NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA Class 2 Resubmission
Application Number(s)	217338
Priority or Standard	Standard
Submit Date(s)	July 7, 2025
Received Date(s)	July 7, 2025
PDUFA Goal Date	January 7, 2026
Division/Office	Division of Nonprescription Drugs I (DNPD I)
Review Completion Date	January 7, 2026
Established/Proper Name	Guaifenesin, dextromethorphan hydrobromide and naproxen Sodium
(Proposed) Trade Name	Mucinex 12HR Cold & Fever Multi-Symptom
Pharmacologic Class	Expectorant, antitussive, analgesic/antipyretic
Applicant	RB Health (US) LLC
Dosage form	Extended-release tablets
Dosing Strength	Each tablet contains 600 mg guaifenesin, 30 mg dextromethorphan hydrobromide, and 110 mg naproxen sodium
Applicant proposed Dosing Regimen	• Adults and children 12 years and older: Take 2 tablets every 12 hours. Not to exceed 4 tablets per 24 hours. • Children under 12 years of age: Do not use.
Applicant Proposed Indication(s)/Population(s)	• 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 ○ Minor aches and pains due to headache and the common cold • Temporarily reduces fever
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	22253000 Pain (finding), 386661006 Fever (finding), 417850002 Respiratory tract congestion and cough (disorder), 82272006 Common Cold (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For adults and children 12 years and older: • 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 ○ Minor aches and pains due to headache and the common cold • Temporarily reduces fever
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	22253000 Pain (finding), 386661006 Fever (finding), 417850002 Respiratory tract congestion and cough (disorder), 82272006 Common Cold (disorder)
Recommended Dosing Regimen	• Adults and children 12 years and older: Take 2 tablets every 12 hours. Not to exceed 4 tablets per 24 hours. • Children under 12 years of age: Do not use.

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE=Office of Surveillance and Epidemiology

DEPI=Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

Signatures

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Glossary

AE	adverse event
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRL	Complete Response Letter
CSS	Controlled Substance Staff
ECG	electrocardiogram
ER	extended-release
FDA	Food and Drug Administration
FDC	fixed dose combination
IR	integrated review
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
PDP	principal display panel
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SOC	standard of care
SOI	statement of identity
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

RB Health (US) LLC resubmitted NDA 217338 on July 7, 2025, seeking marketing approval of for Mucinex 12HR Cold & Fever Multi-Symptom (guaifenesin 600 mg, dextromethorphan hydrobromide 30 mg, and naproxen sodium 110 mg) extended-release (ER) tablets for nonprescription use. It is the first drug product with a combination of these three active pharmaceutical ingredients. The proposed indications are:

- 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 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,
    - minor aches and pains due to headache and the common cold
- temporarily relieves fever.

The proposed dosing instruction for this fixed dose combination (FDC) ER formulation in adults and children 12 years of age and older is to take two tablets every 12 hours.

The proposed product is a bilayer tablet comprising an immediate-release portion (b) (4) and an extended-release layer (b) (4) (b) (4).

This 505(b)(2) application relies on FDA's previous findings of safety and effectiveness for NDA 021620 (Mucinex DM), NDA 020204 (Aleve), and NDA 021076 (Aleve-D Sinus and Cold).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action for this resubmission is Approval.

The Applicant has demonstrated substantial evidence of effectiveness through establishing appropriate scientific bridges between the proposed product and the listed drugs via the 505(b)(2) pathway. The scientific bridges consist of two relative bioavailability studies (Study RB5-US-1505 and Study 0225104).

In the original submission dated September 29, 2023, Study RB5-US-1505 cross-referenced their own Mucinex DM (NDA 021620) by demonstrating the bioequivalence of the guaifenesin

and dextromethorphan components between the proposed product and Mucinex DM under fasted condition with the 90% confidence intervals of geometric mean ratios of C_{max} and AUCs within the acceptance range of 80.00-125.00%. The study also demonstrated that there is no clinically relevant food effect on the guaifenesin component of the proposed product; and the food effect on the dextromethorphan is similar between the proposed product and Mucinex DM.

In addition, the same study demonstrated the bioequivalence of the naproxen component between the proposed product and the listed drug (Aleve, NDA 020204) under fasted condition with the 90% confidence intervals of geometric mean ratios of C_{max} and AUCs within the acceptance range of 80.00-125.00%. The study also demonstrated that there is no clinically relevant food effect on the naproxen component of the proposed product.

A Complete Response Letter (CRL) was issued on July 26, 2024, primarily based on a potential efficacy concern of the naproxen component of the proposed drug product, as the proposed dosing interval is every 12 hours whereas the approved dosing interval for the listed drug (Aleve, NDA 020204) is every 8 to 12 hours.

To address the efficacy concern, the Applicant conducted another relative bioavailability Study 0225104 and resubmitted the NDA on July 7, 2025. A different naproxen-containing listed drug (Aleve-D Sinus and Cold, NDA 021076) with an approved dosing interval of every 12 hours was used in Study 0225104. Study 0225104 demonstrated the bioequivalence of the naproxen component between the proposed product and the listed drug (Aleve-D Sinus and Cold, NDA 021076) under fasted condition with the 90% confidence intervals of geometric mean ratios of C_{max} and AUCs within the acceptance range of 80.00-125.00%.

The appropriately established bioequivalence-based scientific bridges allow the Applicant to cross-reference guaifenesin and dextromethorphan to their own product Mucinex; and rely on FDA's finding of safety and effectiveness for the listed drugs for naproxen, including the approved dose, dosing regimen, and relevant indications.

1.3. Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The common cold is one of the most frequently occurring illnesses that affect millions of Americans annually (Heikkinen and Järvinen 2003[1]). • Colds can be caused by more than 200 different respiratory viruses (Eccles 2023[2]). • Routine diagnosis by virology is neither feasible nor pragmatic given the sheer number of causative viruses and high incidence rate; nonetheless, specific diagnosis is not medically necessary. Laypersons' familiarity with the symptoms of the common cold makes it a self-diagnosable condition (Eccles 2023[3]). • Symptoms of the common cold may include cough, mucus production, minor aches and pains, headache, and fever among other symptomatology. • Though they are self-limited and generally not considered a serious medical condition, colds can be bothersome to consumers and affect quality of life.	• The common cold affects millions of Americans annually. • Symptoms caused by the common cold can be uncomfortable and can temporarily affect quality of life. • Symptoms associated with the common cold are generally self-diagnoseable and self-manageable for lay consumers.

[1] Heikkinen, T and A Järvinen, 2003, The common cold, Lancet, 361(9351):51-59

[2] Eccles, R, 2023, Common cold, Front Allergy, 4:1224988

[3] Eccles, R, 2023, Common cold, Front Allergy, 4:1224988

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The high incidence of the common cold imposes a great economic burden in terms of increased healthcare seeking behaviors and lost productivity. The economic cost of infections caused by the common cold has been estimated to be $40 billion annually in the United States (Fendrick et al. 2003[4]).	
Current Treatment Options	• Nonprescription medications indicated for the common cold may relieve some symptoms of the condition though they do not prevent, cure, or shorten the duration of illness. • A wide selection of nonprescription drug options is currently available for relief of a variety of different symptoms associated with the common cold. This includes single ingredient products as well as combination products that are allowed under the OTC Monograph M012[5] and those approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act.	• Consumers rely on available safe and effective nonprescription drugs for symptomatic relief of symptoms associated with the common cold. • A variety of treatment options are currently available for multi-symptom management of the common cold.

[4] Fendrick, AM, AS Monto, B Nightengale, and M Sarnes, 2003, The economic burden of non-influenza-related viral respiratory tract infection in the United States, Arch Intern Med, 163(4):487-494

[5] Final Administrative Order (OTC000026) Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; October 14, 2022; https://www.accessdata.fda.gov/drugsatfda_docs/omuf/Order/OTC%20Monograph_M012-Cough%20Cold%20Allergy%20Bronchodilator%20and%20Antiasthmatic%20Drug%20Products%20for%20OTC%20Human%20Use%2010.14.2022_0.pdf

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The proposed FDC product is intended to provide the convenience of having three ingredients that target different symptoms in one product that is dosed every 12 hours. • In two relative bioavailability studies, the proposed FDC product demonstrated BE of each of its three active pharmaceutical ingredients with those of the approved Mucinex DM (guaifenesin/dextromethorphan HBr, a product owned by the same Applicant, NDA 021620) and the listed drug Aleve-D Sinus and Cold (naproxen sodium, NDA 021076), under fasted condition. • The proposed FDC product's dosing instruction of every 12 hours is identical to the dosing interval for Mucinex DM and Aleve-D Sinus and Cold.	• The proposed FDC product would present consumers with another alternative for nonprescription management of symptoms caused by the common cold. • The Applicant has provided sufficient data to support its proposed dose and dosing interval based on the listed drugs.
Risk and Risk Management	• Single ingredient products containing guaifenesin, dextromethorphan HBr, and naproxen sodium have been marketed as nonprescription drugs for decades. • The safety profile for each active pharmaceutical ingredient is well characterized. • The safety data from the clinical program showed a small number of AEs overall and no SAEs. The AEs noted were generally mild and self-limited. The AE profile of the proposed product appeared similar to that of the approved listed treatment arms when taken concomitantly. • In the postmarketing safety data evaluating cases reporting concomitant use of all three active ingredients, there were	• There were no SAEs or significant safety findings from the clinical program for this FDC product. • There were no significant findings in the postmarketing safety data when looking at concomitant use of all three active ingredients. • The dose of dextromethorphan HBr in the proposed FDC product is not greater than that of currently marketed products containing this ingredient and does not present an increased abuse potential

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	generally few cases identified and among those, few were considered serious or involved fatal outcomes. Fatal cases were generally confounded by the involvement of multiple concomitant drugs. • Dextromethorphan is a known drug of abuse; however, the dose presented in the proposed FDC product is no greater than that present in already approved nonprescription dextromethorphan products. There were no findings in the clinical program that indicated an increased abuse potential.	relative to existing products.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		

	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Other: (Please specify):	
X	**Patient experience data was not submitted as part of this application.**		

2 Therapeutic Context

2.1. Analysis of Condition

The common cold is one of the most common illnesses that affect Americans each year. Colds are caused by viruses and are typically characterized by a constellation of symptoms, which may include rhinorrhea, nasal congestion, sore throat, sneezing, cough, malaise, headache, and fever. These symptoms are generally self-diagnosable and self-manageable and typically peak within 1- 3 days and last 7-10 days (Heikkinen and Järvinen 2003[6]; Arroll 2011[7]). Colds are usually self-limited illnesses and are unlikely to cause mortality or serious morbidity in healthy individuals. Nevertheless, symptoms caused by the common cold can be uncomfortable and can temporarily affect quality of life.

