CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205352Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	January 16, 2014
From	Theresa M. Michele, MD Director, Division of Nonprescription Clinical Evaluation
Subject	Division Director Summary Review
NDA/BLA # Supplement #	205,352
Applicant Name	Bayer HealthCare
Date of Submission	March 20, 2013
PDUFA Goal Date	January 20, 2014
Proprietary Name / Established (USAN) Name	Aleve PM/ naproxen sodium and diphen hydramine HCl
Dosage Forms / Strength	220 mg naproxen/25 mg diphenhydramine per tablet 2 tablets at bedtime
Proposed Indication(s)	• Relief of occasional sleeplessness when associated with minor aches and pains • Helps you fall asleep and stay asleep
Action:	Approval

1. Introduction

Bayer Health Care (Bayer) submitted this 505(b)(1) new drug application for over-the-counter (OTC) use of Aleve PM (naproxen sodium and diphenhydramine HCl) for the relief of occasional sleeplessness when associated with minor aches and pains. The proposed dose is 2 tablets at bedtime, with each tablet containing 220 mg naproxen and 25 mg diphenhydramine, for a total daily dose of 440mg/50 mg.

The application is based primarily on two pivotal efficacy and safety studies, only one of which assesses efficacy of the proposed product, naproxen/diphenhydramine (NP/DH). A pilot efficacy study, 10-day multiple dose safety study, and bioavailability study were also submitted to support the application. This summary review provides an overview of the application, with a focus on the clinical efficacy and safety trials.

2. Background

Naproxen is a NSAID approved for the symptomatic treatment of pain and inflammation in a number of different diseases. It was first approved as an over the counter (OTC) product as 200 mg tablets in 1994 (NDA 20-204, Aleve). Uses include temporary relief of minor aches and pains due to minor pain of arthritis, muscular aches, backaches, menstrual cramps, headaches, toothaches, and the common cold, in addition to temporary reduction of fever. Diphenhydramine hydrochloride is an OTC antihistamine and a nighttime sleep aid. The OTC final monograph (21 CFR 338) Nighttime Sleep-Aid Drug Products for Over-The-Counter

Human Use allows diphenhydramine 50 mg and diphenhydramine citrate 76mg to be active ingredients for use as nighttime sleep aids in adults and adolescents 12 years of age and older.

There are a variety of other OTC products containing a combination analgesic/sleep aid including Advil PM, Motrin PM, Tylenol PM Extra Strength, and Excedrin PM. The analgesics include ibuprofen or acetaminophen, and the sleep aids include diphenhydramine or diphenhydramine citrate. In general, for patients experiencing pain and temporary sleeplessness, the analgesic component of these combinations is thought to shorten sleep latency (i.e. time to fall asleep), while the diphenhydramine component helps with sleep maintenance.

The Agency and Bayer had milestone meetings typical of development for a first-cycle NDA submission. In the Pre-IND meeting, FDA advised the sponsor that the product would need to meet the requirements of the combination policy. At several points during the development program, FDA further advised the sponsor to adequately address dose selection, and recommended that the sponsor include a lower dose arm NP 220/ DH 25 in clinical trials.

3. CMC/Biopharmaceutics

The drug substances in this combination product, NP/DH, are active ingredients of previously approved drug products, and are referenced to DMF. The film coat composition is contained within the application and deemed acceptable by the chemistry review team. All other components are compendial.

Aleve® PM (naproxen sodium/diphenhydramine HCl) tablets will be packaged in 20-, 40-, and 80-count HDPE bottles and a 2-count foil laminate pouch. The 2- count foil laminate pouch will not have a (b) (4) closures; the 20-, 40-, and 80-count configurations will have (b) (4) closures. The drug product should be stored are (b) (4) (b) (4) .

I concur with the conclusions reached by the chemistry and biopharmaceutics reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted in this application. Instead, the sponsor references NDA 20-204 for naproxen 220 mg and the Final Monograph 21CFR338 for diphenhydramine. There were no novel excipients or issues regarding impurities or degradants. NSAIDS are not recommended women in the third trimester of pregnancy due to risk of premature closure of the ductus arteriosus. The Drug Facts label will include appropriate warnings regarding use in pregnant and nursing mothers.

