

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205352Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 205352
Supporting Documents: S000
Applicant's letter date: 03/20/2013
CDER stamp date: 03/20/2013
Product: Aleve PM (Naproxen sodium, diphenhydramine HCl combination)
Indication: Night time pain reliever
Applicant: Bayer Healthcare, LLC-Consumer Care
Review Division: Division of Nonprescription Clinical Evaluation
Reviewer: Cindy Xinguang Li, Ph.D.
Secondary Reviewer: Paul Brown, Ph.D., ODE IV Associate Director for Pharmacology/Toxicology, Office of New Drugs
Division Director: Theresa M. Michele, M.D.
Project Manager: Jeffrey Buchanan, Regulatory Health Project Manager

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of the present New Drug Application (NDA) submission (NDA 205352) are owned by the applicant or are data for which the applicant has obtained a written right of reference. Any information or data necessary for approval of the present NDA submission that the applicant does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of the present NDA submission.

1 Executive Summary

1.1 Introduction

The present New Drug Application (NDA) is submitted by Bayer Healthcare, LLC-Consumer Care for their product, Aleve PM. The proposed drug product is a new over-the-counter (OTC) fixed-combination which is indicated for (b) (4) pain relief/sleep-aid. Each combination tablet contains 220 mg naproxen sodium and 25 mg diphenhydramine hydrochloride. The recommended dosing regimen is two-tablets before bedtime for no more than 10 consecutive days for adults and children 12 years of age and over.

1.2 Brief Discussion of Nonclinical Findings

Both naproxen and diphenhydramine have been used in previously approved drug products and their individual mechanisms of action and toxicology are well characterized in both nonclinical and clinical studies. The combination of naproxen and diphenhydramine was not evaluated in animals but has been studied clinically by the applicant.

No new nonclinical studies have been conducted or submitted under this NDA. The nonclinical information for the present NDA refers to the data and the Agency's assessment of safety for Bayer's approved naproxen sodium 220 mg under NDA 20204 and the OTC monograph for products containing diphenhydramine hydrochloride under 21CFR338.

1.3 Recommendations

1.3.1 Approvability

Based on the previous agency's assessment of safety for naproxen and diphenhydramine as well as the lack of novel nonclinical issues identified during the current review, there is no impediment to approval of this NDA from a Pharmacology/Toxicology perspective.

1.3.2 Additional Nonclinical Recommendations

Based on clinical and nonclinical findings with NSAIDs, this product is not recommended for nursing mothers and not for women in late pregnancy, in labor and delivery.

1.3.3 Labeling

None.

2 Drug Information

2.1 Drug

2.1.1 Naproxen Sodium

CAS Registry Numbers:
26159-34-2

Generic Names:
Naproxen

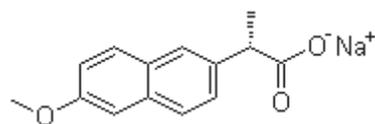
Trade Name:
Not Available

Code Names:
Not Available

Chemical Names:
(S)-6-methoxy- α -methyl-2-naphthaleneacetic acid, sodium salt

Molecular Formulae/Molecular Weights:
 $C_{14}H_{13}NaO_3$ / 252.2

Structure:



Pharmacologic Class:
Nonsteroidal anti-inflammatory drugs (NSAIDs)

2.1.2 Diphenhydramine Hydrochloride

CAS Registry Numbers:
147-247-0

Generic Names:
Diphenhydramine HCl

Trade Name:
Not Available

Code Names:
Not Available

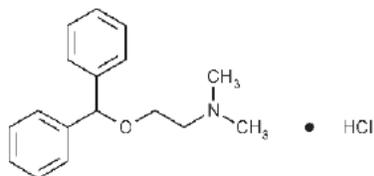
Chemical Names:

2-(Diphenylmethoxy)-N,N-dimethylethylamine hydrochloride

Molecular Formulae/Molecular Weights:

 $C_{17}H_{21}NO \cdot HCl$ / 291.8

Structure:



Pharmacologic Class:

Antihistamine

2.2 Relevant INDs, NDAs, DMFs and other documents

IND 103,407: Naproxen sodium + diphenhydramine HCl

NDA 20204: Aleve® Tablets, naproxen sodium 220 mg

NDA 200364: Naproxen sodium extended release, 660 mg

DMF [REDACTED] (b) (4)

DMF [REDACTED] (b) (4)

Diphenhydramine: Final monograph for Nighttime sleep-aid drug products for over-the-counter human use, 21CFR338

2.3 Drug Formulation

The drug product is a blue film-coated tablet, capsule-shaped, with the dimension of 1.5 cm x 0.6 cm, weighing 391.4 mg. The following descriptions of the product formulations are adapted from the submission:

Each film-coated tablet contains:

