/tablet (600/30 mg)
Guaifenesin	1200.0	600.0
Dextromethorphan HBr	60.0	30.0
Microcrystalline cellulose		
Sodium starch glycolate		
Hypromellose		
Carbomer 934P		
Magnesium stearate		
FD&C Blue #1 aluminum lake		
D&C Yellow #10 Aluminum Lake		
Water, purified		
Total weight (mg)	1530.4	765.2

Release specifications for Mucinex® DM include methods and criteria for description, identification of guaifenesin via HPLC and _____ identification of dextromethorphan via HPLC and TLC, average tablet weight, average tablet thickness, average tablet hardness, friability, _____ dose uniformity, assay for each drug substance, degradation products (guaifenesin) _____ unspecified impurities, total degradation and dissolution for both drug substances.

Once manufactured, Mucinex® DM tablets will be packaged for commerce in (10-count, 20-count, and 40-count) bottles. Physician's samples will be packaged in (2-count) bottles.

1200/60 mg dosage strength	600/30 mg dosage strength
2-count bottle (physician sample)	2-count bottle (physician sample)
10-count bottle	20-count bottle
20-count bottle	40-count bottle

The Sponsor has provided up to of real-time stability data, of accelerated data, and photostability testing data, obtained for three batches of each dosage strength. For the lower dosage strength, each of the three stability batches contained tablets. For the higher dosage strength, one of the three stability batches contained of proposed production scale) tablets. The other two stability batches contained tablets/each. Each stability batch was packaged in both and bottles.

The Sponsor has proposed a expiry (controlled room temperature) based on the provided stability data.

In a 19-AUG-2003 teleconference, the Agency requested a tabulation of the clinical and stability formulations, indicating the use of the to-be-marketed formulation in both clinical and stability protocols. In a fax recieved on 25-AUG-2003, the Sponsor provided the requested tabulation. This tabulation has been formally submitted as a minor CMC amendment to NDA 21-620 (document date 26-AUG-2003).

**Appears This Way
On Original**

Comments (non-filing review issues)

1. Please provide a step-by-step explanation of the friability test method (Volume 1.6, pages 94-95). This description should include a sample calculation for each dosage strength, along with a detailed description of any steps not specifically outlined in USP <1216>.
2. ██████████ real-time stability data should be submitted when the data are available.
3. Provide a brief description of the preparation, composition, and properties of the directly compressible guaifenesin (guaifenesin DC ██████████).
4. Describe the improvements and/or changes addressed in any ongoing optimization batches (Vol. 1.3, page 114).
5. Provide further detail regarding the ██████████ process leading to the clinical batches CB00-03 and CB00-04. This description should include the timing of the addition of ██████████, as well as the reported "██████████" in the modified release (MR) layer (Vol. 1.3, page 116).
6. The batch 12LB-33 is mentioned twice in the Development History Report (Appendix 4.1.3.10, pages 117 and 119). Please confirm that both mentions of 12LB-33 refer to an identical manufacture and formulation. If any differences exist in manufacture or formulation for the two noted references, they should be clearly noted and described.
7. Further detail regarding the ██████████ of batches PB01-H30 and 12LB-33 is requested. A detailed description of the ██████████ process for both batches, including the timing of the addition of ██████████, should be provided.

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

/s/

Sarah Pope
8/26/03 02:08:42 PM
CHEMIST

Guiragos Poochikian
8/26/03 02:18:47 PM
CHEMIST

REQUEST FOR CONSULTATION

To (Division/Office):

Ms. Claudia Karwoski, HFD-430

Division of Drug Risk Evaluation (OPSS)

FROM:

Leah Cutter, PM HFD-560

Marina Chang, IDS Team Leader HFD-560

DATE
8/8/03

IND NO.

NDA NO.