I concur with the conclusions reached by the pharmacology/toxicology reviewer regarding the acceptability of preclinical data. There are no outstanding pharmacology/toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

The sponsor submitted one single dose drug-drug interaction trial that also evaluated potential food effect. Trial 16135 was a randomized, open-label, single-dose, 4-way crossover trial in 32 healthy adults. Subjects were dosed with a single dose of two tablets in each treatment arm: NS 220 mg/DH 25 mg fasted, NS 220 mg (Aleve) fasted, DH 25 mg (Allergy Relief) fasted, and NS 220/DH 25 mg fed. Results demonstrated no drug-drug interaction with the combination product compared to the individual ingredients. Food had no effect on overall exposure (AUC) for either ingredient, although the Cmax was decreased 19% and Tmax was modestly delayed (3 hours versus 1.25 hours). See Table 1. This is consistent with what is known about single ingredient naproxen. The Drug Facts label will contain a warning "if taken with food, this product may take longer to work," which is consistent with the Aleve label.

Table 1: Trial 16135: Summary of PK parameters

PK Parameters (units)	NS 440/DH 25 Fasted N=27	NS 440 Fasted N=27	DH 50 Fasted N=27	NS 440/DH 25 Fed N=27
NP			Not applicable	
C_{max} (µg/mL)[a]	74.6 (10.4)	80.4 (11.5)	↓	60.8 (11.1)
AUC_{0-t} (mg*hr/mL)[a]	913.2 (135.8)	909.1 (124.8)	↓	882.4 (119.2)
AUC_{0-inf} (mg*hr/mL)[a]	1063 (156.9)	1060 (147.1)	↓	980.1 (138.8)
$t_{1/2}$ (h)[a]	17.0 (3.8)	16.5 (2.6)	↓	16.4 (2.9)
t_{max} (h)[b]	1.25	0.75	↓	3.00
DPH		Not applicable		
C_{max} (µg/mL)[a]	67.7 (27.1)	↓	68.9 (22.4)	77.1 (35.0)
AUC_{0-t} (mg*hr/mL)[a]	613.9 (238.5)	↓	598.2 (233.5)	685.3 (263.5)
AUC_{0-inf} (mg*hr/mL)[a]	646.5 (239.6)	↓	636.4 (257.6)	709.5 (267.0)
$t_{1/2}$ (h)[a]	11.0 (2.7)	↓	10.9 (2.5)	10.8 (1.9)
t_{max} (h)[b]	2.50	↓	1.75	2.50

a: Mean (SD); b: Median
Source: Modified from Table 2.1.1, Module 2.7.2 Clinical Summary of Efficacy

In addition, the clinical pharmacology team evaluated PK data from Trial 16135 in comparison to other DH-containing products and concluded that NS/DH does not have higher DH concentrations in comparison to other approved products. This issue has clinical relevance due to the concern that DH may cause next day drowsiness and impairment of driving ability, although there are insufficient data from the literature to determine a specific cut off above which next day drowsiness would be a concern. Overall, I concur with the conclusions reached by the clinical pharmacology team that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

7.1. Overview of the clinical program

Some characteristics of the relevant clinical trials that form the basis of review and regulatory decision making for this application are shown in Table 2. Reviewers from the Division of Neurology Products and the Division of Anesthesia, Analgesia, and Addiction Products were consulted to collaborate in the review of sleep and pain endpoints, respectively.

Table 2: Relevant clinical studies with DSG

ID [Year*]	Study Characteristics - Population - Study design - Study duration	Treatment groups	N‡	Primary endpoint	Country
13053 [2008]	- dental pain/ adv phase sleep - parallel grp -single dose	NS440 + DH50 NS220 + DH50 NS440 NS220 DH50 IB400/DC76	27 27 27 27 27 27	Total sleep time	US
14837 [2011]	- dental pain/ adv phase sleep - parallel grp - single dose	NS440/DH50 NS220/DH50 NS440 DH50	203 204 203 102	WASO (vs NS) Sleep latency (vs DH)	US
15881 [2012]	- dental pain/ adv phase sleep - parallel grp - single dose	NS440/DH25 NS440 DH50	107 106 54	WASO (vs NS) Sleep latency (vs DH)	US
15560 [2011]	- occ sleeplessness and pain - parallel grp - 10 days	NS440/DH50 Placebo	217 109	Safety	US

*Year study enrollment ended; ‡Number randomized and received at least one dose
NS = naproxen sodium; DH = diphenhydramine; IB = buprofen; DC= diphenhydramine citrate ; WASO = wake after sleep onset; US = United States