Composition	Reference to Std.*	Function	Amount, mg		
(b) (4)					
Naproxen Sodium	USP	Drug substance	220.0		
Diphenhydramine Hydrochloride	USP	Drug substance	25.0		
Microcrystalline Cellulose	NF	(b) (4)	(b) (4)		
Povidone	USP				
Purified Water	USP				
Talc	USP				
Magnesium Stearate	NF				
<i>Total</i>	(b) (4)			<i>Weight :</i>	
Magnesium Stearate	NF			(b) (4)	(b) (4)
(b) (4)	USP USP	(b) (4)	(b) (4)		
Carnauba Wax	NF	(b) (4)	(b) (4)		
<i>Total</i>	(b) (4)	<i>Weight :</i>	391.4		
(b) (4)					
(b) (4)					
Hypromellose 2910	USP	(b) (4)	(b) (4)		
Titanium Dioxide	USP				
FD&C Blue #2 Aluminum Lake	FCC				
Polyethylene Glycol 8000	NF				
(b) (4)					

2.4 Comments on Novel Excipients

There are no novel excipients in the proposed product. All excipients present in the drug product are widely used in the pharmaceutical industry and are within the acceptable range for an oral drug product as listed in the FDA’s “Inactive Ingredient Search for Approved Drug Products” database. ONDQA review team (Office of New Drug Quality Assessment) assessed the formulation and confirmed that all ingredients

(b) (4) comply with the corresponding USP and NF monographs. (b) (4)
Individual ingredients (b) (4) meet compendial requirements while the aluminum lake meets the Food Chemical Codex (FCC) requirements.

2.5 Comments on Impurities/Degradants of Concern

There are no concerns on impurities/ degradants from nonclinical perspective. The impurities and degradation products in the proposed drug product are at acceptable levels according to ICH Q3B(R2) "Impurities in New Drug Products".

2.6 Proposed Clinical Population and Dosing Regimen

The product is intended: 1) for relief of occasional sleeplessness associated with minor aches and pains and 2) for helping fall asleep and staying asleep. Each tablet contains 220 mg naproxen sodium and 25 mg diphenhydramine hydrochloride. The recommended dosing regimen is two-tablets before bedtime for no more than 10 consecutive days for adults and children 12 years of age and over.

2.7 Regulatory Background

Both naproxen and diphenhydramine have been used in previously approved drug products and their individual mechanisms of action and toxicology are well characterized. Naproxen sodium (Aleve) was approved in the United States (US) for prescription use on March 11, 1976 and for OTC use in 1994 at a dose of 220 mg under Bayer's NDA 20204. Diphenhydramine hydrochloride at 50 mg is codified in monograph 21CFR338 for the relief of occasional sleeplessness use. Currently, there is no OTC nighttime analgesic/sleep-aid combination product available in the US that combines the analgesic naproxen sodium with the sleep-aid diphenhydramine hydrochloride.

Bayer's clinical development program in support of the NDA for naproxen sodium / diphenhydramine tablets include one pilot study, two pivotal efficacy studies, one multiple-dose safety study, and one pharmacokinetic (PK) study. The pilot proof-of-concept study evaluated whether naproxen sodium taken together with diphenhydramine (DPH) would provide added benefit over naproxen sodium alone in subjects with postoperative dental pain and phase-advanced sleep.

Bayer submitted the new IND# 103407 for the naproxen sodium/DPH combination and a Special Protocol Assessment (SPA) request on November 25, 2009. The first pivotal study was to evaluate the efficacy and safety of 2 different dose combinations of naproxen sodium and diphenhydramine HCl (naproxen sodium 440 mg/ diphenhydramine 50 mg and naproxen sodium 220 mg/DPH 50 mg). The naproxen sodium 220 mg/DPH 50 mg dose combination failed to show a significant difference compared with naproxen sodium 440 mg alone for the primary efficacy endpoint. Bayer concluded that a lower dose of the combination product (naproxen sodium 220 mg/DPH 25 mg) was not a viable candidate for further development and did not include this dose combination in the second efficacy study. A second efficacy study was conducted to

evaluate the naproxen sodium 440 mg/ diphenhydramine 25 mg dose combination in subjects with postoperative pain and phase-advanced sleep.

A multiple-dose safety study was conducted to evaluate the safety profile of the naproxen sodium 440 mg/ diphenhydramine 50 mg dose combination compared with placebo taken for 10 consecutive days in a population representative of the expected OTC users of analgesic/nighttime sleep-aid combination, including approximately 25% elderly subjects (>65 years of age).

In addition, a PK study was conducted by Bayer to determine any potential interaction between naproxen sodium and diphenhydramine in the combination formulation and to assess any food effect on the selected dose combination (naproxen sodium 440 mg/ diphenhydramine 50 mg).

The Pre-NDA meeting for the current submission was held on October 09, 2012 through teleconference.