TYPE OF DOCUMENT
Request for FDA feedback

DATE OF DOCUMENT

NAME OF DRUG
Dextromethorphan

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
OTC Cough and Cold

DESIRED COMPLETION DATE
9/8/03

NAME OF FIRM: NA

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|---|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input checked="" type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please conduct a safety update review of dextromethorphan-containing products since November 13, 2000. Mucinex DM (NDA 21-620) is a product currently under review by HFD 570 and HFD 560. It contains guaifenesin and dextromethorphan and the sponsor wants to market it in 2 different concentrations:

guaifenesin 600mg/dextromethorphan 30 mg

guaifenesin 1200 mg/dextromethorphan 60 mg

Your division conducted a safety evaluation of dextromethorphan for the Federal Bureau of Investigation that covered the time period from 1969 through November 13, 2000 (Attachment 1). On June 25, 2002 the Controlled Substance Staff found evidence that teenagers abused Coricidin HBP, a product containing dextromethorphan hydrobromide (Attachment 2). Coricidin HBP has been the subject of congressional inquiry (Attachment 3).

We have concerns about the abuse potential for NDA 21-620 and wonder if the formulation relates to abuse potential.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		OPDRA POSTMARKETING SAFETY REVIEW	
TO: Patrick J. Donnelly, Supervisory Special Agent Federal Bureau of Investigation 26 Federal Plaza New York, NY 10278		FROM: DDRE I (HFD-430) Joyce Weaver, Pharm D. Safety Evaluator	OPDRA PID # D000694 November 19, 2000
DATE REQUESTED: 11/09/2000	REQUESTOR/Phone #:		
DATE RECEIVED: 11/09/2000	Brian Murphy, FBI Squad C-11 212-384-3290		
DRUG (Est): Dextromethorphan	NDA/IND # NA	SPONSOR: NA	
DRUG NAME (Trade): numerous products		THERAPEUTIC CLASSIFICATION: OTC Cough and Cold	
EVENT: Adverse events involving dextromethorphan			
Executive Summary:			
<p>In response to your request for information regarding dextromethorphan, we searched the FDA's Adverse Event Reporting System (AERS) and Spontaneous Reporting System (SRS) databases for reports submitted to the FDA since 1969. Before interpreting any of the information in this document it is important to consider that for any given report, there is no certainty that the suspect drug is responsible for the event, or that the report fully describes the event. Unless there is reason to question the report, or a need to obtain additional detail, the reports are accepted at face value.</p>			
<p>Our database contains a total of 616 reports of adverse events for dextromethorphan as of November 13, 2000. In 226 of the total 616 reports in the database, a central nervous system (CNS) effect was reported and in 130 reports a psychiatric effect was reported. Included in these reports are 103 unduplicated cases of drug abuse, dependence, addiction, non-accidental overdose, withdrawal syndrome, and tolerance.</p>			
<p>In general the 103 reports did not indicate that the individuals used the product to get "high". Of the 103 reports reviewed, 27 specifically mentioned drug abuse, dependence or addiction. Of all reports, there were 35 in individuals \leq 17 years old. The majority of reports were coded as overdose, overdose intent, or non-accidental overdose. However it is not clear whether these overdoses were with the intent to get "high" or to commit suicide. Ten reports received in 2000 described non-accidental overdose in children 13 to 17 years of age. Four of the reports received in 2000 involved the purchase of dextromethorphan in powder form by children from an internet web site.</p>			
<p>Approximately half of the 103 reports were foreign mostly from Sweden and Switzerland. Many of the domestic overdose reports involved individuals who took Nyquil either in a possible suicide attempt with another acetaminophen product or as an accidental overdose. We cannot rule out however that the individuals were not consuming Nyquil for either the dextromethorphan or the alcohol content. Many of the reports also reported concomitant suspect medications, however these were not evaluated with regard to the possible role in causing the event. We also searched MEDLINE to identify the medical literature which reference possible abuse or misuse potential of dextromethorphan. The literature reports were not reviewed or evaluated, however some are referenced for your information.</p>			
Reason for Request/Review: FBI Inquiry			
Relevant Product Labeling: The usual adult dose of dextromethorphan for cough suppression is 10 to 20 milligrams every 4 hours or 30 milligrams every 6 to 8 hours (Prod Info Benylin Adult Formula(R), 1999; Prod Info Pertussin DM(R), 1999).			
Usage Information: NA			
Search Date: 11/13/00	Search Type(s): X AERS/SRS X Literature Other		
Search Criteria:			
Drug names: Active ingredient dextromethorphan and approximately 80 tradename cough and cold products thought to contain dextromethorphan.			
Adverse Events:			
1. All reports in the database linked to dextromethorphan - 616. 2. CNS adverse events - 226 3. Psychiatric adverse events - 130 4. Reports involving drug dependence, addiction, abuse, and overdose - 144 (specific search terms in SRS include drug depend addict, drug depend, withdraw synd, toler inc, med error, withdraw synd, overdose intent and overdose; specific search terms in AERS include drug dependency, tolerance, non-accidental overdose, drug and chemical abuse, drug withdrawal convulsions, and drug withdrawal syndrome).			