7.2. Design and conduct of the trials

To support the new indications for relief of occasional sleeplessness when associated with minor aches and pain and helps you fall asleep and stay asleep, Bayer conducted a pilot efficacy trial that used individual components dosed simultaneously, two single dose Phase 3 efficacy trials, and a Phase 3 safety trial with dosing for 10 consecutive days. Of the two Phase 3 efficacy trials, only one included the to-be-marketed dose. The other trial was conducted with a lower dose of diphenhydramine in order to address dose ranging for this component. As such, primary efficacy data comes from trial 14837. Consistent with the requirements of the combination rule, both Phase 3 efficacy trials evaluated the contribution of each component to the efficacy of the combination, using primary endpoints of wake after sleep onset (WASO) compared to naproxen and sleep latency compared to diphenhydramine. Sleep latency was defined as the time to sleep onset from the time of dosing, and WASO was defined as the total wake time after sleep onset during the ten-hour in-bed time. Both were measured using actigraphy.

Trial 13053 was a single-center, double-blind, randomized single dose trial assessing the analgesic and hypnotic efficacy of naproxen and diphenhydramine given concomitantly in 162 patients with post-operative dental pain and phase-advanced sleep (3 hours). The trial included 6 arms with an active control arm of ibuprofen 200 mg/diphenhydramine citrate 38 mg (Advil PM). Patients were 16-45 years of age, underwent surgical removal of one to three impacted third molars, had moderate to severe postoperative pain (visual analog score of ≥50), and were otherwise healthy. The primary efficacy endpoint was total sleep time measured by actigraphy. A number of secondary efficacy assessments of sleep and pain were measured.

Trial 14837 was a multi-center, double-blind, randomized, parallel-group, single dose trial assessing the analgesic and hypnotic effect of NS/DH in 712 patients with post-operative dental pain and phase advanced sleep (5 hours). The trial was a factorial design trial including two different combination doses of NS/DH (NS440/DH50 and NS220/DH50). Patients were 16 to 48 years of age, underwent surgical removal of at least 2 third molars, had moderate to severe post-operative pain, and a VAS of at least 50 mm.

Trial 15888 was similar in design to Trial 14837 except that it compared a combination therapy with a lower dose of diphenhydramine (NS440/DH25) with both agents alone. A total of 237 patients aged 12 to 49 years were randomized.

7.3. Dose selection

Bayer explored dose selection in Phase 2 as well as in the Phase 3 trials. Regarding the Phase 2 study, because the combination product met bioequivalence criteria to the individual components, it is reasonable to consider that the results of Trial 13053 may apply to the Phase 3 program even though it used single ingredients dosed concomitantly. Further limitations of the trial are the small size and that the primary endpoint is not consistent with those required in Phase 3. With these caveats, the results did show benefit of the combination over diphenhydramine alone for total sleep time and also for various pain relief scores. A clear dose response was not demonstrated

Both of the Phase 3 trials were limited in that the lower dose combinations were compared to a higher dose single ingredient, which may have biased against the lower dose. However, Trial 14837 did appear to demonstrate a dose response, with greater efficacy observed for the higher analgesic dose (NS440/DH50). Unfortunately, conclusions for the dose selection of the diphenhydramine component are not clearly demonstrated due to the small sample size of Trial 15881 and lack of a higher dose combination arm in the same trial for direct comparison. Based on this trial, the sponsor proposed the NS440/DH50 dose over the NS440/DH25 dose. The trial data do not support this conclusion. However, review of the PK data in comparison with the literature, bioequivalence to the marketed single ingredients, lack of an identified new safety signal, long marketing history of diphenhydramine at a dose of 50 mg as a sleep aid, and large number of other combination products on the market at a similar dose of diphenhydramine are sufficient to support approval of the sponsor's proposed dose.

7.5. Efficacy results and conclusions

Trial 14837 demonstrated that NS440/DH50 significantly shortened sleep latency as compared to diphenhydramine 50 mg alone. In addition, NS440/DH50 significantly increased the time to wake after sleep onset compared to naproxen 440 mg alone. See Table 3 and Table 4. Overall,

these findings suggest that each component of the combination NS440/DH50 contributes to the efficacy of the product. For the lower analgesic dose combination, the results demonstrate a significant benefit for sleep latency compared to diphenhydramine alone, but no benefit on WASO compared to naproxen alone, consistent with a dose response.