The common cold affects millions of Americans annually with adults experiencing an average of 2-4 episodes a year and children experiencing an average of 6-8 episodes a year (Heikkinen and Järvinen 2003[8]). The National Institute of Allergy and Infectious Disease estimated that individuals in the United States suffer more than 1 billion colds annually (Wein 2009[9]). Though generally not considered a serious medical condition, the high incidence of colds imposes a great economic burden in terms of increased healthcare seeking behaviors and lost productivity. The economic cost of the common cold is estimated to be $40 billion annually (Fendrick et al. 2003[10]).

2.2. Analysis of Current Treatment Options

There is a wide selection of combination nonprescription drug options intended for relief of multiple symptoms associated with the common cold. These different combination drug products aim to provide consumers greater convenience by combining different active ingredients that target different symptoms in a single product. A myriad of nonprescription options that combine analgesics/antipyretics with cough and cold ingredients, which are listed in Table 1 (NDA approved products) and Table 2 (monograph drug products). Due to the large

[6] Heikkinen, T and A Järvinen, 2003, The common cold, Lancet, 361(9351):51-59

[7] Arroll, B, 2011, Common cold, BMJ Clin Evid, 2011

[8] Heikkinen, T and A Järvinen, 2003, The common cold, Lancet, 361(9351):51-59

[9] Wein, H, 2009, Understanding a Common Cold Virus, NIH Research Matters, (April 13)

[10] Fendrick, AM, AS Monto, B Nightengale, and M Sarnes, 2003, The economic burden of non-influenza-related viral respiratory tract infection in the United States, Arch Intern Med, 163(4):487-494

number of monograph cough and cold combination products, the compiled lists are limited to include oral combination products containing an analgesic/antipyretic for adults and children 12 years and older and exclude products containing phenylephrine.

Table 1. Summary of NDA Approved Oral Treatment Options for Nonprescription Multi-Symptom Cough and Cold Combination Products Containing an Analgesic/Antipyretic for Adults and Children 12 Years and Older

Product Name	Active Ingredients and Dose	Purpose	Route, Dosage Form, and Dosing Instructions
Advil Cold and Sinus	• Ibuprofen 200 mg • Pseudoephedrine HCl 30 mg	• Pain reliever/fever reducer • Nasal decongestant	Oral capsule: 1 capsule every 4 – 6 hours
Advil Cold and Sinus	• Ibuprofen 200 mg • Pseudoephedrine HCl 30 mg	• Pain reliever/fever reducer • Nasal decongestant	Oral caplet: 1 caplet every 4 – 6 hours
Aleve-D Sinus and Cold	• Naproxen sodium 220 mg • Pseudoephedrine HCl 120 mg	• Pain reliever/fever reducer • Nasal decongestant	Oral caplet: 1 caplet every 12 hours

Source: Generated by reviewer from information collected on DailyMed and FDALabel
Note that phenylephrine containing products have not been included in this table.
Abbreviations: HCl, hydrochloride; mg, milligram; NDA, new drug application

Table 2. Summary of OTC Monograph Multi-Symptom Cough and Cold Combination Oral Products Containing an Analgesic/Antipyretic for Adults and Children 12 Years and Older

Active Ingredients	Purpose	Dosage Form(s)
Acetaminophen, Dextromethorphan HBr	Pain reliever/fever reducer Cough suppressant	Tablet, capsule, solution
Acetaminophen, Chlorpheniramine maleate	Pain reliever/fever reducer Antihistamine	Tablet, capsule
Acetaminophen, Guaifenesin	Pain reliever/fever reducer Expectorant	Capsule, solution
Acetaminophen, Dextromethorphan HBr, Guaifenesin	Pain reliever/fever reducer Cough suppressant Expectorant	Capsule, solution
Acetaminophen, Dextromethorphan HBr, Doxylamine succinate	Pain reliever/fever reducer Cough suppressant Antihistamine	Tablet, capsule, solution

Active Ingredients	**Purpose**	**Dosage Form(s)**
Acetaminophen, Dextromethorphan HBr, Chlorpheniramine maleate	Pain relief/ fever reducer Cough suppressant Antihistamine	Tablet, solution
Acetaminophen, Dextromethorphan HBr, Diphenhydramine	Pain relief/ fever reducer Cough suppressant Antihistamine	Solution
Acetaminophen, Dextromethorphan HBr, Pseudoephedrine HCl	Pain reliever/fever reducer Cough suppressant Nasal decongestant	Tablet
Acetaminophen, Dextromethorphan HBr, Chlorpheniramine, Pseudoephedrine HCl	Pain reliever/fever reducer Cough suppressant Antihistamine Nasal decongestant	Tablet
Acetaminophen, Dextromethorphan HBr, Guaifenesin, Pseudoephedrine HCl	Pain reliever/fever reducer Cough suppressant Expectorant Nasal decongestant	Tablet

Source: Generated by reviewer from information collected on DailyMed and FDALabel
Note: Phenylephrine containing products have not been included in this table.
Abbreviations: HBr, hydrobromide; HCl, hydrochloride; OTC, over-the-counter

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The proposed combination product contains three active pharmaceutical ingredients: naproxen sodium 110 mg, dextromethorphan HBr 30 mg, and guaifenesin 600 mg. There is no such triple-combination product currently marketed in the United States.

The individual active pharmaceutical ingredients have established U.S. marketing histories. Specifically, the listed drug or cross-reference drug for this application have been widely marketed in the United States as stated below:

- Mucinex DM (guaifenesin 600 mg/dextromethorphan HBr 30 mg extended-release tablets, NDA 021620) was owned by the same Applicant and originally approved on April 29, 2004, and has been marketed in the United States since that date.
- Aleve (naproxen sodium 220 mg tablets, NDA 020204) was originally approved on January 11, 1994, and has been marketed in the United States since that date.
- Aleve-D Sinus and Cold (naproxen sodium 220 mg/pseudoephedrine HCl 120 mg extended-release tablets, NDA 021076) was originally approved on November 29, 1999, and was marketed in the United States; however, this product is currently discontinued. The current Orange Book reference standard for this product is naproxen sodium and pseudoephedrine HCl extended-release tablets (ANDA 076518, Application holder: Perrigo), which was approved on March 17, 2004.

3.2. Summary of Presubmission/Submission Regulatory Activity

September 29, 2023

NDA 217338 was submitted, seeking marketing approval for the fixed-dose combination extended-release drug product Mucinex 12HR Cold & Fever Multi-Symptom (each tablet contains naproxen sodium 110 mg, dextromethorphan hydrobromide 30 mg, and guaifenesin 600 mg) for nonprescription use. The proposed dosing regimen is two tablets every 12 hours for adults and children 12 years and older. This 505(b)(2) application relies on FDA's previous findings of safety and effectiveness for NDA 021620 (Mucinex DM), NDA 020204 (Aleve), and NDA 021076 (Aleve-D Sinus and Cold).

July 26, 2024

FDA issued a CRL (Reference ID 5420432)[11] with following primary deficiency:

> *You have not provided sufficient evidence to support the proposed 12-hour duration of action and dosing regimen for your proposed ER product. The submitted pharmacokinetic (PK) data demonstrate that each component of the proposed fixed dose combination product is bioequivalent (BE) with that from approved listed drugs, Mucinex DM (guaifenesin 600 mg; dextromethorphan hydrobromide 30 mg ER tablet [NDA 021620]) and Aleve (naproxen sodium tablet [NDA 020204]). However, Aleve has a dosing direction that instructs consumers to take 1 tablet (i.e., 220 mg naproxen sodium) every 8 to 12 hours while symptoms last and allows consumers to take 2 tablets within the first hour for the first dose. Demonstration of BE of the naproxen component from your drug to Aleve is not adequate to support the modification of the dosing interval to the proposed 12-hour dosing interval.*

In addition, the CRL listed two potential approaches to address this deficiency:

1. *Provide clinical efficacy data to support a 12-hour duration of use when studied in a relevant patient population, or*
2. *Conduct a relative bioavailability study to establish a scientific bridge between the proposed product and Aleve-D Sinus and Cold (naproxen sodium 220 mg; pseudoephedrine HCl 120 mg extended-release tablet [NDA 021076]).*

September 26, 2024

A Type A meeting request and briefing package was submitted. FDA provided preliminary meeting comments on October 28, 2024 (Reference ID 5469432), which disagreed with PBPK approach; meanwhile generally agreed with the primary endpoints (i.e., C_{max}, AUC_{0-t}, and AUC_{0-inf}) and the listed drug (i.e., ANDA 076518) of the proposed Study 0225104.

July 7, 2025

NDA 217338 was resubmitted to address the deficiencies outlined in the July 26, 2024 CRL. The resubmission included the clinical study report for Study 0225104 and supporting analyses demonstrating bioequivalence between the naproxen sodium component of the proposed product and Aleve-D Sinus and Cold.

[11] FDA Complete Response Letter, NDA 217338, July 26, 2024, DARRTS Reference ID 5420432

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Product Quality

Regarding quality aspects of the application, the drug substance, drug product, biopharmaceutics, process, and facility sections were reviewed during the previous review cycle and found adequate to support approval of the application. The drug product has been granted a shelf life of 36 months in all container closure configurations.

In brief, no new CMC information is included in the resubmission of this NDA. The manufacturing facilities remain in acceptable status and the product quality information for this application remain adequate to support the NDA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new or original nonclinical data were requested or submitted to support safety of the active ingredients or excipients in the proposed drug product. During the previous review cycle, the Pharmacology/Toxicology reviewer conducted a safety assessment of the proposed excipients in the proposed formulation. At that time, it was determined that the proposed excipients were supported by their use in the approved drug products with similar clinical conditions of use and/or by a supportive food additive regulation published in the Code of Federal Regulations (CFR). Furthermore, there are no proposed changes to the proposed formulation provided in the current resubmission compared to the original submission. For additional details, refer to the nonclinical pharmacology/toxicology review and safety assessment provided during the original review cycle.

6 Clinical Pharmacology

6.1. Executive Summary

RB Health (US) LLC resubmitted NDA 217338 on July 7, 2025, seeking to address the dosing regimen-related clinical efficacy concern listed in the CRL dated July 26, 2024 (refer to Section 3.2).

In this submission (July 7, 2025), the Applicant included the study report from a newly conducted relative bioavailability study (Study 0225104). Study 0225104 is a phase 1, open-label, single-dose, randomized, 2-way crossover relative bioavailability study comparing the naproxen component of the proposed product to the listed drug Aleve-D Sinus and Cold (NDA 021076) under fasted condition. The study established bioequivalence between the naproxen component of the proposed product and the listed drug, Aleve-D Sinus and Cold, providing the necessary scientific bridge to support the proposed every 12-hour dosing regimen.

The clinical pharmacology program for this NDA consists of data from Studies RB5-US-1505 and 0225104, provides adequate scientific justification for the proposed every 12-hour dosing regimen for all three active pharmaceutical ingredients of the proposed FDC product. Study RB5-US-1505 established bioequivalence of guaifenesin and dextromethorphan between the proposed product and the cross-reference product Mucinex DM, while Study 0225104 specifically addressed the dosing interval concern by demonstrating bioequivalence to a naproxen-containing product (Aleve-D Sinus and Cold) that is approved for dosing every 12 hours. The data included in the current resubmission resolves the naproxen dosing regimen-related concern listed in the CRL dated July 26, 2024.