From nonclinical perspective, there were no issues raised during the IND development.

3 Studies Submitted

3.1 Studies Reviewed

There are no nonclinical studies conducted or submitted under this NDA.

3.2 Studies Not Reviewed

There are no nonclinical studies conducted or submitted under this NDA.

3.3 Previous Reviews Referenced

Reference is made to the nonclinical pharmacology and toxicology information under NDA 20204 for Aleve Immediate-Release tablets 220 mg and in the 21CFR338 final monograph for Nighttime sleep-aid drug products for over-the-counter human use.

4 Integrated Summary and Safety Evaluation

Naproxen sodium is a non-steroidal anti-inflammatory drug (NSAID). It inhibits prostaglandin synthesis by decreasing cyclooxygenase activity, which in turn reduces the formation of prostaglandin chemical precursors. Naproxen sodium (Aleve) was approved in 1994 in the US at a dose of 220 mg under Bayer's NDA 20204.

Diphenhydramine is a first generation antihistamine, an H1-antagonist of the ethanolamine class. Diphenhydramine and its hydrochloride salt have been shown to possess antihistaminic, anti-inflammatory, sedative, anti-tussive and anti-emetic properties. Some of these effects are achieved through competitive antagonism with

histamine for binding to histamine receptors. Other effects are thought to be due to the compound's anticholinergic properties. Diphenhydramine hydrochloride was codified in monograph 21CFR338 for use by adults and children 12 years of age or older at a dose of 50 mg at bedtime for the relief of occasional sleeplessness.

No nonclinical studies were conducted or submitted for the present NDA. Both naproxen and diphenhydramine have been used in previously approved drug products and their individual mechanisms of action and toxicology are well characterized. The nonclinical safety information refers to the data and information supporting NDA 20204 and the Final Monograph 21CFR338.

During the nonclinical review of the present NDA, there are no novel findings or unexplained toxicity observed. Based on the published information:

1. Naproxen exhibits low toxicity in single dose studies in hamsters, rats, dogs, and mice. In subacute and chronic oral studies in a variety of species, the principal pathological effect was gastrointestinal irritation and ulceration.

Reproduction studies have been performed in rats at 20 mg/kg/day, rabbits at 20 mg/kg/day, and mice at 170 mg/kg/day with no evidence of impaired fertility or harm to the fetus due to the drug. In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. Naproxen-containing products are not recommended in late pregnancy, labor and delivery and in nursing mothers.

A 2-year study was performed in rats to evaluate the carcinogenic potential of naproxen at doses of 8, 16, and 24 mg/kg/day. No evidence of tumorigenicity was found.

2. Diphenhydramine exhibits low toxicity in several animal species. Dose-dependent adverse effects noted in animals included behavioral excitement, convulsions and somnolence.

When diphenhydramine hydrochloride was administered to pregnant CD rats during organogenesis at oral doses up to 100 mg/kg/day, no clear evidence of a teratogenic effect was observed even at the highest dose, which produced clear signs of maternal and fetal toxicity. In CD-1 mice, diphenhydramine hydrochloride tends to increase the incidence of cleft palate, but only at dose levels which produce overt signs of fetal and maternal toxicity.

Equivocal evidence of carcinogenic activity of diphenhydramine hydrochloride in rats was found in a 2-year feeding study conducted by the NTP. Under the study conditions of the two year diphenhydramine hydrochloride feed studies, there were marginally increases in the incidences of brain neoplasm (astrocytomas or gliomas) and of alveolar/bronchiolar neoplasms in male F344/N rats, and a marginal increase in the incidence of pituitary gland adenomas in female F344/N rats. The mechanisms for these findings are unknown and could possibly be

species specific. No evidence of carcinogenic activity was found in the studies with mice.

3. There are no data suggesting increased toxicity of the combination of naproxen and diphenhydramine compared with the individual components.

Both naproxen sodium and diphenhydramine hydrochloride are well absorbed orally, extensively bound to plasma proteins, metabolized by the liver and excreted principally in urine. In humans, 70% of naproxen is excreted unchanged. The remaining drug is metabolized primarily by CYP2C9, a hepatic cytochrome P450 isozyme to 6-O-desmethylnaproxen. Both unchanged naproxen and the metabolite are conjugated into naproxen acyl glucuronide or 6-O-desmethylnaproxen glucuronide, respectively. In contrast, metabolism of diphenhydramine occurs primarily by the CYP2D6 cytochrome P450 isozyme, which suggests an independent metabolic pathway for each ingredient. No safety signals have been identified in human studies when the two ingredients are co-administered or given as a combination product. Based upon the different mechanisms of action, as well as different toxicity profiles, no pharmacodynamic interactions are expected for the combination of naproxen sodium and diphenhydramine hydrochloride.

