CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-282

MEDICAL REVIEW

MEDICAL TEAM LEADER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:	NDA 21-282	APPLICATION TYPE:	Amendment
SPONSOR:	Adams Laboratories	PRODUCT/PROPRIETARY NAME:	Mucinex
INDICATION:	Loosen phlegm	USAN / Established Name:	Guaifenesin modified release bilayer tablets
STRENGTHS:	600 mg		
CATEGORY OF DRUG:	Expectorant	ROUTE OF ADMINISTRATION:	Oral
MEDICAL REVIEWER:	Purucker	REVIEW DATE:	10 December 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	Document ID #:	Submission type/Comments:
25 June 2001	N-000 B2	Complete response to approvable letter of 26 April 2001
01 August 2001		Annual report for containing further safety information

	RELATED APPLICATIONS	
Document Date:	Document ID #:	Comments:
29 August 2001 7 Sept. 2001	N 000 BL	Revised carton and immediate container labeling consistent with 21 CFR 201.66
29 June 2000	NDA 21-282	Original NDA submission, 505 (b)(2)

Overview: This amendment was submitted as a complete response to the approvable letter of 26 April 2001. It is comprised of a safety update, draft labels and response to specific deficiencies identified in the letter. The submission was filed, then later amended following feedback from a joint meeting of DPADP and DOTCDP with the sponsor on 25 August 2001. The subsequent amendments were comprised of container and carton labeling that were submitted as consistent with the recommended OTC format and were reviewed by DOTCDP. From a clinical perspective, the application is approvable, with final approval held pending resolution of several issues identified by the CMC and OCPB reviewers. With regard to the clinical and regulatory deficiencies identified in the approvable letter, each has been satisfactorily addressed and the application should be approved, following incorporation of minor labeling changes identified by DOTCDP.

1. With regard to labeling, on its face, the sponsor's submission appears consistent with the final monograph for expectorant drug products, 21 CFR 341.78 and with OTC drug products, 21 CFR 201.66, pending resolution of the issues identified by HFD-560. The container and carton labeling is in the "Drug Facts" format annotated for type size and font style for guaifenesin 600 mg modified release formulation. The trade name "Mucinex" has been proposed and accepted following OPDRA consult. The specific labeling issues identified in the MO clinical review during the first review cycle have been adequately addressed:
   - The Directions section of the product monograph now includes information appropriate to the strength and modified release characteristics of the product.
   - Statements instructing against chewing or breaking the tablet and taking it without regard to meals have been added.
   - A recommendation to take the tablet with a full glass of water has been added (see rationale, below).
2. The sponsor has committed to removing the from the tablets.

4. The sponsor has removed labeling not in the product monograph, specifically ".. ———

DPADP concurs with DOTCDP's labeling comments. Specifically, the statement ——— implies an onset of action claim or comparative claim and is not supported by the data submitted and is not part of the monograph. It should be removed.

Outstanding Issues: None. From a clinical perspective, pending resolution of minor labeling issues, the application is approvable. Substantive CMC and OCPB issues will prevent final approval during the current review cycle.

Recommended Regulatory Action:	N drive location:
NDAs:	
Efficacy / Label Supp.: ___x___ Approvable	_____ Not Approvable

Signed: Medical Team Leader: _____ Date: _____

Division Director: _____ Date: _____

CC: *Purucker/Clin.TL/HFD-570*
Jafari/PM/HFD-570

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

/s/

Mary Purucker
12/12/01 10:18:27 AM
MEDICAL OFFICER

Robert Meyer
12/12/01 10:24:05 AM
MEDICAL OFFICER

MEDICAL TEAM LEADER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:	**NDA 21-282**	**APPLICATION TYPE:**	**Original NDA**
SPONSOR:	**Adams Lab., Inc. Fort Worth, TX**	**PRODUCT/PROPRIETARY NAME:**	**Guaifenesin ER (extended release)**
INDICATION:	**Chronic bronchitis**	**USAN / Established Name:**	**Guaifenesin**
CATEGORY OF DRUG:	**Expectorant**	**ROUTE OF ADMINISTRATION:**	**Oral**
MEDICAL REVIEWER:	**Purucker**	**REVIEW DATE:**	**28 March 2001**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date/ CDER Stamp Date:	Document ID #:	Submission type/Comments:
29 June 2000/ 30 June 2000	NDA #21-282 000	21-volume paper submission to show BA/BE between IR guaifenesin and MR guaifenesin 600 mg
8 November 2000/ 14 November 2000	21-282 BM	4-Month Safety Update
5 January 2001/ 9 January 2001	21-0282 C	Comprehensive literature review of guaifenisen for labeling purposes