Recommendation: The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP), recommends **approval** of this application from a clinical pharmacology perspective. The submitted data adequately support the proposed every 12-hour dosing regimen and establish appropriate scientific bridges to the cross-referenced or listed drugs.

6.2. Summary of Clinical Pharmacology Assessment

The clinical pharmacology assessment for this resubmission included review of pharmacokinetic data from a relative bioavailability study 0225104, as well as associated bioanalytical methods. The resubmission assessment focused on establishing bioequivalence with naproxen listed drug and specifically addressing the 12-hour dosing interval for the proposed FDC product. The current review focuses on Study 0225104, which established the scientific basis for the every 12-hour regimen of the naproxen component. For detailed assessment of Study RB5-US-1505 to establish the scientific bridge between the other two active ingredients (i.e., guaifenesin and dextromethorphan) and Mucinex DM, refer to the original NDA 217338 Integrated Review

6.2.1. Pharmacology and Clinical Pharmacokinetics

Naproxen

Naproxen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. The mean $AUC_{0\text{-}inf}$ and C_{max} of naproxen following a single dose of the proposed product

(220 mg naproxen sodium, 60 mg dextromethorphan HBr, and 1200 mg guaifenesin) under fasted condition is 604 ± 118 µg·h/mL and 39 ± 10 µg/mL, respectively (Study 0225104). The median T_{max} is 1.5 hours. High fat meal does not have a clinically relevant effect on AUC and C_{max} of naproxen (Study RB5-US-1505).

According to drug label of NDA 018164, naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. Naproxen is extensively metabolized to 6-O-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-O-desmethyl naproxen (less than 1%) or their conjugates (66% to 92%).

Dextromethorphan

Dextromethorphan is an uncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor and a sigma-1 receptor agonist. The mean $AUC_{0\text{-}inf}$ and C_{max} of dextromethorphan following a single dose of the proposed product (220 mg naproxen sodium, 60 mg dextromethorphan HBr, and 1200 mg guaifenesin) under fasted condition is 272 ± 657 ng·h/mL and 302 ± 695 µg/mL, respectively (Study RB5-US-1505). The median T_{max} is 6 hours. High fat meal does increase $AUC_{0\text{-}inf}$ and C_{max} of dextromethorphan by 34% and 24%, respectively. The magnitude of increase in exposure is similar between the proposed drug product and the Mucinex DM.

According to drug label of NDA 215430, dextromethorphan is primarily metabolized by CYP2D6 to dextrorphan. In CYP2D6 extensive metabolizers, approximately 37-52% of the orally administered dose of dextromethorphan is recovered in the urine. Less than 2% of the administered dose is excreted as unchanged parent drug in the urine. In CYP2D6 poor metabolizers, approximately 45-83% of the administered dose is recovered in the urine.

Approximately 26% of the administered dose is excreted as unchanged parent drug in the urine.

Guaifenesin

Guaifenesin is an expectorant, the action of which promotes or facilitates the removal of secretions from the respiratory tract. The mean $AUC_{0\text{-}inf}$ and C_{max} of naproxen following a single

dose of the proposed product (220 mg naproxen sodium, 60 mg dextromethorphan HBr, and 1200 mg guaifenesin) under fasted condition is 8059 ± 3240 µg·h/mL and 1871 ± 793 µg/mL, respectively (Study 0225104). The median T_{max} is 1 hour. High fat meal does not have a clinically relevant effect on AUC and C_{max} of guaifenesin (Study RB5-US-1505).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen is 220 mg naproxen sodium, 60 mg dextromethorphan HBr, and 1200 mg guaifenesin (i.e., two tablets with the dosing strength of each tablet as 110 mg naproxen sodium, 30 mg dextromethorphan HBr, and 600 mg guaifenesin) every 12 hours in adults and children 12 years of age and older.

Therapeutic Individualization

No specific dose adjustments are proposed. The product follows the same age restrictions as the listed drugs (to be used in adults and children 12 years and older).

Outstanding Issues

None.

6.3.Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Throughout the review, the proposed drug product has been designated as (b) (4) tablets which was the initial proprietary name used by the Applicant in the product development studies prior to submission of the current NDA.

Study 0225104 was a phase 1, open-label, single-dose, randomized, 2-way crossover relative bioavailability study conducted to establish a scientific bridge between the proposed product and Aleve-D Sinus and Cold. Twenty-six healthy participants were randomized and dosed

(19 male, 7 female; mean age 31.3 years) with a 5-day washout period. Participants received either two (b) (4) tablets (total 220 mg naproxen sodium, 60 mg dextromethorphan HBr, and 1200 mg guaifenesin) or one Aleve-D Sinus and Cold tablet (220 mg naproxen sodium and 120 mg pseudoephedrine) under fasted conditions, using the current Orange Book reference standard (ANDA 076518) as agreed upon by the FDA. Refer to Section 14.4.1 for detail review on Study design and analysis plan.

The PK profiles and statistical summary of naproxen systemic exposures from two treatment groups observed in Study 0225104 are provided in Figure 1 and Table 3, respectively. The study

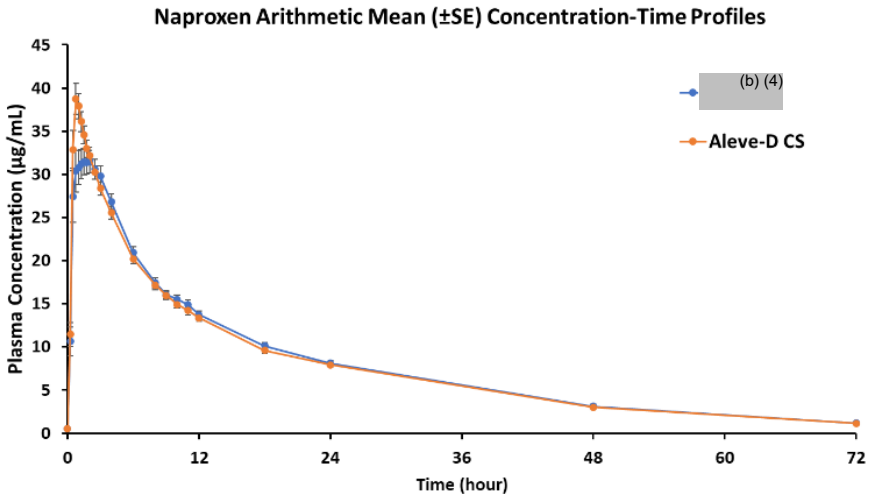
demonstrated similar PK profiles between the proposed product and Aleve-D Sinus and Cold under fasted conditions for the naproxen component (Figure 1). The median T_{max} of naproxen was delayed by 0.75 hours for the proposed product compared to Aleve-D Sinus and Cold. The clinical meaning of the slight difference between two median T_{max} values is unclear, as both of them are within the historically reported ranges. For example, in the Biopharmaceutics review of Aleve-D Sinus and Cold[12], Study S97-050 conducted under fasted condition demonstrated that, naproxen T_{max} was 1.26±0.95 hours for Aleve-D Sinus and Cold and 1.13±0.92 hours for the reference product, Aleve. Similarly, the Clinical Pharmacology review of Aleve PM showed that in Study 16135, under fasted conditions, naproxen T_{max} was 1.25 hours (range: 0.33-3.0 hours) for the combination product[13].

The mean elimination half-life was similar between treatments (17.63 hours for (b) (4) vs. 17.84 hours for Aleve-D Sinus and Cold). These PK findings are consistent with the naproxen PK results from Study RB5-US-1505 included in the original NDA submission, which demonstrated comparable elimination half-life (~18-20 hours) and bioequivalence with Aleve.

[12] The FDA's biopharmaceutics review of Aleve-D Sinus and Cold (NDA 21-076); https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21-076_Aleve_biopharmr.pdf

[13] The FDA's clinical pharmacology review of Aleve PM (NDA 205352) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205352Orig1s000ClinPharmR.pdf

Figure 1. Observed Arithmetic Mean PK Profiles of Naproxen Following 220 mg Single Dose in Study 0225104



Source: FDA Analysis using ADPC.xpt from Study 0225104. All the post-dose BLQ concentrations were imputed with 1/2 value of LLOQ
(0.5 µg/mL).
Abbreviations: Aleve-D CS; Aleve-D Sinus & Cold, mg, milligram; min, minute; mL, milliliter; µg, microgram; PK, pharmacokinetic; SE, standard error

Table 3. Statistical Summary of PK Parameters of Naproxen Obtained From Study 0225104

Parameter[1]	**Treatment A (N=26) ((b) (4) tablets)**	**Treatment B (N=26) (Aleve-D Sinus and Cold tablet)**
$AUC_{0\text{-}inf}$ (µg·h/mL)	604.36 ± 117.85	595.14 ± 109.86
$AUC_{0\text{-}72h}$ (µg·h/mL)	572.55 ± 99.83	563.13 ± 88.11
C_{max} (µg/mL)	39.01 ± 9.73	41.47 ± 7.09
Elimination half-life, $t_1/_2$ (h)	16.94 ± 3.08	17.12 ± 3.74
T_{max} (h)[2]	1.5 (0.5 - 4.0)	0.75 (0.5 - 2.5)

Source: FDA Analysis using ADPC.xpt from Study 0225104. All the post-dose BLQ concentrations were imputed with 1/2 value of LLOQ
(0.5 µg/mL).
1 All values are expressed in Arithmetic mean ± SD
2 Median (min, max)
Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve estimated to infinity; $AUC_{0\text{-}72h}$, area under the concentration-time curve from time 0 to 72 hours; C_{max}, maximum plasma concentration; h, hour; mL, milliliter; N, number (of population); µg - microgram; SD, standard deviation; Tmax, time to maximum concentration; $t_{1/2}$, half-life

Study 0225104 showed that all primary PK parameters met bioequivalence criteria, with 90% CIs for geometric mean ratios of C_{max} (87.07-98.25%), AUC_{0-72h} (99.31-103.56%), and AUC_{0-inf} (98.8-104.01%) within the acceptance range of 80.00-125.00% as shown in Table 4.