Search Results:

There were 616 reports of adverse events in the AERS database for dextromethorphan. This number may include duplicate reports. These reports represent numerous dextromethorphan-containing products, including many combination products that contain other active ingredients in addition to dextromethorphan. In 226 reports a CNS effect was reported, and in 130 reports a psychiatric effect was reported. In cases in which a CNS effect was reported, the following specific CNS effects were reported most frequently: dizziness (52), headache (25), insomnia (22), sedation (24), and tremor (22). In cases in which a psychiatric effect was reported, hallucinations were reported most frequently (23).

After duplicates were matched, a total of 144 reports of drug abuse, dependence, addiction, overdose, withdrawal syndrome, and tolerance were reviewed. Those reports with a coded term of drug abuse or dependence or addiction were not individually reviewed. Those with a reported term of overdose, withdrawal syndrome, and tolerance were individually reviewed to determine if they were cases of abuse and or misuse of the product. Forty-one were not considered to be reports of abuse and or misuse of the dextromethorphan-containing product and are described below:

- Thirty-one were determined to be accidental overdose cases or overdoses occurring in very young children unlikely to intentionally abuse or misuse the product (age's between 20 months and 6 years old). There was also one 11-year-old autistic female who took an overdose of dextromethorphan and propoxyphene.
- There were six cases of tolerance reported with Delsym. There was no mention or indication that there was misuse or abuse of this product in these reports.
- Four reports did not indicate misuse or abuse of a dextromethorphan-containing product.

Of the remaining 103 reports of drug abuse, dependence, addiction, overdose, withdrawal syndrome, and tolerance, the following findings were noted:

- The ages of the individuals ranged from 13 to 67 years old, median age of 21.5. Fifteen reports did not report the age. Thirty-five reports were in individuals \leq 17 years old.
- Gender distribution was females -37, males -60, and not reported - 6.
- Twenty-seven reports were specifically coded as drug abuse and/or dependence and addiction. The remaining event codes were overdose, overdose intent, non-accidental overdose (76), and withdrawal syndrome (2). Two additional reports mentioned that the dextromethorphan product was abused.
- About half of the reports were from Sweden (32) and Switzerland (14). The Swedish reports indicated dextromethorphan doses ranging from 300 to 2250 mg. Many of the domestic reports were overdose of Nyquil either in a suicide attempt with another acetaminophen product or as an accidental overdose. We cannot rule out however that the individuals were not consuming Nyquil for either the dextromethorphan or the alcohol content
- Ten reports received in 2000 described non-accidental overdose in children 13 to 17 years of age. Two of these reports stated the purpose of ingestion of dextromethorphan was to get "high" or to hallucinate. In another four reports, the intent of ingestion of dextromethorphan appeared to be to get "high" although the intent was not specifically stated in the report. In these reports, initially reported by a news agency, the children purchased dextromethorphan in powder form from an internet web site and had the dextromethorphan delivered to their high school.
- The following CNS and psychiatric effects were listed in reports in which dextromethorphan was the sole suspect product. However, ingestion of a combination product could not be ruled out in all these reports.
 - Anxiety
 - Ataxia
 - Clouded consciousness
 - Confusion
 - Euphoria
 - Excitement
 - Hallucinations
 - Lethargy
 - Psychosis
 - Somnolence
 - Unconsciousness
 - Vertigo

A line listing of the 103 reports is attached.