RELATED APPLICATIONS

Document Date:	Document ID #:	Comments:
5 June 1998		

Overview of Application/Review: The sponsor has submitted a 505(b)(2) application to market a modified release formulation of guaifenesin, 600 mg. The nominal 12-hr dose for both products complies with OTC Monograph dosages of guaifenesin, that is, 200 – 400 mg every four hours not to exceed 2400 mg in 24 hours.

The application itself is comprised mainly of PK and CMC data, with clinical safety data obtained from the 53 volunteers enrolled in the two pivotal PK studies, from published literature sources, and from the AERS adverse event database. These clinical safety data in general support OTC Monograph labeling as appropriate for these products, and do not support the necessity to use the format defined in 21 CFR § 201.57.

Outstanding Issues: If the proposed products are approved based on a finding of adequate bioequivalence as compared to the reference OTC Monograph product, they would be eligible, and should be labeled as an OTC products, as specified in 21 CFR § 341.78.

Recommended Regulatory Action: | **N drive location:**

NDAs:

Efficacy / Label Supp.: ___X___ **Approvable** _____ **Not Approvable**

Signed: Medical Team Leader: LS 3/28/01

Division Director: LS 3/28/01

BACKGROUND:

This is a 505(b)(2) New Drug Application for [redacted] a modified release formulation of the expectorant guaifenesin. The products, Guaifenesin ER 600 mg [redacted], are proposed to be administered as oral tablets every 12 hours. These daily doses are consistent with the OTC Monograph process, which has established that guaifenesin is safe and effective as an expectorant in doses of 200 and 400 mg every four hours, not to exceed 2400 mg per day in adults. An appropriate dose for a modified-release formulation intended to be given every 12 hours is between 600 and 1200 mg. The sponsor has followed a development plan that includes demonstration of bioequivalence of [redacted] the [redacted] products to an immediate release formulation administered every four hours.

The submission is comprised of 21 paper volumes including data from five clinical pharmacology studies. Only two of these studies were conducted using the proposed to-be-marketed formulation and hence are directly relevant to this application. There are no controlled clinical studies to support the safety or efficacy of the new formulation because the sponsor has primarily relied upon the OTC monograph determinations of safety and efficacy. The sponsor has included a brief literature review to support the specifics of the proposed product labeling, which follows the format described in 21 CFR 201 for prescription-only drug products.

In addition to this NDA, Adams Laboratories has [redacted]

CMC ISSUES

[redacted] products are [redacted] bilayer tablets comprised of an extended release and an immediate release layer. [redacted]. The [redacted] tablet contains 600 mg guaifenesin, USP, has total weight including excipients of [redacted] and has a diameter of approximately [redacted]

Please see detailed assessment conducted by CMC reviewers Drs. Ross and Poochikian. One major approvability issue with these products is the level of unidentified impurities, which is [redacted] for the 600 mg product, compared to ≤ 0.1 % per ICH standards. For this reason, and others, neither product is approvable from a CMC perspective. Additional deficiencies include stability specifications that are too wide, an unacceptable [redacted] assay method, and an unacceptable dissolution profile.

BIOEQUIVALENCY ISSUES

Please see detailed assessments conducted by OCPB reviewers Drs. Choi and Wakelkamp regarding the pharmacokinetic and bioequivalency outcome of these trials. Two pivotal trials were reviewed, (1) a single-dose, 3-period crossover, dose proportionality and food interactions study and (2) a multi-dose, 2-period crossover, bioavailability and bioequivalency study. While both Guaifenesin 600 mg ER and [redacted] were found to meet AUC criteria for bioequivalency with the immediate release Organidin reference product, [redacted] failed to meet C_{min} and C_{max} criteria [redacted] The 600 mg tablet is approvable.

CLINICAL PHARMACOLOGY TRIALS

A total of five studies were conducted in support of these drug products. Protocols 98-01, 99-01, and 99-04 used a formulation of guaifenesin other than the to-be-marketed products and will not be described further. The two remaining protocols, 99-06 and 99-05, were single and multiple-dose studies involving 27 and 26 volunteers, respectively.