Table 4. Statistical Comparisons of PK Parameters of Naproxen Under Fasted Conditions from Study 0225104

Parameter	Listed Drug (Aleve-D Sinus & Cold) GeoLSM	Proposed Product ((b) (4) GeoLSM	T/R Ratio [90% CI]
C_{max} (µg/mL) (n=26)	40.89	37.82	92.49% (87.07-98.25%)
AUC_{0-72h} (µg*h/mL) (n=26)	556.98	564.87	101.41% (99.31-103.56%)
AUC_{0-inf} (µg*h/mL) (n=26)	586.38	594.43	101.37% (98.8-104.01%)

Source: FDA Analysis using ADPC.xpt from Study 0225104. All the post-dose BLQ concentrations were imputed with 1/2 value of LLOQ
(0.5 µg/mL).
Abbreviations: AUC_{0-inf}, area under the concentration-time curve estimated to infinity; AUC_{0-72h}, area under the concentration-time curve from time 0 to 72 hours; CI, confidence interval; C_{max}, maximum plasma concentration; GeoLSM, geometric least squares mean; h, hour; mL, milliliter; N, number (of population); T/R, test/reference ratio; µg - microgram

Study 0225104 therefore established bioequivalence between the naproxen component of the proposed product and Aleve-D Sinus and Cold, providing the necessary scientific bridge to support the every 12-hour dosing regimen and addressing the deficiency identified in the CRL dated July 26, 2024. The bioanalytical methods were reasonably validated and the Office of Clinical Pharmacology has no outstanding concerns regarding this application.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology program provides supportive evidence of effectiveness through establishment of appropriate scientific bridges to the cross-reference drug and the listed drugs for all three active pharmaceutical ingredients. The proposed dosing regimen of two tablets every 12 hours is supported by the same approved dosing regimen of the listed drug products.

The scientific bridges are established by demonstration of bioequivalence between the proposed product and the cross-reference drug and the listed drugs through two key studies. Study RB5-US-1505 demonstrated bioequivalence of all three active pharmaceutical ingredients to Mucinex DM and Aleve under fasted conditions, with 90% confidence intervals of geometric mean ratios of C_{max} and AUCs within the acceptance range of 80.00-125.00%. Study 0225104 specifically addressed every 12-hour dosing interval concern by establishing bioequivalence

between the naproxen component and Aleve-D Sinus and Cold, which is approved with every 12-hour dosing interval. The overall clinical program in this resubmission provides the necessary scientific bridge to allow the Applicant to rely on FDA's finding of safety and effectiveness for the listed drugs.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen of 220 mg naproxen sodium, 60 mg dextromethorphan HBr, and 1200 mg guaifenesin every 12 hours in adults and children 12 years of age and older is appropriate for the general patient population, as the same dosing regimen is approved for the listed drugs.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Refer to the drug facts of the cross-reference drug product [Mucinex DM (NDA 021620) and the listed drug product Aleve-D Sinus and Cold (NDA 021076)], no alternative dosing regimens are needed for subpopulations based on intrinsic factors.

The Applicant did not seek approval of drug product in children under 12 years of age, as naproxen is not approved for nonprescription use in this population. Per the agreed initial pediatric study plan (dated June 1, 2019), the FDA granted clinical study waivers for subjects aged 0-17 years, allowing extrapolation of adult PK data to support use in the 12-17 age group.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No clinically relevant food-drug interactions were identified. Study RB5-US-1505 demonstrated no significant food effect on systemic exposure of guaifenesin and naproxen components, with 90% CIs of geometric mean ratios for C_{max} and AUCs between fasted and fed conditions within 80-125%. Dextromethorphan showed increased exposure with food (34% increase in C_{max}); however, this effect was similar to the cross-reference drug product Mucinex DM and supports administration regardless of food. The proposed labeling recommends taking with food or milk if stomach upset occurs, consistent with the labeling for Aleve-D Sinus and Cold and Aleve.

No dedicated drug-drug interaction studies were conducted under this NDA. The proposed labeling incorporates established drug interaction warnings from the listed drugs. Key interactions include contraindication with monoamine oxidase inhibitors for dextromethorphan and potential serotonin syndrome with concomitant serotonergic drugs. The naproxen component includes standard NSAID warnings regarding interactions with anticoagulants and potential interference with aspirin's cardioprotective effects. The Applicant conducted an in

vitro dose dumping study and concluded that alcohol does not significantly impact dissolution of the three ingredients compared to the listed drugs[14].

Were the bioanalytical methods supporting the two pivotal studies for this application adequate?

Yes, the bioanalytical methods supporting both pivotal studies were adequate. Both methods were conducted at qualified laboratories and met regulatory standards for bioequivalence studies. *Refer to Section 14.4.2 in this review for detail assessment*.

For Study RB5-US-1505, a validated LC-MS/MS bioanalytical method simultaneously determined concentrations of all three analytes in human plasma with appropriate lower limits of quantification (0.01 ng/mL for dextromethorphan, 5 ng/mL for guaifenesin, and 50 ng/mL for naproxen). The method demonstrated acceptable precision (CV ≤6.8%), accuracy (relative error within ±4.8% to 6.7%), and satisfactory in-study performance with passing rates >94% for all analytes and incurred sample reanalysis meeting acceptance criteria. *Refer to the original NDA 217338 Integrated Review, Section 14 for detail assessment.*

For Study 0225104, a validated HPLC-MS/MS method was used for naproxen determination with a lower limit of quantification of 1.00 µg/mL. The bioanalytical laboratory ((b) (4)) conducted the analysis using established validated methods, with all samples analyzed within the established storage period.

7 Sources of Clinical Data and Review Strategy

7.1.Table of Clinical Studies

[14] \\CDSESUB1\EVSPROD\nda217338\0003\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\rbhi-mi-2251\rbhi-mi-2251.pdf

Table 5. Listing of Clinical Studies Relevant to this NDA

Study Identifier	Objective of Study	Study Design and Type of Control	Test Product (s)	Treatment Duration	No. of patients enrolled	Study Population
Pivotal Clinical Studies						
RB5-US-1505	Relative BA vs. reference product	Open label, randomized, balanced, 4-treatment, 4-period, crossover BA study of an experimental combination ER test product vs. co-administration of reference products under fasted and fed conditions	Test product: ER guaifenesin 600 mg/dextromethorphan HBr 30mg/ naproxen 220 mg bilayer tablet Reference product: Co-administration of Mucinex DM (guaifenesin 600 mg/dextromethorphan HBr 30mg) tablet and naproxen sodium (220mg) tablet	Single dose	102	Healthy Subjects
0225104	Relative BA vs. reference product	Open label, randomized, 2-way crossover relative BA study to analyze the naproxen sodium IR plasma concentrations from 2 x ER test product vs. reference product under fasting conditions	Test product: ER guaifenesin 600 mg/dextromethorphan HBr 30mg/ naproxen 220 mg bilayer tablet ((b) (4) Reference product: Naproxen sodium 220 mg IR and pseudoephedrine hydrochloride 120 mg ER (Aleve-D Sinus and Cold)	Single dose	26	Healthy Subjects

Pilot Clinical Studies						
2009-GGE-TRI-DM	Relative BA vs. reference product	Open label, randomized, balanced, 4-treatment, 4-period, crossover BA study of 2 experimental combination ER test product under fasted and fed condition vs co-administration of reference products under fasted conditions	Treatment A: (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30mg/naproxen 220 mg bilayer tablet under fasting condition Treatment B: (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30mg/naproxen 220 mg bilayer tablet under fasting condition Treatment C: (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30mg/naproxen 220 mg bilayer tablet under fed condition Reference product: Co-administration of Mucinex (guaifenesin) 600mg, Vicks Formula 44 Custom Care 30 mg syrup, and Aleve (naproxen sodium 220mg)	Single dose	30	Healthy Subjects

2014-MUCDM-NAP-02	Relative BA vs. reference product	Open label, randomized, balanced, 5-treatment, 5-period, crossover BA study of 2 experimental combination ER test products vs. co- administration of reference products under fasted and fed conditions	Treatment A: 2 (b) (4) of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30mg/naproxen 110 mg bilayer tablet under fasting condition Treatment B: 2 (b) (4) of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30mg/naproxen 110 mg bilayer tablet under fed condition Treatment C: 2 (b) (4) of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr 30mg/naproxen 110 mg bilayer tablet under fasting condition Treatment D: 2 (b) (4) of (b) (4) formulation ER guaifenesin 600 mg/ dextromethorphan HBr	Single dose	25	Healthy Subjects

			30mg/naproxen 110 mg bilayer tablet under fed condition <u>Reference product</u>: Co-administration of 2 Mucinex DM (guaifenesin 600 mg/dextromethorphan HBr 30mg) tablets and 1 naproxen sodium (220mg) tablet under fasting condition			

7.2.Review of Safety

7.2.1. Safety Review Approach

This safety review centers on clinical safety data from PK study 0225104. For the comprehensive safety assessment of this drug product, refer to the Integrated Review (IR) dated July 26, 2024 (DAARTS Reference ID: 5420429).

The safety review for this proposed fixed-dose combination (FDC) product establishes that while each of the three active ingredients has well-established individual safety profiles from longstanding nonprescription use, the main focus is determining whether the combination can be safely used without a healthcare intermediary.

The Applicant supported combination safety through PK study data with pivotal PK study RB5-US-1505 demonstrating bioequivalence (Section 7.6 of IR) and through two exploratory PK studies (Section 17 of IR) that were conducted with earlier formulations of the FDC product (Pilot studies 2009-GGE-TRI-DM and 2014-MUCDM-NAP-02). Additionally, comprehensive postmarketing safety evaluations (Section 7.6.2 of IR) were completed using multiple databases (internal pharmacovigilance, FAERS, WHO Vigibase, NPDS) and literature reviews (Section 7.6.2.2 of IR) to identify any unexpected or serious adverse events associated with concomitant use of guaifenesin, dextromethorphan, and naproxen. Furthermore, given dextromethorphan's known abuse potential, the Controlled Substance Staff (CSS) was consulted to evaluate abuse and misuse risks for the proposed product, with their full review completed on January 22, 2024 (Section 7.7.3 of IR).

7.2.2. Review of the Safety Database

Overall Exposure

A total of 183 subjects were randomized across all four PK studies and received at least one dose of the study drug. 102 subjects were enrolled in Study RB5-US-1505, 26 subjects were enrolled in Study 0225104, 30 subjects were enrolled in Study 2009-GGE-TRI-DM and 25 subjects were enrolled in Study 2014-MUCDM-02.

Adequacy of the Safety Database:

Study RB5-US-1505 and Study 0225104 both used the intend-to-market formulation. Given the well-established safety profiles of each active ingredient and extensive postmarketing experience, the safety database generated from the PK studies is adequate.

The Applicant’s evaluation of postmarketing safety data and published literature for safety issues related to the independent and concomitant nonprescription use of the three active ingredients was reviewed in the Integrated Review. These evaluations were conducted

according to expectations for a nonprescription application and were considered adequate to support the review.

7.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

None.

Categorization of Adverse Events

FDA defines an adverse event (AE) as any untoward medical occurrence associated with the use of a drug in humans, whether it was considered drug-related or not. Therefore, an AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with use of a drug product. The categorization of AE from the clinical developmental program is acceptable. AEs were attributed to the most recent treatment received prior to the AE. Treatment-emergent adverse events (TEAEs) were defined as any AEs not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. Case reports categorized as having serious outcomes are defined as having any adverse drug event that results in death, a life-threatening event, hospitalization, disability or permanent damage, congenital anomaly or birth defect, requirement of an intervention to prevent permanent impairment or damage, or other serious important medical events.