Discussion / Conclusions:

Dextromethorphan hydrobromide is an antitussive agent used in cough and cold preparations, many of which are OTC products. Although dextromethorphan does not cause physical addiction, strong psychological dependence is reported in the literature. Of the total 616 reports of adverse events with dextromethorphan, 226 and 130 reported at least one CNS and/or psychiatric adverse event, respectively.

One hundred and three reports involved drug abuse, dependence, addiction, overdose, withdrawal syndrome, and tolerance. Of the 103 reports, 27 specifically mentioned drug abuse, dependence or addiction. Of all reports, there were 35 in individuals ≤ 17 years old. The majority of reports were coded as overdose, overdose intent, or non-accidental overdose. In most of the reports of overdose, overdose intent, and non-accidental overdose, it is not clear whether these overdoses were with the intent to get "high" or to commit suicide. Ten reports received in 2000 described non-accidental overdose in children 13 to 17 years of age. Two of these reports stated the purpose of ingestion of dextromethorphan was to get "high" or to hallucinate. In another four cases, the intent of ingestion of dextromethorphan appeared to be to get "high" although the intent was not specifically stated in the report.

Reported CNS and psychiatric effects resulting from dextromethorphan in cases of drug abuse, dependence, addiction, overdose, withdrawal syndrome, and tolerance included anxiety, ataxia, clouded consciousness, confusion, euphoria, excitement, hallucinations, lethargy, psychosis, somnolence, unconsciousness, and vertigo. Many of the reports also reported concomitant suspect medications, however these were not evaluated with regard to the possible role in causing the event.

Reviewer's Signature / Date:

Signed 11-17-00 by Joyce Weaver

Team Leader's Signature / Date:

Signed 11-17-00 by Claudia Karwoski

Division Director Signature / Date:

Signed 11-19-00 by Julie Beitz

References: (not all inclusive)

1. Buss WF, Reynolds MS. Dextromethorphan abuse potential. DRUGDEX, Drug Consults 12/95.
2. Bornstein S, Czermak M & Postel J. A case of intentional drug poisoning with dextromethorphan hydrobromide. Ann Med Psychol 1968; 1:447-451.
3. Degkwitz R: Dextromethorphan (Romilor) als rauschmittel. Nervenarzt 1964; 35:412.
4. Dodds A & Revai E: Toxic psychosis due to dextromethorphan. Med J Aust 1967; 2:231.
5. Fleming PM. Dependence on dextromethorphan hydrobromide. Br Med J 1986; 293:597.
6. Helfer J & Kim OM. Psychoactive abuse potential of Robitussin-DM (letter). Am J Psychiatry 1990; 147:672-673.
7. Isabell H & Fraser HF. Actions and addiction liabilities of dromoran derivatives in man. J Pharmacol Exp Ther 1953; 107:524-530.
8. Darboe MN. Abuse of dextromethorphan-based cough syrup as a substitute for licit and illicit drugs: A theoretical framework. Adolescence 1996; 31 (121): 239-44.
9. Darboe MN, Keenan GR, Richards TK. The abuse of dextromethorphan-based cough syrup: A pilot study of the community of Waynesboro, Pennsylvania. Adolescence 1996; 31 (123): 633-44.
10. Marsh LD, Key JD, Spratt E. Bulimia and dextromethorphan abuse. A case study. J Subst Abuse Treat 1997; 14 (4): 373-6.
11. Schultz S. Turning to anything, just to get that high. A cough syrup ingredient is a popular drug [news]. US News World Rep 2000 Jun 5; 128(22): 60.
12. Price LH, Lebel J. Dextromethorphan-induced psychosis [letter]. Am J Psychiatry 2000; 157(2): 304.