Protocol #99-05: This was an open-label, randomized, multiple-dose, 2-period crossover study of Guaifenesin ER 1200 mg tablet administered every 12 hours compared to guaifenesin immediate release 2 x 200 mg every 4 hours. The Guaifenesin ER 600 mg tablet was not studied in this repeat-dose trial.

A total of 26 patients received the modified release formulation, comprised of a total of 11 doses administered over 6 days (Period A). Twenty-five volunteers were crossed over to receive the immediate release product (Organidin NR® Tablets, Wallace Labs) comprised of 33 doses over 6 days (Period B). There was a single dropout who did not receive the immediate release product. She is recorded to have dropped out for "personal reasons." No further details are available.

Volunteers ranged in age from 19 to 50 years, with a mean age of 31 years. Gender breakdown was 31% male and 69% female. With regard to ethnicity, all but two were Caucasian.

Screening safety assessments were comprised of medical history, concomitant medication use, physical exam including vital signs, height, and weight, ECG, CBC, urinalysis, urine drug screen, and pregnancy test. Vital signs were taken prior to dosing at the start of each of the two study periods, but no further measurements were made. Physical exam, ECG, CBC, and UA were not repeated. Volunteers were queried concerning adverse events and concomitant medication use on days 1, 4, 5, 6, and 7 of the two dosing periods.

There were no adverse events that met the regulatory definition of serious. Adverse events recorded in the case report forms included headache (6 events in 5 subjects), sore throat, indigestion, epistaxis, and eye infection. All were reported to be mild and self-limited. Headache as an AE was as likely to be reported while using the guaifenesin IR formulation as with the study drug. The only concomitant medication recorded was oral contraceptive pills.

Protocol #99-06: This was an open-label, randomized, single-dose, 3-period crossover, food-effect study of Guaifenesin ER 1200 mg tablet, Guaifenesin ER 600 mg tablet, and Guaifenesin ER 1200 mg tablet administered with food.

A total of 27 volunteers received the Guaifenesin ER 600 mg tablet (Period A), 26 were crossed over to the Guaifenesin ER 1200 mg tablet (Period B), and 26 received Guaifenesin ER 1200 mg tablet with food (Period C). There were two dropouts from the latter two periods who did not receive the Guaifenesin ER 1200 mg tablets. These volunteers did not return for follow-up. No further details are available.

Volunteers ranged in age from 20 to 54 years, with a mean age of 34 years. Gender breakdown was 44% male and 56% female. With regard to ethnicity, all but two were Caucasian.

Screening safety assessments were comprised of medical history, concomitant medication use, physical exam including vital signs, height, and weight, ECG, CBC, glucose, creatinine, BUN, SGPT, GGT, alkaline phosphatase, urinalysis, urine drug screen, and pregnancy test. Vital signs

were taken prior to dosing at the start of each of the three study periods, but no further measurements were made. Physical exam, ECG, and laboratory assessments were not repeated. Volunteers were queried concerning adverse events and concomitant medication use following completion of each of the three study periods.

There were no adverse events that met the regulatory definition of serious. Adverse events recorded in the case report forms included headache, thirst, dizziness, acute bronchitis, flu symptoms, and common cold. All were reported to be self-limited. The only concomitant medication recorded was oral contraceptive pills.

AERS SAFETY DATABASE REVIEW

The sponsor included 95 cases from the AERS database reported between 11/01/97 and 3/15/2000 for which guaifenesin was included as a co-suspect medication. There were only three cases among these 95 in which guaifenesin was listed as the only suspect medication. The remaining 92 included cases in which it was co-administered with other usually multiple active drug products. This is not unexpected, since guaifenesin is usually only one of the active ingredients in combination cough-cold preparation. However, it is extremely difficult to assess causality.

The three cases for which guaifenesin was listed as the sole suspect medication included one report of insomnia/restlessness, a report of dysphagia, and a case of Stevens-Johnson Syndrome.

Of the 92 case reports of guaifenesin as a co-suspect drug in an adverse event, the following cases are notable because they fulfill the regulatory definition of serious or resulted in death. There was a single report of a congenital malformation (ASD with Situs Inversus) associated with DuratussG co-administered with amoxicillin, toxic epidermal necrolysis (TEN) associated with the combination product Dayquil, and Stevens-Johnson Syndrome assoicated with co-administered terfenadine. There was a single reported death, discussed in greater detail below, associated with co-suspect drugs diphenhydramine and chlorpheniramine taken in overdose.