In the PK study, investigators were required to report all directly observed AEs and all AEs spontaneously reported by study subjects. Study subjects were questioned about AEs at all post-baseline assessments. The investigator made severity assessments and causality assessments for all AEs. The terms "mild," "moderate," and "severe" were used to describe the severity of an AE using the definitions in Table 6.

Table 6. Definitions for Adverse Event Severity

Adverse Event Severity	Definition
Mild	AE does not limit usual activities; the subject may experience slight discomfort
Moderate	AE results in some limitation of usual activities; the subject may experience significant discomfort
Severe	AE results in an inability to carry out usual activities; the subject may experience intolerable discomfort or pain

Source: Adapted from eCTD Module 5.3.1.1 Study Report Body
Abbreviation: AE, adverse event

The causality assessment determined if there is a reasonable possibility that the investigational product caused or contributed to an AE. The investigator determined this relationship using the definitions in Table 7.

Table 7. Definitions for Adverse Event Causality

Relationship	Description
Unrelated	No possibility that the AE was caused by the test product
Unlikely	Slight, but remote, chance that the AE was caused by the test product, but the balance of judgment is that it was most likely not due to the test product
Possible	Reasonable suspicion that the AE was caused by the test product
Probable	Most likely that the AE was caused by the test product
Certain	The AE was definitely caused by the test product

Source: Adapted from eCTD Module 5.3.1.1 Study Report Body
Abbreviation: AE, adverse event

7.2.4. Safety Results

Overview and Objectives

Study 0225104

The primary objective of this study was:

To assess the relative BA in rate and extent of exposure of active ingredient IR naproxen sodium from Treatment A (two (b) (4)] tablets) relative to that from Treatment B (one Aleve-D Sinus and Cold tablet) in healthy adults in the fasted state.

The secondary objectives of this study were to:

- Assess other pharmacokinetic (PK) parameters for naproxen sodium related to rBA between Treatment A (b) (4) and Treatment B (Aleve-D Sinus and Cold)
- Assess the safety and tolerability of test product and reference product in healthy adults

Methodology

The study consisted of a pre-study screening visit followed by two treatment periods, a washout period and an end of study visit conducted at Day 5 (+2 days) after the last dose. Each of the treatment periods were 5 days in duration. The total duration of study participation was 6 weeks.

Subjects who met the inclusion and exclusion criteria were assessed for final eligibility and admitted to the Clinical Unit for an overnight fast. Subjects were randomized to receive the treatment sequence AB or BA on Day of Treatment Period 1. Randomized participants received either Treatment A ((b) (4) or Treatment B (Aleve-D Sinus and Cold).

The treatments for each period included:

- A: Two (b) (4) bi-layer ER tablets each containing 600 mg guaifenesin, 30 mg dextromethorphan hydrobromide, and 110 mg naproxen sodium, administered with 240 mL of water after an overnight fast of 10-hours

- B: One Aleve-D Sinus and Cold ER Tablet containing 220 mg naproxen sodium and 120 mg pseudoephedrine hydrochloride, administered with 240 mL of water after an overnight fast of 10 hours

During the study, blood samples were collected at various time points to measure the concentration of naproxen in the participants' plasma. There was washout of 5 days between the last dose of Treatment Period 1 and first dose of Treatment Period 2 to allow complete elimination of the study drug before subsequent dosing, based on 5 elimination half- lives of naproxen.

Adverse events (AEs), medical history, vital signs, physical exam (PE), electrocardiogram (ECG), routine laboratory tests (hematology, biochemistry, urinalysis, urine for drugs of abuse, and urine pregnancy [if applicable]) were measured as safety endpoints.

Demographics

The study population consisted of 19 male subjects (19/26; 73.1%) and 7 female subjects (7/26; 26.9%). Most subjects were White (20/26; 76.9%); the rest were Black or African American (6/26;23.1%). All (100%) of subjects were Hispanic or Latino. Subjects' ages ranged from 21-41 years with a mean age of 31.3. The mean BMI (SD) was 25.35 kg/m^2.

Deaths

There were no deaths.

Serious Adverse Events

There were no serious adverse events.

Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts and/or discontinuations from the study.

Significant Adverse Events

There were no significant adverse events.

Treatment Emergent Adverse Events and Adverse Reactions

Twenty- six subjects were randomized, received a dose of the study drug, and completed the treatment period. Two participants (2/26; 7.7%) did not return for the follow up visit and did not complete the study and were considered lost to follow up per the study protocol. Twenty-four (24/26; 92.3%) of participants completed the study. All 26 randomized participants who received a dose of the study drug were included in the safety population.

Seven participants (7/26; 26.9%) reported a total of fifteen Treatment Emergent Adverse Events (TEAEs). Four participants (4/26; 15.4%) reported seven TEAEs after receiving Treatment A ([redacted] and five participants (5/26; 19.2%) reported eight TEAEs after receiving Treatment B (Aleve-D Sinus and Cold). Thirteen of the total TEAEs (13/15; 86.7%) were considered mild in severity. Two TEAS (2/15;13.3%) reported in one participant after receiving Treatment B (Aleve-D Sinus and Cold) were moderate in severity (Table 8).

Table 8. TEAEs and Severity by Treatment Group

	Total (N=26)	**Treatment A** [redacted] **(N=26)**	**Treatment B** **Aleve-D** Sinus and Cold **(N=26)**
Number of subjects reporting AEs	7 (26.9%)	4 (15.4%)	5 (19.2%)
TEAEs	15	7	8
Severity			
Mild	13	7	6
Moderate	2	0	2
Severe	0	0	0

Source: Table generated by reviewer. Adapted from data in eCTD, Module 5.3.1.1 Study 0225104.
Abbreviations: AE, adverse event; N, number (of population); [redacted] TEAE, treatment-emergent adverse event

Among the 15 TEAEs, the most frequent System Organ Class (SOC) was Investigations with 8 out of 15 (8/15; 53.3 %) of TEAEs. The second most affected SOC was Musculoskeletal and Connective Tissue Disorders with two TEAEs (2/15;13.3%) in this category. Other SOCs with single occurrences were in the Cardiac Disorder, Infections and Infestations, Nervous system disorders, Injury, poisoning, and procedural complications and Skin and subcutaneous tissue disorder (Table 9).

There were 3 TEAEs out of 15 that were not resolved by the end of the study and 2 that needed intervention.

Table 9. Reported TEAEs by Treatment Group, Severity, Resolution and Need for Intervention

SOC /PTs	Total (N=26)	Treatment A (N=26)	Treatment B (N=26)	Severity	Resolved by EOS	Need for intervention
Investigations	**8 (53.3%)**					
ALT increased			1	Mild	yes	no
CPK		1		Mild	yes	no
Eosinophil increase			2	Mild	No (1 of 2)	no
Heart rate increased		1		Mild	yes	no
Nitrite urine increased		1		Mild	No	no
WBC increased			1	Mild	yes	no
WBC in urine positive		1		Mild	No	no
Musculoskeletal & connective tissue disorders	**2 (13.3%)**					
Pain in extremity		1	1	Moderate	yes	yes
Cardiac Disorders	**1 (6.7%)**					
Palpitations			1	Mild	yes	no
Infections and Infestations	**1 (6.7%)**					
Cellulitis			1	Moderate	yes	yes
Injury, poisoning and procedural complications	**1 (6.7%)**					
Skin abrasion		1		Mild	yes	no
Nervous system disorder	**1 (6.7%)**					

Presyncope			1	Mild	yes	no
Skin and subcutaneous tissue disorders	**1 (6.7%)**					
Pruritus		1		Mild	yes	Yes

Source: Table generated by reviewer.
Adapted from data in eCTD, Module 5.3.1.1 Study 0225104.
Abbreviations: SOC, System Organ Class; PT, Preferred Terms; N, number (of population); ALT, alanine transaminase; CPK, creatinine phosphokinase; WBC, white blood cell count, EOS, end of study

Analyses of TEAEs by Treatment Group (Table 9)

Treatment A ((b) (4))

Four participants (4/26;15.4%) reported seven TEAEs after receiving Treatment A ((b) (4)). All TEAEs were considered mild in intensity. All TEAES except for two TEAES in one participant were resolved by the end of the study. One TEAE needed intervention.

TEAEs that were unresolved and/or needed treatment

1. Participant (b) (6) was found to have nitrite and white blood cells in the urinalysis. No treatment was given for this event. The event was ongoing at the end of the study (not recovered/ not resolved). These two TEAEs were considered to be mild in intensity and unrelated to the treatment.
2. Participant (b) (6) had pruritus that was treated with Aquaphor and resolved without further intervention. The TEAE was considered to be mild in intensity and was thought to be unrelated to the treatment.

Treatment B (Aleve-D Sinus and Cold)

Five participants reported eight TEAEs after receiving Treatment B (Aleve-D Sinus and Cold). Six of the eight TEAEs were considered mild in intensity, two TEAEs reported in one participant were moderate in intensity and required treatment and one TEAE in the Treatment B group was not resolved by the end of the study.

TEAEs that were unresolved and/or needed treatment

1. Participant (b) (6) had leg pain that was eventually diagnosed as cellulitis of the left leg. The participant received saline gauze, oral antibiotics (cephalexin) and acetaminophen. The events were considered to be moderate in intensity. The events were resolved by the end of the study and were not considered to be related to the treatment.
2. Participant (b) (6) had progressively increased ALT levels reaching a peak on Day 5 (received Treatment A on Day 1). The subject had marginally elevated levels before receiving study drug (Pre dose level) which was considered to be clinically insignificant by the personal investigator (PI). The increased ALT level resolved by the end of the

study. The TEAE was considered to be mild in intensity and did resolve without intervention.

3. Participant (b) (6) had increased eosinophilic, and leukocyte count after receiving Treatment A. This elevated count remained increased by the end of the study period (unresolved). This TEAE was considered mild in intensity and thought to be related to an allergic reaction per the PI and unrelated to the treatment. No treatment was given for the event.

Reviewer's comment:

All TEAES except for two were mild in severity. The two TEAEs considered moderate in severity were due to pain and cellulitis of the leg unrelated to the study drug. Almost all TEAEs were considered unrelated to study drug. The one TEAE thought to be possibly related to Treatment A had an elevated ALT level that possibly had an onset preceding the study drug.

Laboratory Findings

Laboratory evaluations (performed pre and post study) included complete blood count with differential; serum chemistry (sodium, potassium, chloride, urea, creatinine) total protein, albumin, total bilirubin, alkaline phosphatase, ALT, AST, creatinine kinase, fasting glucose, total cholesterol, triglycerides, HDL/ LDL cholesterol and urinalysis. Also tested were antibodies to HIV, hepatitis B and hepatitis C and urine screen for drugs of abuse (opiates cannabis amphetamines), alcohol breath test and pregnancy test (urine and serum).