Attachments: Line listing of reports reviewed

Dextromethorphan Chemical Suppliers and Manufacturers

Cc: NDA # NA

HFD-560 (Division File)/Ganley

HFD-430/Beitz/Trontella/Karwoski/Weaver /Dextromethorphan

HFD-400

HFD-2 (Medwatch)

Electronic File Name: N:\WEAVER\JDM INFO REQUEST.DOC

MEMORANDUM

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

Date: June 25, 2002

To: Director, Division of Over-the-Counter Drug Products (HFD-560)

Through: Deborah B. Leiderman, M.D., M.A.
Director, Controlled Substance Staff (HFD-009)

From: James R. Hunter, R.Ph., MPH
Controlled Substance Staff (HFD-009)

Subject: Controlled Substance Staff Consultation:
Coricidin HBP (dextromethorphan hydrobromide 30mg and
chlorpheniramine maleate 4mg)
Sponsor: Schering Plough
Request for review of attached published article and analysis of current
use of Coricidin HBP by "street users". CSS recommendation for safety
update by ODS.

The purpose of this memo is to provide follow up information regarding current abuse of Coricidin HBP. Please refer to your recent telephone conversation with Ms. Corinne Moody of HFD-009. Ms. Moody said that she had contacted Ms. Grethen Feussner of the Drug Enforcement Agency (DEA) and requested information or reports of abuse with the use of Coricidin HBP. Ms. Feussner told Ms. Moody that DEA did not actively monitor for abuse of this product because it is not a controlled substance. She also told Ms. Moody that DEA has not received reports of abuse for this product.

Also in response to your request, CSS reviewed a standard report from AERS that identified Adverse Reaction Reports associated with Coricidin HBP. This search identified a cluster of reports in the 12 to 20 age groups. (See attachment 1.) Out of 54 total reports during the time frame 01-01-2000 and 04-04-2002, 46 occurred in the 12-20 age group. A review of the narrative case reports from these 46 reports identified 26 cases associated with excessive doses of Coricidin HBP use and include wording consistent with a motive of intentional drug use for psychotropic drug effects (See attachment 2.)

Based on these preliminary signals, CSS recommends that HFD-560 request that the Office of Drug Safety (ODS) investigate whether the abuse of Coricidin HBP is resulting in an increase in ADRs for this product. CSS also suggests that HFD-560 specify the name of the product, Coricidin HBP in their request for a safety update by ODS.

HFD-560/ L MChang
HFD-009/ D Leiderman/ M Klein/ C Moody/ D Locklear



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 13 2001

The Honorable Joseph I. Lieberman
United States Senate
Washington, D.C. 20510-0703

Dear Senator Lieberman:

Thank you for your letter of May 7, 2001, on behalf of your constituent, ~~_____~~ regarding the misuse of an over-the-counter (OTC) product, Coricidan Cough and Cold, which contains the active ingredient dextromethorphan hydrobromide.

We appreciate knowing ~~_____~~ concerns regarding the problems that have arisen from children misusing products, solely intended for medical use. However, dextromethorphan hydrobromide, which falls under Title 21, Code of Federal Regulations, § 341, Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use, is recognized as safe and effective when used according to the label.

Consumers can play an important public health role by reporting any adverse reactions or other problems with products the Food and Drug Administration (FDA or the Agency) regulates through our voluntary reporting system, MedWatch. If the Agency receives sufficient reports on one particular drug product, showing that there may be a health hazard associated with the product, we would then take necessary actions. ~~_____~~ can telephone our MedWatch Office at 1-800-FDA-1088 or another option is to submit the adverse event/problem electronically via the Internet. A link to the Internet voluntary reporting form can be found by going to the MedWatch homepage at <http://www.fda.gov/medwatch/index.html>, and click on "How to Report."

State Boards of Pharmacy play a role in pharmaceutical dispensing within each particular State. We suggest ~~_____~~ contact the ~~_____~~ Commission of Pharmacy and express her

Attachment 3 p. 2

Page 2 - The Honorable Joseph I. Lieberman

concerns regarding the placement of these products behind the counter. They can be contacted at the following address:

~~_____~~
~~_____~~

We have forwarded your letter to the Division of OTC Drug Products, which is responsible for the review of dextromethorphan hydrobromide.

Thanks again for contacting us concerning this matter. If you have further questions, please let us know.