In contrast to the results of Trial 14837, NS440/DH25 showed no significant benefit of the combination over the single agents for either sleep latency or WASO, although there was a small numerical difference. The sample size for Trial 15881 was only about half as large as that for Trial 14837, suggesting that the trial may have been underpowered. As such, definitive conclusions cannot be drawn from these data.

Table 3: Phase 3 trials: sleep latency

	Trial 14837			Trial 15881
	NS 440 / DH 50 vs DH 50	**NS 220 / DH 50 vs DH 50**	**NS 440 / DH 50 vs NS 220 / DH 50**	**NS 440 / DH 25 vs DH 50**
Primary	25.5 vs 41.4 min* P<0.0001** N=201 vs 102	30.2 vs 41.4 min p=0.0003 N=204 vs 102	25.5 vs 30.2 min p=0.0096 N=201 vs 204	23.5 vs 27.5 min p=0.1677 N=107 vs 54

*Median time; **Kaplan-Meier analysis, log-rank test
Source: Adapted from draft DNP clinical review (Table 69) for NDA 205352 by Veneeta Tandon; clinical study report for Study 37, Tables 14.2.2a, b, and c; clinical study report for Study 81, Tables 14.2.2a, b, and c

Table 4: Phase 3 Trials:WASO

	Trial 14837			Trial 15881
	NP 440 / DPH 50 vs NP 440	**NP 220 / DPH 50 vs NP 440**	**NP 440 / DPH 50 vs NP 220 / DPH 50**	**NP 440 / DPH 25 vs NP 440**
Primary	-70.3 min* p=0.0002** N=203 vs 203	16.9 min p=0.3627 N=204 vs 203	-87.2 min p<0.0001^ N=203 vs 204	-24.8 min p=0.3047 N=107 vs 106

*LS Mean treatment difference ; **ANCOVA model ; ^as specified in the protocol, this comparison is ineligible to be declared significant because the comparison between NP 220 / DPH 50 and NP 440 was not statistically significant.
Source: Adapted from DNP clinical review (Table 68) for NDA 205352 by Veneeta Tandon; clinical study report for Study 37, Tables 14.2.1a, b, and c; clinical study report for Study 81, Tables 14.2.1a, b, and c

Because Trial 15881 fails to demonstrate benefit and was conducted with a different dose of NS/DH, efficacy of this application is primarily demonstrated by a single Phase 3 trial. Drs. Yang (CDTL) and Dr. Tandon (DNP) note that the results of Trial 14837 are statistically very persuasive, and the results of the secondary endpoints for total sleep time, sleep efficiency, global assessment as sleep aid, and the Karolinska Sleep Diary are supportive. Further, the results of the Phase 2 trial 15053, while not compelling in and of themselves, also go in the right direction for the combination. Another factor is that the combination is bioequivalent to the two single ingredients, naproxen and diphenhydramine, which are each individually approved for the treatment of pain and as a sleep aid, respectively. For all of these reasons, I concur with Dr. Yang's conclusion that the data are sufficient to demonstrate efficacy of the combination over the single ingredients.

8. Safety

8.1. Consumer studies

Because combination analgesics and sleep aids are a well-established OTC product, label comprehension, self-selection, and actual use studies were neither conducted nor required.

8.2. Clinical safety data

As a NSAID, this product is expected to have the typical class effects of GI bleeding risk, cardiovascular risk (anti-platelet effects), hepatic and renal effects. The Drug Facts label will carry standard warnings and will be consistent with that for Aleve.

The clinical trials submitted with this application enrolled 1556 subjects, of whom 447 received at least one dose of NS 440/DH 50. 217 patients received this dose for 10 days. The most common adverse events reported in these trials were nausea, headache, dizziness, and vomiting. In the PK study, somnolence was the most common adverse event; of note, in this trial subjects were dosed at approximately 8am. In the 10 day placebo-controlled safety trial there were no serious adverse events and no deaths. As requested by FDA, approximately 25% of patients were more than 65 years of age. Adverse events occurring more frequently in the NS/DH group than placebo were somnolence, dizziness, nausea, back pain, diarrhea, abdominal discomfort, and dyspepsia. Overall, the adverse event profile was generally consistent with that expected with the individual components. Notably, dizziness occurred more frequently in patients over 60 years of age compared to placebo; otherwise, no age related differences were observed.

Safety data were also reviewed from a variety of post-marketing sources including AERS, emergency department drug abuse, and poison control databases. Overall, no new safety signals were observed, although there is a notable but low incidence of abuse/misuse of diphenhydramine, along with both intentional (suicide attempts) and unintentional overdoses. Another concern with the use of diphenhydramine as a nighttime sleep aid is the risk of residual next day drowsiness and driving impairment. Review of the FAERS database using data mining techniques to evaluate for traffic accidents, falls, impaired driving ability, injury, and accidents at work did not reveal any scores that would raise the level of concern for diphenhydramine. The Drug Facts label will contain the standard warning regarding somnolence and caution needed when driving or using heavy machinery.

9. Advisory Committee Meeting

This application was not taken to an Advisory Committee meeting since the components are approved OTC products, it is not a first in class switch product, and the indication is not novel for OTC use.

10. Pediatrics

This application triggers PREA due to the new active ingredient (combination of NS/DH). (b) (4)

the sponsor requested labeling down to age 12 based on the monograph for sleep aids, which

permits use of diphenhydramine in the 12-17 year old age group, and on data from the clinical trial program.

Overall, a total of 243 adolescent patients aged 12 to 17 years were enrolled in the clinical program, including 115 in trial 14837. Efficacy was demonstrated in adolescents, with significant benefit on both sleep latency and WASO. The age distribution of adolescent patients is primarily in the 16 and 17 year old age groups, with very few patients enrolled in the younger age groups. However, based on the age range for diphenhydramine under the monograph for sleep aids and the age range down to 12 years for other approved OTC naproxen products (Aleve), it is appropriate to approve this combination product for the same age range.

PeRC recommended that a partial waiver be granted in patients aged birth to 12 years because the product would be ineffective/unsafe. Insomnia does not routinely occur in children except when associated with other disorders. This is consistent with labeling for other OTC products for this indication. (b) (4)

ecause the product will be labeled for use in adolescents down to age 12.

11. Other Relevant Regulatory Issues

11.1. DSI Audits

The Division of Clinical Investigation (DSI) inspected two clinical sites that enrolled patients in the Phase 3 trials. No irregularities were identified that would impact data integrity. During review of this application, the review did not identify irregularities that would raise concerns regarding data integrity. All trials were conducted in accordance with acceptable ethical standards.

11.2. Financial Disclosure

The sponsor submitted acceptable financial disclosure statements. According to the sponsor, there were no sites with reportable payments or financial arrangements.

11.3 Environmental Assessment

An environmental assessment was not required for this product.

12 Labeling

12.1. Proprietary name

The sponsor submitted the proposed proprietary name Aleve PM, which was reviewed by DMEPA and deemed acceptable.

12.2. Patient labeling

Bayer submitted Drug Facts label, outer carton labels, and immediate container labels. Labeling reviews consults were completed by DMEPA, DRISK, and DNRD in addition to labeling reviews completed by the various review disciplines. The Drug Facts label contains standard NSAID warnings for allergy, GI bleeding, risk of stroke, and pregnancy/breast feeding. Based on PK data from the food effect trial, the label contains a statement that "if taken with food, this product may take longer to work." In addition, the Drug Facts Label contains drowsiness warnings as follows: when using this product drowsiness will occur; do not drive a motor vehicle or operate machinery.

The Division and Bayer have agreed on the final label language.

12. Decision/Action/Risk Benefit Assessment

13.1. Regulatory Action

Bayer has submitted adequate data to support approval of Aleve PM (NS/DH) for OTC use for the relief of occasional sleeplessness when associated with minor aches and pains. The product will be labeled for use in adults and adolescents down to age 12 at a dose of 2 tablets at bedtime, with each tablet containing 220 mg naproxen and 25 mg diphenhydramine.

13.2. Risk Benefit Assessment

The overall risk-benefit assessment supports approval of Aleve PM (NS/DH) for the OTC indication the relief of occasional sleeplessness when associated with minor aches and pains and for the indication that it helps you fall asleep and stay asleep. The efficacy of this application is primarily supported by Trial 14837 demonstrating that NS440/DH50 significantly shortened sleep latency and increased the time to wake after sleep onset as compared to the single ingredient components. PK parameters for the combination meet bioequivalence criteria compared to the single ingredients, both of which have a long OTC marketing history. No new safety signals were identified as part of this application, although the product will carry standard NSAID warnings for allergy, GI bleeding, risk of stroke, and pregnancy/breast feeding and will also carry a warning regarding drowsiness.

13.3. Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

13.4. Recommendation for other Postmarketing Requirements and Commitments

None.

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/s/

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01/16/2014