Laboratory Abnormalities:

5 subjects had at least one abnormal laboratory result (Table 10)

- Subject (b) (6) had increased leukocyte and neutrophil count. These elevated counts were closely related to possible cellulitis of the leg. Both increased counts resolved by the end of the visit.
- Subject (b) (6) had increased eosinophil and eosinophil/leukocyte counts. These events were considered to be related to an allergic reaction. The increased counts were not resolved by EOS.
- Subject (b) (6) had an increased creatinine kinase level. Levels normalized without treatment at the EOS visit.
- Subject (b) (6) had increased ALT levels that normalized without treatment by the EOS visit.
- Subject (b) (6) had a positive nitrite and white blood cells in the urine. The events were ongoing and unresolved by the EOS.

Table 10. Subjects With Abnormal Laboratory Values by Treatment Groups

Preferred Term	Treatment A	Treatment B
WBC count Increased		1
Eosinophil count Increased		1
Blood creatinine kinase increased	1	
Alanine aminotransferase Increased		1
Nitrite urine and White blood cells urine present	1	

Source: Table generated by reviewer.
Adapted from data in eCTD, Module 5.3.1.1 Study 0225104.
Abbreviations: WBC, white blood cell count

Reviewer Comment: Laboratory testing did not reveal any specific or clinically significant safety findings.

Vital Signs

Vital signs including blood pressure, heart rate, respiratory rate and temperature were collected at baseline and end of study.

One participant (Participant (b) (6)) had an elevated heart rate 4 days after administration of Treatment A and 1 day prior to receiving Treatment B. The increased heart rate remained elevated until the end of the study. The elevated level was not considered clinically significant. No treatment was given for this AE and the event resolved by the end of the study.

Reviewer Comment: On review of this participant's vital signs, the heart rate was elevated on Treatment Day 5 (112 beats/minute), 4 days after receiving Treatment A, then peaked at 122 beats/minute, 5 days post dose Treatment A, pre dose Treatment B on Day 6. The heart rate remained elevated at the follow up visit at 108 beats per minute. The fact that the elevated heart rate occurred 4 days after receiving treatment A makes this AE unlikely to be related to the study drug. Vital signs did not reveal any specific or clinically significant safety findings.

Electrocardiograms (ECGs)

ECG was collected at baseline and at EOS visit for all patients. The Applicant reports no clinically significant abnormal ECG results during the study.

QT

Not applicable

Immunogenicity

Not applicable

Physical Exam

One subject had clinically significant physical exam findings:

- Subject (b) (6) had cellulitis of the left leg. The details of this subject's care were provided above under analysis by Treatment group.

Reviewer Comment: Physical exam findings did not reveal any specific or clinically significant safety findings. Leg pain and cellulitis findings in one subject were unlikely related to the drug products.

7.2.5. Analysis of Submission-Specific Safety Issues

None

7.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable

7.2.7. Safety Analyses by Demographic Subgroups

Not applicable

7.2.8. Specific Safety Studies/Clinical Trials

Not applicable

7.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable

Human Reproduction and Pregnancy

Except for urine pregnancy tests obtained in screening of subjects, no human reproduction or additional pregnancy data was included in this NDA submission.

Pediatrics and Assessment of Effects on Growth

There was no assessment of effects on pediatric growth in this NDA. Refer to Section 9 for review of pediatric assessment under the Pediatric Research and Equity Act (PREA).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The proposed drug product is an ER combination product containing 30 mg of dextromethorphan HBr. Due to the established abuse potential of dextromethorphan, the Controlled Substance Staff (CSS) was consulted to evaluate the abuse and misuse potential of dextromethorphan in this formulation.

Dr Chad Reissig from CSS conducted a comprehensive evaluation and concluded that the proposed drug product does not present an increased abuse potential relative to existing FDA approved products containing dextromethorphan. Based on this assessment, no specific regulatory actions or additional labeling information were recommended to address misuse and abuse potential concerns.

For additional details regarding this evaluation, refer to Section 7.7.3 of the Integrated Review dated July 26, 2024, and to CSS consult memorandum by Dr Chad Reissig dated

January 22, 2024 (DARRTS Reference ID: 5314327).

7.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Refer to Section 7.6.2. of the Integrated Review dated July 26, 2024 (for extensive review of the postmarking data submitted for this drug product).

Expectations on Safety in the Postmarket Setting

Refer to Section 7.6.2. of the Integrated Review dated July 26, 2024 (for extensive review of the postmarking data submitted for this drug product).

7.3. Conclusions and Recommendations

The safety evaluation of this new FDC consisted of a comprehensive evaluation of four clinical studies (two pivotal and two pilot clinical pharmacology studies) and a review of postmarketing surveillance data from multiple sources including FAERS, WHO Vigibase, Applicant's internal safety database, NPDS and literature review.

The integrated safety analysis did not identify any new or unexpected safety signals that would preclude nonprescription use of this product in adults and children 12 years and older. The benefit-risk assessment remains favorable for the proposed indications.

The Division of Nonprescription Drugs 1 recommends approval of this application from a safety perspective. The totality of evidence supports the safe use of this FDC product for the proposed nonprescription indications when used according to the proposed labeling.

8 Advisory Committee Meeting and Other External Consultations

As no review issues were determined to require discussion by outside experts, an advisory committee meeting was not held during this marketing application review.

9 Pediatrics

Pediatric Research and Equity Act (PREA) was triggered for this submission because the proposed product represents a new fixed dose combination product. The Applicant submitted an initial Pediatric Study Plan (iPSP) that proposed a request for a pediatric waiver in children less than 12 years and extrapolation to support use in children 12 years and older. This was discussed by the Pediatric Research Committee (PeRC) on January 23, 2019, and the Applicant received an agreed PSP on June 1, 2019.

In this current submission, consistent with the agreed PSP, the Applicant has requested a partial waiver of pediatric studies in children under 4 years because the drug would be unsafe. The Applicant has also requested a partial waiver for children 4 to less than 12 years of age and FDA agreed to this partial waiver because the product would not represent a meaningful therapeutic benefit.

The Applicant proposed to use identical dosing instructions for adolescents (12 to less than 17 years) and adults. This would mirror the dosing directions of the cross-reference drug Mucinex DM and the listed drug Aleve, which are both approved for use in children 12 years and older with the same directions as for adults. The pediatric assessment relies on the premise that the course of the disease and the effects of the active ingredients are sufficiently similar in adults and pediatric patients 12 years and older. Since the adult PK study demonstrated BE of each FDC component with its corresponding cross-reference or listed drug (Mucinex DM or Aleve), the adult PK data can be extrapolated to support safety and efficacy in the pediatric population down to 12 years without requiring additional pediatric studies.

No new nonclinical studies or pediatric clinical studies were conducted to support pediatric use of this new FDC product. The proposed product contains no novel excipients, and no reformulation was needed for the proposed pediatric use.

The proposed labeling for this product includes the contraindication, “Do not use” for children under 12 years of age.

The PeRC meeting was held on November 4, 2025, and deemed the pediatric study plan acceptable.

10. Labeling Assessments

10.1. Nonprescription Drug Labeling

The Applicant submitted outer carton and immediate container (blister) labeling for its proposed drug (see Table 11). The proposed labeling reflects aspects of the approved labeling for NDA 021620 (Mucinex DM), NDA 021076 (Aleve-D Sinus and Cold), and NDA 020204 (Aleve) given this application relies on the safety and efficacy from these NDAs.

The interdisciplinary scientist review team in the Division of Nonprescription Drugs 1 (DNPD I) was tasked with assessing the labeling proposed in NDA 217338 to determine if it:

1. Follows nonprescription labeling regulations,
2. Makes truthful and non-misleading claims,
3. Appropriately integrates requirements for naproxen sodium nonprescription labeling.

The proposed draft labeling for the product was assessed to determine whether it was presented in accordance with all applicable regulations[15]. The review team identified minor labeling issues that are summarized below. The Applicant was notified of these issues in the October 15, 2025, Information Request letter. The Applicant resolved these issues in its October 24, 2025, submission.

Summary of Labeling Issues Identified

Principal Display Panel (PDP):

- The proprietary name, “Mucinex 12HR Cold & Fever Multi-Symptom,” was not consistently prominent. The term “Multi-Symptom” appeared as a descriptor rather than part of the proprietary name due to inconsistent type sizing.
- The statement of identity (SOI) formatting did not comply with bold face type requirements under 21 CFR 201.61(c).
- "Value-size" promotional flags were inconsistently used across different package sizes without clear justification.
- Inconsistent placement of "Bi-Layer Tablets" term across different count sizes.

[15] 21 CFR 201.60 – 201.80; Draft guidance for industry Statement of Identity and Strength — Content and Format of Labeling for Human Nonprescription Drug Products (September 2022)

Drug Facts Label (DFL) Regulatory Compliance Issues:

- Incorrect use of singular "**Purpose**" heading instead of required plural "**Purposes**" form per 21 CFR 201.66(c)(3).
- Improper footnote formatting using (b) (4) instead of an asterisk for the term "NSAID." Per 21 CFR 201.326(a)(2)(ii), the Active ingredients section must contain the term "(NSAID*)" after the naproxen sodium active ingredient, where an asterisk immediately follows the term "NSAID" to direct the consumer to the full term "Nonsteroidal anti-inflammatory drug."

Drug Facts Label (DFL) Clinical Concern:

- The allergy warning was not positioned as the first bullet point under "**Do not use**" subheading.

Table 11. Proposed Draft Labeling

Proposed Labeling	**Dates Submitted**
4-count outer carton (HCP sample)	September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025
8-count outer carton	September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025
16-count outer carton	September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025
32-count outer carton	September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025
60-count outer carton	September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025
4-count blister card	September 29, 2023, February 22, 2024, July 7, 2025
8-count blister card	September 29, 2023, February 22, 2024, July 7, 2025
10-count blister card	September 29, 2023, February 22, 2024, July 7, 2025
4-count peel-back DFL	September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025
8-, 16-, 32-, and 60-count peel-back DFL	September 29, 2023, February 22, 2024, July 7, 2025, October 24, 2025

Website mock-ups	October 24, 2025

Source: Reviewer generated table using labeling materials from NDA Module 1.14.1.1 submitted September 29, 2023, February 22, 2024, July 7, 2025, and October 24, 2025.
Abbreviations: DFL, Drug Facts label; HCP, health care professional

Figure 2. Outer Carton

Source: NDA 217338 submitted October 24, 2025

10.2. Drug Facts Label

The proposed Drug Facts label (DFL) is presented in two peel-back labels, one label will be contained on the 4-count outer carton label and the other label will be used on the 8-count, 16-count, 32-count, and 60-count outer carton labels (Figure 3). Both proposed peel back presentations display the "**Drug Facts**" title, "***Active ingredient***" heading, and "***Purpose***" headings without needing to peel back the label. A statement instructing the consumer to "PEEL CORNER FOR COMPLETE DRUG FACTS" is contained in the lower left corner of the first page of the label. The proposed DFL is acceptable.