Sincerely,


Melinda K. Plaisier
Associate Commissioner
for Legislation

Attachment 3 p.3

Page 3 - The Honorable Joseph I. Lieberman

bcc: HFW-10

HFW-14

HFW-12

HFW-1

HFD-560 (Ganley)

One copy to Fwooten

Faxed to CDER:Fwooten:6/19/01

Emailed to OL:Llemley:6/28/01

R/D: Llemley 6/26/01

Concur: Kroberts 6/26/01

Clearance: Dhenderson 6/26/01

Edits:Fwooten:6/28/01

Reviewed:Dprince:

Sent to typing: lmt:7/2/01

F/T:lmt:7/6/01(G/WP/CDER Team Letters/01-2725.doc)

(G:\WP\WOOTEN\CDER Letters\01-2725.doc)

Control no. 01-2725

Attachment 3 p. 4

JOSEPH I. LIEBERMAN
CONNECTICUT
COMMITTEES:
ARMED SERVICES
ENVIRONMENT AND PUBLIC WORKS
GOVERNMENTAL AFFAIRS
SMALL BUSINESS

United States Senate
WASHINGTON, DC 20510-0703

SENATE OFFICE BUILDING
WASHINGTON, DC 20510
(202) 224-4041
STATE OFFICE:
ONE STATE STREET
14TH FLOOR
HARTFORD, CT 06103
860-549-8463
TOLL FREE: 1-800-275-5805
INTERNET ADDRESS:
senator_lieberman@lieberman.senate.gov
HOME PAGE:
<http://www.senate.gov/~lieberman/>

May 7, 2001

Dr. Bernard Schwetz
Acting Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Schwetz:

I'm enclosing a copy of an electronic mail message which I recently received from one of my constituents, ~~XXXXXXXXXX~~ regarding her concerns about Schering-Plough's over-the-counter medication called "Coricidan Cough and Cold."

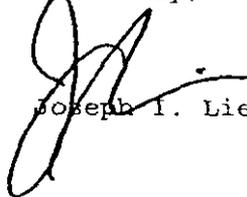
According to my constituent, this drug is being abused by teenagers which is cause for concern because it contains the active ingredient Dextromethorphan, a dissociative drug in the same family as PCP and Ketamine (special K). Other name brand products also contain Dextromethorphan, including Benylin DM, Pertussin, Vicks Formula 44, and Robitussin Pediatric, among others.

While my constituent is not advocating the removal of this medication from the market, she is concerned about recent hospitalizations of children from abuse of products containing this active ingredient, her 16-year-old daughter being among them.

My constituent believes that these products should be placed behind pharmaceutical counters for greater accountability.

I would greatly appreciate it if you would provide me with a response which addresses the concerns my constituent has raised.

Sincerely,



Joseph I. Lieberman

JIL:vh
Enclosure

01-2725

Attachment 3 p. 5

Date: 5/1/2001 2:41 AM
Sender: nobody@w1.senate.gov
To: senator lieberman
Priority: Normal
Subject: email Senator Lieberman

comment= There is an epidemic facing American teens that I would like to share.

Schering-Plough is the manufacture of an over the counter drug named "CORICIDAN COUGH AND COLD." This drug is being abused to an epidemic proportion by today's teen agers. The main ingredient of abuse is Dextromethorphan, it is a dissociative drug in the same family as PCP and Ketamine (special K) There are currently two children hospitalized as a result of talking this over the counter drug for fun!!! One of them being my sixteen year old daughter.

I called the pharmacy and was told that it is an over the counter drug and there are no guidelines for removing it. Schering-Plough is making money the employees of the chain stores are not interested and our children are being destroyed. I am not suggesting that they be taken off the market by any means, just put all cough medications with the active ingredient Dextromethorphan behind the counter! (It is sold under the brand names Benylin DM, Pertussin, Vicks Formula 44 and Robitussin Pediatric among others) I am including information on DXM and some sites of interest. With your voice we can force Big drug companies to put this drug in the pharmacy behind the counter where it belongs. With your help we can save our teenagers from themselves.