LITERATURE REVIEW

The sponsor has included a brief review of the medical literature to support the safety and efficacy of guaifenesin as well as to support the proposed labeling.

A total of 16 citations were included. There was a single report of death due to suicide associated with guaifenesin ingestion. In this case report, a 48 year old woman was found to have elevated levels of chlorpheniramine, diphenhydramine, and guaifenesin in her blood, urine, bile, and other bodily fluids. The two antihistamine concentrations were between 10 and 100 times greater than the average peak blood concentration after a single therapeutic dose. The concentration of of guaifenesin was 20 times greater than the average peak blood concentration after a single therapeutic dose. Cause of death was considered due to the combined effect of all three drugs.

There was a report of guaifenesin metabolites being found in uroliths in combination with ephedrine. This effect appears to be generally attributable to guaifenesin and not specifically associated with its co-administration with ephedrine because other reports of guaifenesin urolithiasis associated with chronic use/abuse have been reported.

There was a suggestion that guaifenesin may interfere with *in vitro* tests of serum uric acid concentrations. It may also have a mild uricosuric effect.

There was no indication that guaifenesin increased the risk of birth defects or was unsafe to take during pregnancy.

LABELING

The sponsor has proposed product labeling following the format of prescription-only drug products, following the required format defined in 21 CFR § 201.57. Although no electronic copy was included in the application to provide line-by-line commentary, such a tool would be irrelevant because the nominal dose and dosing interval proposed for this modified release formulation would place it within the monograph dosage limits is set forth in 21 CFR § 341.78. This product, if approved, would be required to conform to the monograph labeling, which has been reproduced below:

21 CFR § 341.78 Labeling of expectorant drug products.

(a) Statement of identity. The labeling of the product contains the established name of the drug, if any, and identifies the product as an "expectorant."

(b) Indications. The labeling of the product states, under the heading "Indications," the following: "Helps loosen phlegm (mucus) and thin bronchial secretions to" (select one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive"). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(c) Warnings. The labeling of the product contains the following warnings, under the heading "Warnings":

(1) "A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by a fever, rash, or persistent headache, consult a doctor."

(2) For expectorant drug products labeled for adults or for adults and children under 12 years of age. "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema, or where cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

(3) For expectorant drug products labeled only for children under 12 years of age. "Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

(d) Directions. The labeling of the product contains the following information under the heading "Directions" for products containing guaifenesin identified in § 341.18: Adults and children 12 years of age and over: oral dosage is 200 to 400 milligrams every 4 hours not to exceed 2,400 milligrams in 24 hours. Children 6 to under 12 years of age: oral dosage is 100 to 200 milligrams every 4 hours not to exceed 1,200 milligrams in 24 hours. Children 2 to under 6 years of age: oral dosage is 50 to 100 milligrams every 4 hours not to exceed 600 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

SUMMARY AND RECOMMENDATIONS

The sponsor has submitted a 505(b)(2) application to market [redacted] a modified release formulation of guaifenesin, [redacted] 600 mg. The nominal 12-hr dose [redacted] complies with OTC Monograph dosages of guaifenesin, that is, 200 – 400 mg every four hours not to exceed 2400 mg in 24 hours. If the proposed products are approved based on a finding of adequate bioequivalence as compared to the reference OTC Monograph product, they would be eligible, and required, to be labeled as an OTC products, as specified in 21 CFR § 341.78.

The application itself is comprised mainly of PK and CMC data, with clinical safety data obtained from the 53 volunteers enrolled in the two pivotal PK studies, from published literature sources, and from the AERS adverse event database. These clinical safety data in general support OTC Monograph labeling as appropriate for these products, and do not support the necessity to use the format defined in 21 CFR § 201.57.

These products were found not approvable by the CMC reviewers. [redacted] the 600 mg tablet is approvable from a Biopharm perspective. From a purely clinical perspective, [redacted] products are approvable, although the following concerns must be adequately addressed by the sponsor.

The following comments should be conveyed to the sponsor:

1. The proposed approval for marketing of [redacted] Guaifenesin 600 ER would be based upon a finding of adequate bioequivalence as compared to the reference OTC Monograph product. These products would therefore be eligible, and should be labeled as OTC products, as specified in 21 CFR 341.78.

[redacted]