There are no issues identified during the current nonclinical review with regards to the excipients and impurities/degradants of the drug product.

There are no pharmacology/ toxicology issues identified during this review on the active ingredients, excipients, impurities or degradants. Based on the previous human use experience and the agency's previous findings of safety and efficacy of naproxen and diphenhydramine, as well as the lack of novel significant toxicity issues identified during the current review, this NDA can be approved from the nonclinical perspective. Due to the clinical and nonclinical findings with NSAIDs, this product is not recommended for nursing mothers and not for women in late pregnancy, in labor and delivery.

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/s/

XINGUANG LI
12/17/2013

PAUL C BROWN
12/17/2013

I concur that the NDA can be approved from a pharm/tox perspective.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205352 **Applicant:** Bayer Healthcare, LLC **Stamp Date:** 03/20/2013

Drug Name: Aleve PM **NDA/BLA Type:** 505(b)(1)

Background:

The present New Drug Application (NDA) is submitted by Bayer Healthcare for Aleve PM. The proposed drug product, Aleve PM, is a new nighttime sleep-aid/analgesic, fixed-combination over-the-counter (OTC) drug product. Each combination tablet contains 220 mg naproxen sodium and 25 mg diphenhydramine hydrochloride (DPH). The indication is: 1) for relief of occasional sleeplessness associated with minor aches and pains and 2) to help fall asleep and stay asleep. The recommended dosing regimen is a two-tablet dose before bedtime for adults and children 12 years of age and over for no more than 10 consecutive days.

Naproxen sodium is a non-steroidal anti-inflammatory drug (NSAID). It inhibits prostaglandin synthesis by decreasing cyclooxygenase activity, which in turn reduces the formation of prostaglandin chemical precursors. Naproxen sodium (Aleve) was approved in 1994 in the US at a dose of 220 mg under Bayer's NDA 20204. DPH is a first generation antihistamine, an H1-antagonist of the ethanolamine class used as an antitussive, a nighttime sleep-aid and an antihistamine for allergy symptoms. It was codified in monograph 21CFR338 for use by adults and children 12 years of age or older at a dose of 50 mg at bedtime for the relief of occasional sleeplessness.

The nonclinical information for the active ingredients refers to the data and the Agency's assessment of safety for Bayer's approved naproxen sodium 220 mg under NDA 20204, naproxen sodium extended-release tablets 660 mg under NDA 200364, and the OTC monograph for products containing DPH under 21CFR338 (Nighttime sleep-aid drug products for over-the-counter human use).

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

The descriptions of the product formulations are presented in the following tables:

Table 1 Description of the Product Formulations

Each film-coated tablet contains:

Composition	Reference to Std.*	Function	Amount, mg		
(b) (4)					
Naproxen Sodium	USP	Drug substance	220.0		
Diphenhydramine Hydrochloride	USP	Drug substance	25.0		
Microcrystalline Cellulose	NF	(b) (4)	(b) (4)		
Povidone	USP				
Purified Water	USP				
Talc	USP				
Magnesium Stearate	NF				
<i>Total</i>	(b) (4)			<i>Weight :</i>	
<hr/>					
Magnesium Stearate	NF	(b) (4)	(b) (4)		
<hr/>					
(b) (4)					
Carnauba Wax	NF	(b) (4)			
<hr/>					
<i>Total</i>	(b) (4)	<i>Weight:</i> 391.4			
(b) (4)					
	USP	(b) (4)			
	USP	(b) (4)			
(b) (4)					
<hr/>					
(b) (4)					
<i>Hypromellose 2910</i>	(b) (4)	USP	(b) (4)		
<i>Titanium Dioxide</i>		USP			
<i>FD&C Blue #2 Aluminum Lake</i>		FCC			
<i>Polyethylene Glycol 8000</i>		NF			
<hr/>					
(b) (4)					

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

On initial overview of the NDA application:

There are no pharmacology/ toxicology filing issues identified at this time.

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			The applicant is recommended to provide a summary of the nonclinical information in the nonclinical section for the proposed product.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable (N/A). No nonclinical studies were conducted under this NDA.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A. No nonclinical studies were conducted under this NDA.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			N/A. No nonclinical studies were conducted under this NDA.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A. No nonclinical studies were conducted under this NDA.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A. No nonclinical studies were conducted under this NDA.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?			Not applicable due to different labeling as OTC products.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	No impurity issues have been identified at time of submission.
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		X	

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Not Applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

In the nonclinical section of Module 2 in your NDA, it would assist the Agency review if you provided a summary of the nonclinical information for each of the active ingredients, and address whether there are any potential interactions between the two active ingredients. Please also provide a justification why you consider the levels of inactive ingredients, impurities, and degradants present in your proposed drug product as safe for human use.

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/s/

XINGUANG LI
05/16/2013

PAUL C BROWN
05/17/2013