PLEASE HELP ME PUT THIS DRUG BEHIND THE COUNTER !!!

Sincerely,

Background:

DXM has been in use in the USA for approximately 30 years. In the mid 1980s, though, several deaths following ingestion of large doses of dextromethorphan prompted the Swedish government to restrict this compound to prescription-only status. It is, however, still widely available over-the-counter in the United States. The pharmaceutical potential of dextromethorphan does not appear to have been fully explored yet. According to recent studies (performed predominantly on animals), the substance also has shown promise in fighting both epilepsy and Parkinson's disease. Other studies though, have indicated possible fetal abnormalities and brain damage in test cases.

Resources DrugAbuse.com

Lycaeum > Leda > This Is Your Brain On Dissociatives: The Bad News is Finally In

from=

TOPIC= Health

Received: from mailsims2.senate.gov ([156.33.203.11]) by imaexc3.senate.gov with SMTP

(IMA Internet Exchange 3.13) id 001200F1; Tue, 1 May 2001 02:43:40 -0400

Received: from www.senate.gov ([10.2.0.19])

by mailsims2.senate.gov (Sun Internet Mail Server

sims.3.5.1999.07.30.00.05.p8) with SMTP id

<OGCN006I19RAR7@mailsims2.senate.gov> for

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/s/

Andrea Segal
8/8/03 03:39:57 PM

Prototype "Drug Facts" Label

Drug Facts

Active ingredients (in each extended-release bi-layer tablet)	Purpose
<i>Dextromethorphan HBr 60 mg</i>	<i>Cough suppressant</i>
<i>Guaifenesin 1200 mg</i>	<i>Expectorant</i>

Uses ■ helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs more productive

- temporarily relieves:
 - cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants
 - the intensity of coughing
 - the impulse to cough to help you get to sleep

Warnings

Do not use ■ for children under 12 years of age

- if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains a MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have

- persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema
- *cough accompanied by too much phlegm (mucus)*

When using this product

- do not use more than directed

Stop use and ask a doctor if

- cough lasts more than 7 days, comes back, or occurs with fever, rash, or persistent headache. These could be signs of a serious illness.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- do not crush, chew, or break tablet
- take with a full glass of water
- this product can be administered without regard for timing of meals
- adults and children 12 years and older: *[For the 600 mg/30 mg tablets]* one or two tablets every 12 hours; not more than 4 tablets in 24 hours
[For the 1200 mg/ 60 mg tablet], one tablet every 12 hours; not more than 2 tablets in 24 hours

- children under 12 years of age: do not use

Other information

- tamper evident: do not use if seal on bottle printed "SEALED FOR YOUR PROTECTION" is broken or missing
- store at 20-25°C (68-77°F)
- see bottom of bottle for lot code and expiration date

Inactive ingredients carbomer 934P, NF; FD&C blue #1 aluminum lake; hypromellose, USP; magnesium stearate, NF; microcrystalline cellulose, NF; sodium starch glycolate, NF

*The sponsor should follow this Drug Facts label **in content only**. The font sizes for title, headings, subheadings, condensed text and other graphic features must be in accordance as set forth in 21 CFR 201.66.

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this page is the manifestation of the electronic signature.**

/s/

Colette Jackson
2/20/04 02:59:30 PM
CSO

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

/s/

Colette Jackson
3/1/04 02:19:11 PM
CSO

18. USER FEE COVER SHEET

A copy of Form FDA 3397 follows this cover page.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth, Texas 76155

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-620

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(817) 786-1243

3. PRODUCT NAME

Mucinex® DM Extended-Release Tablets

6. USER FEE I.D. NUMBER

4555

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

D. Jeffrey Keyser

TITLE

Vice President,
Development and Regulatory Affairs

DATE

06/09/03

MEMORANDUM

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

DATE: March 1, 2004

TO: Badrul A. Chowdhury, M.D.
Director
Division of Pulmonary Drug Products (HFD-570)

FROM: Michael F. Skelly, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs covering NDA 21-620, Mucinex[®] DM
(Guaifenesin and Dextromethorphan HBr) Extended
Release Tablets (600/30 and 1200/60 mg),
Sponsored by Adams Laboratories, Inc.