The proposed directions (listed below) specify a dosing regimen of two tablets every 12 hours for adults and children 12 years and older. The proposed dosage form is a bilayer tablet that contains 30 mg of dextromethorphan HBr, 600 mg of guaifenesin, and 110 mg of naproxen sodium. The proposed product matches the active ingredient strengths and dosing instructions

of Mucinex DM (NDA 021620), which contains identical amounts of dextromethorphan HBr and guaifenesin per tablet. For the naproxen sodium component, each tablet of the proposed product contains 110 mg, which is half the strength of Aleve tablets (NDA 020204) that contain 220 mg naproxen sodium. While Aleve dosing is one tablet every 8 to 12 hours, the proposed product requires two tablets every 12 hours.

- do not crush, chew, or break extended-release tablet
- do not take more than directed
- take each dose with a full glass of water
- adults and children 12 years and older: take 2 extended-release tablets every 12 hours; not more than 4 extended-release tablets in 24 hours
- children under 12 years of age: do not use

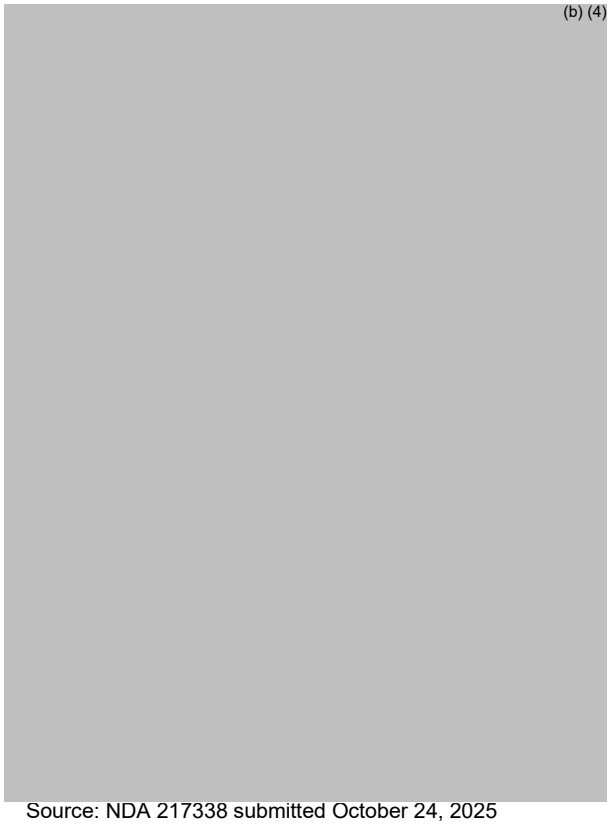
The proposed indications (below) are consistent with the reference drugs.

- 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
    - minor aches and pains due to headache and the common cold
- temporarily reduces fever

The warnings contained in the Drug Facts label (DFL) are consistent with class labeling for dextromethorphan HBr, guaifenesin, and naproxen sodium.

Figure 3. Proposed Drug Facts Label

Peel-back label for 8-ct, 16-ct, 32-ct, and 60-ct outer carton labels



Source: NDA 217338 submitted October 24, 2025

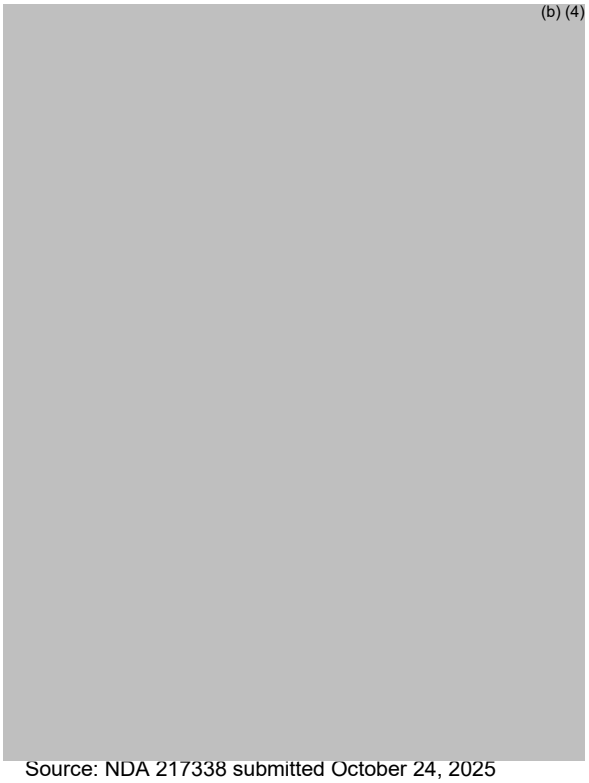
10.3. Principal Display Panel

A new proprietary name was submitted for review on July 11, 2025, Mucinex 12HR Cold & Fever Multi-Symptom. DMEPA reviewed the proposed name for safety and misbranding concerns. They found that the proposed name with the modifier “Cold & Fever Multi-Symptom” is conditionally acceptable (Correspondence to the Applicant dated September 18, 2025).

The proposed proprietary name is located in the upper center of the PDP. The content of the required elements of the PDP, the statement of identity (SOI), proprietary name placement and size, and net quantity statement, are compliant with the requirements under 21 CFR 201.60-201.62 (Figure 4).

The branding of Mucinex products include a subdued 'M' logo that serves as a background design element on the bottom half of the PDP. Each individual product line uses a distinct color for branding to help consumers distinguish between the product lines at the point of purchase (e.g., Mucinex, Mucinex DM, Mucinex Sinus Max, and the proposed product Mucinex 12HR Cold & Fever Multi-Symptom). The color of the branding for this proposed product is light gray.

Figure 4. Proposed PDP for 16-Count Outer Carton



Source: NDA 217338 submitted October 24, 2025

10.4. Blister Package Labeling

The Applicant provided labeling for three immediate container (blister) configurations: 4-count, 8-count, and 10-count cards. The 8-count blister labeling doubles the 4-count card design, and the 10-count labeling doubles a 5-count card design. The same 8-count blister card is used in the 8-, 16-, and 32-count cartons. The 60-count carton contains six 10-count blister cards.

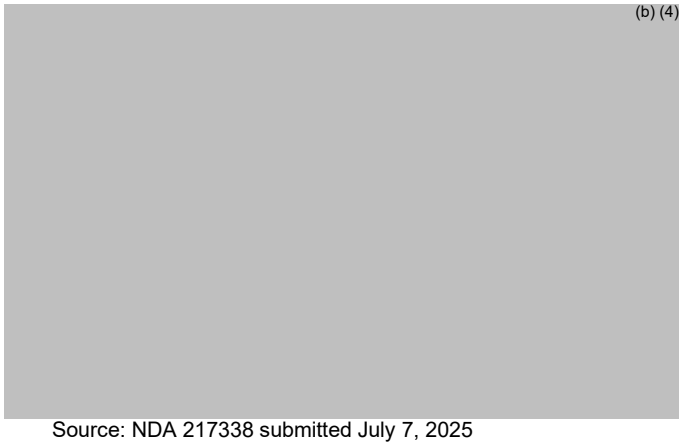
Each blister has a back label containing important information for the consumer. Labels for blisters that contain drug product display the following information: proprietary name, active ingredients, distributor information, country of origin, and a statement to "See warnings before use."

The 4-count blister mats contain two center panels that do not contain drug product (Figure 5). The top panel displays the proprietary name, SOI, and lot numbering. The lower panel contains the statement, "Keep this warning. Do not detach individual blisters until ready to use," and the NSAID stomach bleeding warning. This warning must appear on both outer and immediate container labels, per 21 CFR 326(a)(2)(iii)(A).

The 10-count blister mats (i.e., two 5-count mats) contains five blisters with drug product, replacing the top center panel with a panel that contains drug product (Figure 5). The NSAID stomach bleeding warning is contained on the lower center panel.

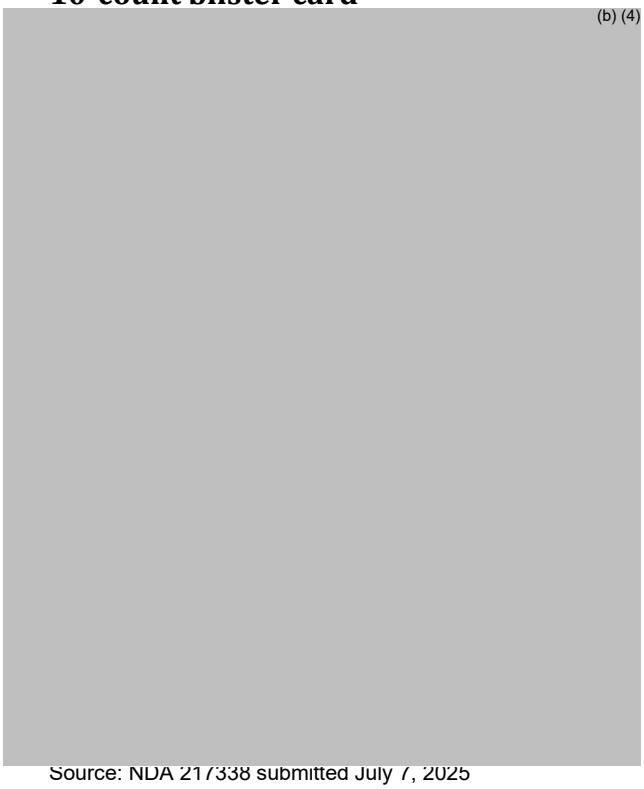
Figure 5. Immediate Container (Blister Mat) Labeling

4-count blister card



Source: NDA 217338 submitted July 7, 2025

10-count blister card



Source: NDA 217338 submitted July 7, 2025

10.5. Review of Website Mock-Ups

Because the website address www.mucinex.com is included on the labeling, the Applicant was requested to submit mock-ups of the proposed webpages for the Mucinex 12HR Cold & Fever Multi- Symptom product. These mock-ups were requested in an Information Request letter dated October 15, 2025. This content was found to be acceptable and is consistent with the proposed product labeling.

10.6. Conclusions

The Division of Nonprescription Drugs 1 recommends approval of this application regarding labeling. The content of the proposed labeling is presented in accordance with all applicable regulations. The labeling issues that were identified in the October 15, 2025, information request were sufficiently addressed by the Applicant and no additional labeling issues have been identified.

11 Risk Evaluation and Mitigation Strategies (REMS)

None

12 Postmarketing Requirements and Commitment

Routine postmarketing surveillance is sufficient to monitor adverse events, particularly focusing on respiratory depression and any unexpected adverse events.

13 DNPD I Division Director/Signatory Comments

I concur with the review team's assessment and recommendations for this resubmission of NDA 217338.

The regulatory action is Approval with the agreed-upon labeling.

No PMR/PMCs are recommended for this NDA.

14 Appendices

14.1. References

References are placed in footnotes under the unireview text.

14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Clinical Study RB5-US-1505 and Study 0225104

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 22		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☐	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.3. Nonclinical Pharmacology/Toxicology

Not applicable

14.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

14.4.1. Study Design, Analysis Plan and Demographics of Study 0225104

Study Design and Treatments

Study 0225104 was a phase 1, open-label, single-dose, randomized, 2-way crossover relative bioavailability study conducted to address the CRL deficiency regarding the 12-hour dosing interval for naproxen. The primary objective was to assess the relative bioavailability of immediate-release naproxen sodium component from the proposed product relative to listed drug, Aleve-D Sinus and Cold (NDA 021076) under fasted conditions.

We note that the study utilized the current Orange Book reference standard (ANDA 076518) as the reference treatment arm given that NDA 021076 (Aleve-D Sinus and Cold) has been discontinued currently. This discontinuation was not due to safety or efficacy reasons. This study design approach was agreed upon by the FDA during pre-study discussions, as documented in the preliminary meeting comments dated October 28, 2024 (Reference ID: 5469432).

Twenty-six healthy subjects were enrolled and completed both treatment periods with a 5-day washout:

- Treatment A: Two (b) (4) tablets (total 220 mg naproxen sodium) after 10-hour fast
- Treatment B: One Aleve-D Sinus and Cold tablet (ANDA 076518, 220 mg naproxen sodium) after 10-hour fast

PK Sampling and Analysis

Blood samples were drawn pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 9, 10, 11, 12, 18, 24, 48, and 72 hours post-dose. Noncompartmental analysis was performed using Phoenix WinNonlin (version 8.3.4).

Study Demographic

The study population consisted of 19 male participants (73.1%) and 7 female participants (26.9%), with all female participants being of childbearing potential. The majority of participants were White (76.9%) with 23.1% Black or African American. All participants (100%) were Hispanic or Latino ethnicity. The mean age was 31.3 years (range 21-41 years), mean height was 1.739 m (range 1.58-1.93 m), mean weight was 77.15 kg (range 52.3-99.5 kg), and mean BMI was 25.35 kg/m² (range 19.0-30.0 kg/m²).

The Study Completion, Discontinuation, and Protocol Deviations

A total of 62 healthy participants were screened for eligibility, with 41 participants enrolled and 26 participants randomized and dosed. Of the 36 participants (58.1%) not randomized, 28 participants (45.2%) did not meet study criteria and 8 participants (12.9%) were excluded for other reasons. No participants were excluded due to adverse events, protocol violations, or withdrawal of consent.

All 26 randomized participants (100%) completed both treatment periods, and all required pharmacokinetic sampling through 72 hours post-dose in each period. Two participants (7.7%) were lost to follow-up as they did not return for the final study visit, resulting in 24 participants (92.3%) completing the entire study. These participants had completed all treatment periods and pharmacokinetic sampling, missing only the final safety follow-up visit. All 26 randomized participants were included in the Safety Population, PK Population, and Per Protocol PK Population.

In Treatment group B, there was one subject with protocol deviation. The deviation involved failure to perform or document the lymph node assessment at screening visit. A repeat assessment of lymph nodes showed no abnormalities, and the participant was not excluded from the Per Protocol PK Population.

Based on the protocol deviation listings (Listing 16.2.2.2), 36 other protocol deviations were reported which were designated at non-important. These were primarily related to vital signs timing issues (26 instances where vital signs were collected 21-34 minutes outside the required 90±15 minute pre-dose window), vital signs documentation problems (8 instances where resting position was not documented), and minor procedural issues including use of different arms for measurements and one blood sample collected 2 minutes outside the acceptable window.

Safety Results

No deaths, serious adverse events, or discontinuations due to adverse events occurred. Seven participants (26.9%) reported 15 treatment-emergent adverse events during the study. Four participants (15.4%) reported 7 events after receiving (b) (4), and 5 participants (19.2%) reported 8 events after receiving Aleve-D Sinus and Cold. Thirteen events were mild in severity

and 2 events in 1 participant were moderate. None of the adverse events were considered related to (b) (4), and 1 event was considered possibly related to Aleve-D Sinus and Cold.

The Applicant's study design for Study 0225104 was adequate. Refer to Section 7 in this review for detail safety assessment.

14.4.2. Bioanalytical Method Validation and Performance

The bioanalytical method and report for Study RB5-US-1505 was previously reviewed during the first submission of NDA 217338 and found to be adequate; refer to Section 14.3 of the Integrated Review for that study for detailed assessment.

For bioanalysis of the PK samples from Study 0225104, a liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay was used. This method determines the concentration of naproxen in K2EDTA human plasma. It was developed and validated by (b) (4) according to test method TM.2956 over an analytical range of 1 to 200 µg/mL. The method was reasonably validated in accordance with current FDA bioanalytical method validation guidelines, demonstrating acceptable accuracy (bias within ±15% for QC levels and ±20% for LLOQ), precision (CV ≤15% for QC levels and ≤20% for LLOQ), selectivity, stability, and method reproducibility with 100% of incurred sample reanalysis samples meeting acceptance criteria.

Table 12. Summary of Method Validation for the Determination of Naproxen in Human Plasma in Study 0225104

Study Information	Method Validation Summary
Method Validation Summary Report Title	Validation of a Liquid Chromatographic Method using Tandem Mass Spectrometry Detection and Automated Extraction for the Determination of Naproxen (1 to 200 µg/mL) in Human EDTA K_2 Plasma
Study Number	205134AXWU
Test Method	TM.2956
Analyte Name	Naproxen
Internal Standard	Naproxen-d_3
Sample Volume	0.05 mL
QC Concentrations	1.00, 3.00, 100.00, and 150.00 µg/mL
Standard Curve Concentrations	1.00, 2.00, 10.00, 20.00, 40.00, 80.00, 160.00, and 200.00 µg/mL

Lower Limit of Quantitation	1.00 µg/mL
Upper Limit of Quantitation	200.00 µg/mL
Calibration Range	1.00 to 200 µg/mL
Calibration Curve Regression	Linear
Weighting Factor	$1/C^2$
Mean Recovery of Analyte (%)	75.03, 73.13, and 74.63% (at QC1, QC2, and QC3 levels)
Mean Recovery of Internal Standard (%)	76.07%
Matrix Effect CV (%)	≤1.15%
Sensitivity	The accuracy at LLOQ was within ±20.0% of nominal values. The %CV at LLOQ was less than 20.0%
LLOQ QC Intra-Run Precision Range (%CV)	3.78 to 8.93%
LLOQ QC Intra-Run Accuracy Range (%RE)	-8.08 to 0.17%
Analytical QC Intra-Run Precision Range (%CV)	0.87 to 8.65%
Analytical QC Intra-Run Accuracy Range (%RE)	-19.67 to 3.49%
LLOQ QC Inter-Run Precision (%CV)	8.93%
LLOQ QC Inter-Run Accuracy (%RE)	-8.08%
Analytical QC Inter-Run Precision Range (%CV)	3.78 to 8.93%
Analytical QC Inter-Run Accuracy Range (%RE)	-8.08 to 0.17%
Stock Solution Stability	1630 days at -20°C
Processed Sample Stability	95h20min at room temperature
Benchtop Stability in Plasma	23h46min at room temperature and 24h08min at 4°C

Freeze/Thaw Stability in Plasma	4 cycles at -20°C and -80°C
Benchtop Stability in Whole Blood	240 minutes in ice/water bath (centrifugation at room temperature and at 4°C)
Long-term Storage Stability in Plasma	6 and 1618 days at -20°C; 6 days at -80°C
Dilution Integrity	20-fold dilution validated
Selectivity	No significant interference observed in 8 out of 8 tested matrices for naproxen and its IS
Specificity	No significant interference observed with acetaminophen
Matrix Effect	Mean IS-Normalized matrix factor: 0.996040 and 1.009345; CV: 0.82% and 1.15%
Carryover	No significant carryover observed

Source: Study 0225104 Bioanalytical Method Validation Report[16]
Abbreviations: C, Celsius; CV, coefficient of variation; IS, internal standard; ISR, incurred sample reanalysis; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; mL, milliliter; QC, quality control; %RE, relative error; µg, microgram

Table 13. Summary of In-Study Performance of LC-MS/MS Method for the Determination of Naproxen in Human Plasma in Study 0225104

Performance Parameters	Results
Assay Passing Rate	Data from incurred sample reproducibility (ISR) showed 100.00% of samples met acceptance criteria
Standard Calibration Curve	8 calibration standards from 1.00 to 200.00 µg/mL
Standard Calibration Performance	Cumulative bias range: -1.49% to 1.83%

[16] \\CDSESUB1\EVSPROD\nda217338\0025\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\0225104\0225104-val-rpt.pdf

QC Performance	Cumulative bias range: -8.08% to 0.17%; Cumulative precision: ≤8.93% CV
Method Reproducibility	ISR was performed and 100.00% of samples met the pre-specified acceptance criteria (percentage difference within ±20% for at least 67% of ISR samples)
Sample Analysis and Storage Time	All samples were analyzed within established long-term storage stability periods

Source: Study 0225104 Bioanalytical Report[17]
Abbreviations: C, Celsius; CV, coefficient of variation; IS, internal standard; ISR, incurred sample reanalysis; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; mL, milliliter; QC, quality control; %RE, relative error; µg, microgram

14.4.3. Summary of OSIS inspection

On July 14, 2025, a request for biopharmaceutical inspections was issued to Office of Study Integrity and Surveillance (OSIS) for two sites supporting the clinical study and bioanalysis of Study #0225104 for this resubmission[18]:

- Clinical Site: Syneos Health Clinical Research Services, LLC; Miami, FL
- Analytical site: (b) (4)

OSIS declined to conduct the requested on-site inspection of the clinical site at Syneos Health Clinical Research Services, LLC (Miami, FL) based on a recent August 2024 inspection conducted under NDA non-responsive . (b) (4) (b) (4) however, OSIS determined that these findings did not compromise data integrity or subject safety. Accordingly, OSIS concluded that no additional inspection of this clinical site is warranted for the current submission[19].

OSIS also declined to conduct the requested on-site inspection of the bioanalytical facility at (b) (4) based on a recent (b) (4) inspection conducted under multiple NDAs non-responsive). OSIS

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[18] OSIS Consult Request for Biopharmaceutical Inspections; DARRTS Reference ID: 5623851

[19] Decline to conduct an on-site inspection for NDA 217338 Clinical Site at Syneos Health Clinical Research Services, LLC; Miami, FL; OSIS Memorandum; DARRTS Reference ID: 5649141

concluded that the data from studies conducted at this facility were reliable and determined that no additional inspection of the bioanalytical site is warranted for NDA 217338[20].

[20] Decline to conduct an on-site inspection for NDA217338 Analytical Site at (b) (4) ; OSIS Memorandum; Reference ID: 5708749

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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