At the request of HFD-650, the Division of Scientific Investigations conducted audits of the following bioequivalence studies:

Study Number: 2002-08
Study Title: A Definitive Bioequivalence Study Designed to Examine the Bioavailability of Guaifenesin and Dextromethorphan from an Experimental Controlled Release Formulation in Normal Healthy Volunteers Compared to Reference Guaifenesin and Dextromethorphan Products

Study Number: 2002-10
Study Title: A Definitive Study Designed to Examine the Steady State Pharmacokinetics of Guaifenesin and Dextromethorphan from an Experimental Controlled Release Formulation in Normal Healthy Volunteers Compared to Reference Guaifenesin and Dextromethorphan Products

Page 2 of 3 - NDA 21-620, Mucinex[®] DM (Guaifenesin and Dextromethorphan HBr) Extended Release Tablets

The clinical portions of the studies were conducted at Bio-Kinetic Clinical Applications, Inc., Springfield, MO. The analytical portions of the studies were conducted at

Following the inspection at Bio-Kinetic Clinical Applications (12/11/2003 - 1/7/2004), no Form 483 was issued. However, the inspection at Bio-Kinetic ascertained that parts of the report for Protocol 2002-10 listed incorrect lot numbers of drug products. The following lots of drug products were actually used to dose subjects:

Protocol 2002-08

Guaifenesin Extended Release Tablets, 1200 mg,
Lot PB01-H34A3
Guaifenesin 1200 mg/Dextromethorphan HBr 60 mg
Extended Release Tablets, Lot PB01-H30A3
Vicks 44 Cough Relief Dextromethorphan HBr, Lot 1141RX

Protocol 2002-10

Guaifenesin Extended Release Tablets, 1200 mg,
Lot PB01-H34A4 (not PB01-H34R4)
Guaifenesin 1200 mg/Dextromethorphan HBr 60 mg
Extended Release Tablets, Lot PB01-H30A4
Vicks 44 Cough Relief Dextromethorphan HBr, Lot 1141RX
(not 1129RX)

Similar errors in accountability records were recognized and corrected during the sponsor's monitoring visits. Errors in the report were recognized in part approximately two days before the inspection began, and in part during the inspection.

Following the inspection at _____ (2/23/2004 - 2/27/2004), Form 483 was issued. The objectionable finding and our evaluation follow.

Failure to reject data and to repeat assays for samples that were suspected or known to contain incorrect amounts of internal standard. Specifically, the samples # (_____) in guaifenesin run _____ and the samples _____ in dextromethorphan run _____ were thought to contain twice the correct amount of internal standard.

~~_____~~ attempted to remedy the errors with unvalidated arithmetic adjustments. However, DSI recommends that the concentration data for the following samples are less accurate than those from the validated methods:

Study 2002-08: Dextromethorphan data for Subject 30, Period 3 Treatment A, from 3 hours through 6.75 hours

Study 2002-10: Guaifenesin data for Subject 32, Period 1, Treatment A, from pre-dose through 125 hours

Following the inspection, ~~_____~~ amended their SOPs to prevent similar events in the future.

Conclusions:

Following our evaluation of the inspectional findings, DSI recommends accepting the data from the studies 2002-08 and 2002-10, except the data from specific samples identified above.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Michael F. Skelly, Ph.D.

Final Classifications:

~~_____~~

cc:
HFD-45/RF
HFD-48/Skelly(2)/Himaya/CF
HFD-570/Jackson/NDA 21-620
HFR-CE3585/Cote
HFR-SW3530/Hampton Thurston
Draft: MFS 2/29/04
Edits: MKY 3/1/04
DSI: 5492; O:\BE\EIRCOVER\21620ada.muc.doc
FACTS ~~_____~~

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this page is the manifestation of the electronic signature.**

/s/

Michael Skelly

3/1/04 04:37:29 PM

PHARMACOLOGIST

Dr. CT Viswanathan signed the paper original. Paper copies
follow.

1 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling