CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-393 & 21-394

MEDICAL REVIEW(S)

MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Office of Nonprescription Products (HFD-560)

Date: December 19, 2005

From: Charles J. Ganley, M.D. _____
Director, Office of Nonprescription Products (HFD-560)

Subject: Advil PM Ibuprofen 400 mg/ Diphenhydramine 50 mg) Decision Memo; NDA # 21-393 and # 21-394

Recommendation:
The application can be approved.

Background:
On August 8, 2002, NDA #21-393 and #21-394 were approvable because the sponsor failed to establish the contribution of the diphenhydramine component of the combination. The combination improved sleep latency compared to placebo but was not better than ibuprofen alone. Subjective sleep duration was greater with the combination compared to ibuprofen and placebo but there were problems in the design of the study that raised concern about the validity of the measure.[1] The sponsor was asked to conduct another study to validate the result using objective measures. The sponsor took this issue to dispute resolution. Dr. Jenkins agreed with the primary review divisions and the sponsor undertook another study.

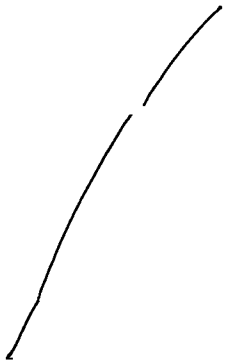
Additional Efficacy Data:
Study AE-04-14A was a randomized, double blind, parallel, single center study in subjects who were status post oral surgery (impacted 3rd molars). The study compared ibuprofen 400 mg/diphenhydramine 50 mg to ibuprofen 400 mg alone for various sleep parameters that included total sleep time by actigraphy, wake after sleep onset (WASO) using actigraphy, sleep latency and time to rescue medication. The study was reviewed by Dr. McNeil in the Division of Neurologic Drug Products.

Total sleep time was significantly longer by 1.2 hours in the combination group (N= 165) compared to the ibuprofen alone group (N = 164): 9.29 hours versus 8.09 hours. The WASO was significantly lower by 1.35 hours in the combination group compared to ibuprofen alone. Sleep latency was not different between the groups. This finding for sleep latency is consistent with the previous studies and suggests that the ability to get to sleep in this population is primarily influenced

[1] Subjects were awoken at 90 and 120 minutes to assess pain relief. This could have influenced the sleep duration endpoint

by pain relief with ibuprofen.[2] Diphenhydramine contribution to the combination appears to be related to an improvement in sleep duration and quality of sleep (WASO).

Based on the data in this submission, the sponsor has established the contribution of diphenhydramine to the combination in prolonging and maintaining sleep.



Pending Labeling Issues

There are no pending labeling issues.

[2] In previous studies, the combination product and ibuprofen alone improved sleep latency compared to placebo.

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-393 & 21-394
Submission Code	AZ
Letter Date	June 27, 2005
Stamp Date	June 27, 2005
PDUFA Goal Date	December 27, 2005
Reviewer Name	Daiva Shetty
Review Completion Date	September 26, 2005
Established Name	Ibuprofen 200 mg/ Diphenhydramine 25 mg
(Proposed) Trade Name	Advil PM
Therapeutic Class	Analgesic/Antihistamine
Applicant	Wyeth Consumer Healthcare
Priority Designation	S
Formulation	Liqui-Gel & Caplet
Dosing Regimen	Take 2 capsules (caplets) at bedtime, or as directed by a doctor
Indication	Nighttime sleep-aid/Pain reliever
Intended Population	12 years of age and older

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The proposed ibuprofen 200 mg/ diphenhydramine hydrochloride 25 mg combination has an acceptable safety profile for the OTC marketing. Therefore, this application is approvable from the safety stand point. Final approvability depends on the outcome of the clinical efficacy study AE-04-14A, which is being reviewed by the reviewers in the Division of Neuropharmacological Drug Products.

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1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special post-marketing risk management activities are recommended.

1.2.2 Required Phase 4 Commitments

No special Phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Wyeth Consumer Healthcare is seeking approval to market a new combination drug product, Advil PM Liqui-Gel/Caplet for adults and children over 12 years of age for the following indications:

- for relief of occasional sleeplessness when associated — minor aches and pains
- helps get to sleep —

The original NDA 21-393 and 21-394 for the proposed combination drug product were submitted on October 16, 2001 under 505 (b) (1). The Approvable Letter was issued on August 8, 2002. The reason for the approvable letter was that the benefit of diphenhydramine in the combination product was not established because of inconsistencies in the results of the primary endpoints, sleep latency and sleep duration. For sleep latency, ibuprofen was numerically superior to the combination. This difference almost achieved statistical significance (p=0.1). For sleep duration, the combination was superior to ibuprofen. The discrepancy between these results was thought to be related to the awakening of the subjects at 90 and 120 minutes after ingestion of medication, which could have had a negative impact on the measure of sleep duration. There were no other endpoints to support the contribution of diphenhydramine to the combination product. Therefore, FDA requested an additional well-designed clinical efficacy study to evaluate sleep duration and sleep latency.

There were no safety issues discovered with any of the two active ingredients or the combination during the review of the original NDA.

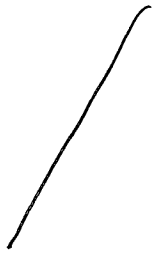
In support of the current submission, the sponsor provided results of one efficacy trial (AE-04-14A), a safety update, and proposed OTC labeling which are being considered in this review.

Altogether, the clinical development program for the ibuprofen/diphenhydramine (IBU/DPH) combination product consisted of eight single dose controlled clinical safety and efficacy trials, one long-term safety trial, and five bioequivalency studies.

1.3.2 Efficacy

Results of the efficacy trial AE-04-14A are being reviewed by the reviewers in the Division of Neuropharmacological Drug Products. Only efficacy data related to the headache sufferers population from the two previously reviewed studies (AE-98-04 and AE-97-08) was reevaluated in this review.

Study AE-98-04



Study-97-08
In this study, Ibuprofen 400 mg/diphenhydramine hydrochloride 50 mg was significantly better than placebo for all subjective sleep assessments:

- duration of sleep (p=0.007),
- sleep latency (p=0.006),
- quality of sleep (p=0.003),
- sleep duration by categorical scale (p=0.012), and
- marginally significant for pain relief rating (p=0.085).

Because of the study design and methodology (subjective assessment based on recall data), at best, this study is only supportive of the efficacy for ibuprofen 400 mg/diphenhydramine 50 mg as a sleep aid.

1.3.3 Safety

Integrated review of safety of the ibuprofen/diphenhydramine HCl (IBU/DPH) combination has been reviewed at the time of the original NDA submission on October 16, 2001. Safety data submitted to the current application consists of safety data gathered from the two clinical (AE-01-11 & AE-04-14A) and one bioequivalence (AE-01-12) trials, overdose and abuse data, postmarketing adverse event data, and the literature review.

There were a total of 18 adverse events (AEs) reported by 13 subjects in the IBU/DPH treatment groups during the three new clinical studies (AE-01-11, AE-04-14A, &AE-01-12). The most common adverse event in subjects taking the IBU/DPH combination was nausea. It was reported by a total of nine subjects. Only one of those nine reports was assessed as severe, four moderate, and four mild.

The safety of the proposed analgesic/sleep-aid dose of IBU 400 mg/DPH 50 mg is supported by data from a total of 14 clinical trials. The updated clinical trials database consists of 3066 subjects from 5 bioavailability studies (n=145), 8 single-dose efficacy trials (n=1947), and a maximum use safety and efficacy multiple-dose trial (n= 974). These numbers reflect an addition of 706 subjects to the original database presented in NDA 21-393 and NDA 21-394. The original database consisted of 2360 subjects comprising 4 bioavailability studies (n=119), 6

single-dose efficacy trials (n= 1267), and a maximum safety and efficacy multiple-dose trial (n= 974).

Of the 1947 subjects in the updated single-dose treatment clinical trials, a total of 191 (9.8%) subjects reported at least one AE: 88 (10.4%) in the IBU 400/DPH 50 group, 35 (29.2%) in the IBU 200/DPH 25 group, 22 (4.5%) in the IBU 400 mg group, 3 (9.7%) in the DPH 50 mg group, 6 (3.8%) in the APAP 1000/DPH 50 group and 37 (12.1%) in the placebo (PBO) group. Four events accounted for most AEs: headache (2.7%), nausea (2.7%), dry mouth (1.4%), and vomiting (1.3%).

A total of 145 subjects were exposed to the new combination product in five crossover bioavailability studies, 119 during the trials of the original NDA and 24 subjects during the study AE-01-12. Overall, the incidence of AEs in the updated safety population is similar to those reported for the four bioavailability studies in the original NDA. Of the 145 subjects in the bioavailability studies, 41 (28.3%) had an AE: thirty-two (22.4%) subjects while on IBU 400/DPH 50 (liquigel or caplet), six (12%) subjects while on IBU 400 mg, and ten (21%) while on DPH 50 mg. For the IBU 400/DPH 50, the most common AEs were: dizziness (4.2%), nausea (3.5%), and headache (3.1%).

Neither postmarketing adverse event reports submitted to the sponsor and FDA, nor the literature review for each ingredient and the combination reveal any unique adverse events that have not been reported previously.

For the years between 2001 and 2004 a total of 77 unique event-coding terms received by the American Association of Poison Control Centers (AAPCC) were associated with the cases involving the concomitant ingestion of single ingredient DPH with IBU. Among those, a total of seven fatalities were reported where single ingredient IBU and single ingredient DPH were ingested together with multiple, additional drug products. Fatalities due to ingestion of IBU and DPH occurred only in cases of an intentional overdose and involved exposures to multiple drug products. None of the fatalities involved ingestion of just single ingredient IBU with single ingredient DPH. Since the proposed IBU/DPH combination product is indicated for occasional use, the possibility of unintentional accidental overdose with this product is unlikely. The overdose issues are addressed by warnings in different sections of the proposed OTC label.

There is no known withdrawal phenomenon or abuse potential associated with the use of ibuprofen and diphenhydramine combination. Both, the Emergency Department and the Medical Examiner data suggest that IBU when combined with DPH is unlikely to possess an abuse potential.

1.3.4 Dosing Regimen and Administration

The proposed dosing directions are:

- adults: take 2 capsules/Liqui-Gels at bedtime, —
- do not take more than 2 capsules / Liqui-Gels in 24 hours
- —

The proposed maximum duration of use is 10 days.

1.3.5 Drug-Drug Interactions

No drug-drug interactions were evaluated in the original NDA, or in this safety update.

1.3.6 Special Populations

The proposed labeling has all the appropriate warnings for consumers of certain age categories, with underlying medical conditions, and for those taking interacting medications.

2 INTRODUCTION AND BACKGROUND

This is a clinical safety update review of the analgesic/sleep-aid combination products, Advil PM Liqui-Gels (ibuprofen 200 mg / diphenhydramine HCl 25 mg liquid filled capsule) and Advil PM Caplets (ibuprofen 200 mg/ diphenhydramine citrate —.ng tablet), filed under two separate NDAs, 21-393 and 21-394, respectively.

2.1 Product Information

Wyeth Consumer Healthcare is seeking approval to market a new combination drug product, Advil PM Liqui-Gels/Caplets for adults and children over 12 years of age for the following indications:

- for relief of occasional sleeplessness when associated with — minor aches and pains
- helps you get to sleep —

The proposed dosing directions are:

- adults: take 2 capsules/Liqui-Gels at bedtime, —
- do not take more than 2 capsules / Liqui-Gels in 24 hours —
- —

The proposed maximum duration of use is 10 days.

Ibuprofen is a propionic acid derivative of the non-steroidal anti-inflammatory class of drugs (NSAIDs). It has been available in the U.S. as an over-the-counter analgesic since 1984. It is indicated for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps, and for the reduction of fever. The recommended dose of OTC ibuprofen for adults is 200 mg tablets/caplets every 4-6 hours. If symptoms persist, 2 (400 mg) tablets/caplets may be taken. The maximum daily dosage of OTC ibuprofen is 1200 mg or 6 tablets/caplets in a 24-hour period. Ibuprofen is also available OTC in combination with pseudoephedrine and chlorpheniramine.

Diphenhydramine is a first generation antihistamine. It has been marketed as an OTC sleep aid product in the U.S. under 21 CFR Part 338 the Final Monograph for Nighttime Sleep-Aid Drug Products for OTC Human Use. Products containing diphenhydramine are labeled to help a consumer to fall asleep if the individual has difficulty falling asleep. The recommended dose for diphenhydramine hydrochloride is 50 mg at bedtime if needed or as directed by a physician.

2.2 Currently Available Treatment for Indications

Acetaminophen (APAP) in combination with diphenhydramine is currently marketed OTC under the OTC monograph review process for the relief of occasional sleeplessness when associated

with [redacted] minor aches and pains. However, to date, there is no final monograph under which this indication is covered.

2.3 Availability of Proposed Active Ingredient in the United States

See section 2.1.

2.4 Important Issues With Pharmacologically Related Products

Use of ibuprofen and other NSAIDs is associated with an increased risk of: gastrointestinal adverse effects, severe skin reactions, and renal insufficiency in individuals with underlying renal compromise.

Diphenhydramine has a pronounced tendency to induce sedation. Concurrent ingestion of alcohol or other CNS depressants produces an additive effect that impairs motor skills. Other adverse events referable to central actions include dizziness, tinnitus, lassitude, incoordination, fatigue, blurred vision, diplopia, euphoria, nervousness, insomnia, and tremors. The next most frequent group of side effects involve the digestive tract, such as nausea, vomiting, epigastric distress, and loss of appetite; however, these events are rare.

The OTC ibuprofen and diphenhydramine labels inform consumers of the potential for serious and most common adverse events. The same warnings are incorporated into the proposed Advil PM label.

2.5 Presubmission Regulatory Activity

The original NDA 21-393 and 21-394 for the proposed combination drug product were submitted on October 16, 2001 under 505 (b) (1). The Approvable Letter was issued on August 8, 2002. The reason for the approvable letter was that the benefit of diphenhydramine in the combination product was not established because of inconsistencies in the results of the primary endpoints, sleep latency and sleep duration. For sleep latency, ibuprofen was numerically superior to a combination. This difference almost achieved statistical significance ($p=0.1$). For sleep duration, the combination was superior to ibuprofen. The discrepancy between these results was thought to be related to the awakening of the subjects at 90 and 120 minutes after ingestion of medication, which could have had a negative impact on the measure of sleep duration. Therefore, FDA requested an additional well-designed clinical efficacy study to evaluate sleep duration and sleep latency.

In addition to clinical issues, the proposed specifications for the drug product were not acceptable.

There were no safety issues discovered with any of the two active ingredients or the combination during the review of the original NDA.

There were several communications between FDA and the sponsor following the approvable letter. Current submission is the sponsor's response to the deficiencies listed in the approvable letter. It includes:

- Additional efficacy trial designed to determine the contribution of the components with sleep duration as the primary endpoint.
- Safety update.
- CMC information: dissolution testing and specifications.

2.6 Other Relevant Background Information

Not applicable.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

A chemistry reviewer will address the CMC portion of the submission.

3.2 Animal Pharmacology/Toxicology

Not applicable.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

In support of the current submission, the sponsor provided results of one efficacy trial (AE-04-14A), safety update, and the proposed OTC labeling which are being considered in this review.

4.2 Tables of Clinical Studies

There is only one clinical efficacy study submitted to this NDA resubmission: Study AE-04-14A Advil PM Oral Surgery Study Using Actigraphy to Objectively Measure Sleep Efficacy. In addition, the sponsor has submitted safety data from two previously submitted trials (AE-01-11 and AE-01-12). A list of all clinical studies conducted by the sponsor in support of this combination is provided in Table 1 below.

Table 1. List of Clinical Studies

Study No.	Study Type/Design	Duration of Treatment Evaluation	Dose	No. of subjects
AE-97-01	Oral surgery, RA, I, PC, DB	Single dose	IBU400/DPH 76[1] IBU 400 DPH 76 Placebo	29 31 31 14
AE-97-05	Headache, RA, O, PC, DB	Single dose	IBU 400/DPH 76 IBU 400 Placebo	49 51 52
AE-98-01	Oral surgery, RA, I, PC, DB	Single dose	IBU 400/DPH 50 IBU 400 Placebo	122 119 40
AE-98-02	Oral surgery, RA, I, PC, DB	Single dose	IBU 400/DPH 50 IBU 400 Placebo	120 123 40
AE-98-03	Oral surgery, RA, I, PC, DB	Single dose	IBU 400/DPH 50 IBU 200/DPH 25 Placebo	123 120 41
AE-98-04	Tension headache, RA, I, PC, DB	Single dose	IBU 400/DPH 50 Placebo	81 81
AE-01-11	Oral surgery, RA, I, PC, DB	Single dose	IBU 400/DPH 50 APAP 1000/DPH 50 Placebo	155 158 38
AE-04-14A	Oral surgery, RA, I, DB	Single dose	IBU 400/DPH 50 IBU 400	165 164
AE-97-08	Maximum use safety, RA, O, PC, DB	10 days	IBU 400/DPH 50 IBU 200/DPH 25 APAP 1000/DPH 50 Placebo	323 158 326 167
WM-716	Bioequivalence, drug interaction, RA, OL, CO	Single dose	IBU 400/DPH 76 IBU 400 DPH 76	23
AE-97-02	Bioequivalence, food effect, RA, OL, CO	Single dose	IBU 400/DPH 50 IBU 400/DPH 50 fed IBU 400/DPH 50	27
AE-97-09	Bioequivalence, formulation effect, RA, OL, CO	Single dose	IBU 400/DPH 50 IBU 400 DPH 50 IBU 400	27
AE-00-10	Bioequivalence, RA, OL, CO	Single dose	IBU 400/DPH 50 IBU 400/DPH 76	42
AE-01-12	Bioequivalence, RA, OL, CO	Single dose	IBU 400/DPH 50 IBU 400/DPH 76	26

[1]diphenhydramine citrate; RA: randomized; I: inpatient; PC: placebo-controlled; O: outpatient; DB: double-blind; OL: open label; CO: cross-over

4.3 Review Strategy

This review covers safety update. The clinical efficacy study (AE-04-14A) will be reviewed by the reviewers in the Division of Neuropharmacological Drug Products.

4.4 Data Quality and Integrity

Not applicable. There were no DSI audits conducted for the study site or data analyses.

4.5 Compliance with Good Clinical Practices

Not applicable to this review.

4.6 Financial Disclosures

The sponsor conducted one new clinical study (AE-04-14A) that involved only one clinical site and only one investigator. The sponsor has submitted the Form 3454 certifying no financial interest by the investigator.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Pharmacokinetic studies to support this application have been reviewed at the time of the original submission of NDA, and were found to be acceptable from the clinical pharmacology and biopharmaceutics perspective. No new pharmacokinetics data were submitted to this application.

5.2 Pharmacodynamics

No new pharmacodynamics data were submitted to this application.

5.3 Exposure-Response Relationships

No new exposure-response relationship data were submitted to this current application.

6 INTEGRATED REVIEW OF EFFICACY

The efficacy trial AE-04-14A submitted by the sponsor will be reviewed by the reviewers in the Division of Neuropharmacological Drug Products. Only safety data gathered during this study will be discussed in the safety portion of this review.

The proposed labeling

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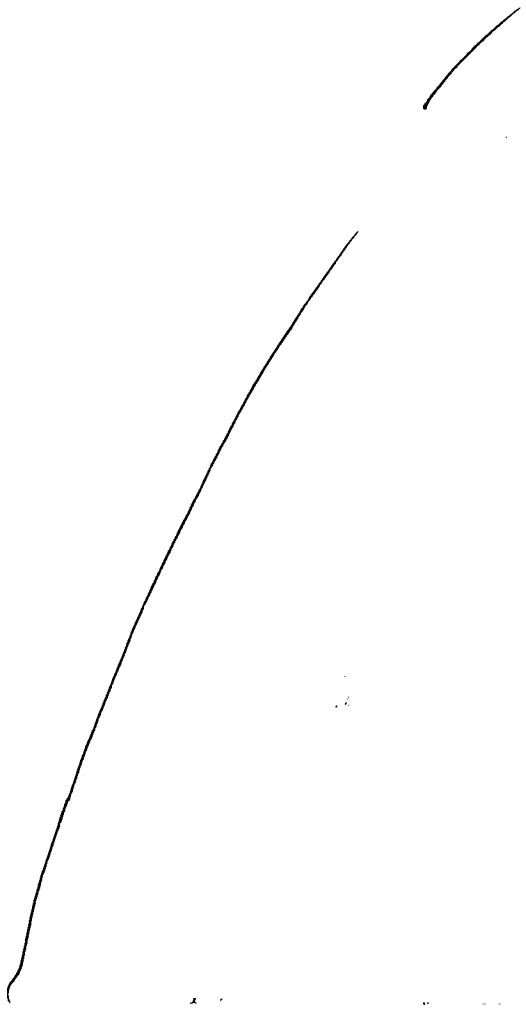
✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling



Study AE-97-08

This was a randomized (stratified by age and gender), double-blind, parallel-group, placebo-controlled, outpatient, multi-center study.

There were four treatment groups:

- IBU 400 mg/DPH 50 mg
- Acetaminophen (APAP) 1000 mg/DPH 50 mg
- IBU 200 mg/DPH 25 mg
- Placebo

The objective of the study was to evaluate and compare the safety among four treatment groups. As a secondary objective, the trial also evaluated the relative efficacy of the four treatments after the first dose of medication.

The study population consisted of subjects with a history of occasional sleeplessness associated with headaches or minor aches and pains. Per protocol, approximately 900 subjects (300 in the 2 Advil PM Liqui-Gel, 300 in the 2 Tylenol PM caplet, 150 in the 1 Advil PM Liqui-Gel, 75 in the liquigel placebo, and 75 in the caplet placebo groups) were to be randomized to the study treatment groups.

Potential subjects were asked to determine whether the test product (Advil PM) was appropriate for them to use, based on the proposed Advil PM label. If the subject met all of the study criteria, he or she was enrolled into the study, regardless of whether or not he or she properly self-selected. Eligible subjects were given two bottles of study medication (Bottles A and B) and a diary with exact instructions for dosing and recording data. Subjects were required to begin administration of study drug for an episode of pain accompanied by sleeplessness within 30 days of enrollment.

Just prior to taking the first dose of study medication, subjects were asked to answer if they are taking the study medication to help them sleep or for the pain relief, record the painful condition they are treating, and describe the severity of their pain.

Subjects were instructed to record their responses to the efficacy assessment questions in their diary when they awakened (with the intention of arising for the day) the morning after taking the first dose of study medication or at the time rescue medication was taken (whichever occurred first).

Sleep assessments included sleep latency (how long did it take them to fall asleep), sleep duration (how many hours did they sleep), and sleep quality. Pain relief assessment was evaluated by asking the subjects to evaluate their pain relief on a 4-point scale.

Primary Efficacy Variables:
Sleep duration (number of hours slept) and pain relief were considered to be the primary sleep and pain parameters, respectively.

Secondary Efficacy Variables:
Sleep duration (categorical scale), sleep latency, sleep quality and the proportion of subjects who were treatment failures were considered secondary efficacy variables.

On the first night of taking the study medication, if a subject took any rescue medication (analgesic and/or sleep-aid, or a sedating antihistamine) after 1 hour of taking the study medication, he/she was considered a treatment failure.

Results

Ten sites screened a total of 1308 subjects, of whom 677 (51.8%) correctly and 603 (46.1%) incorrectly determined whether the product was appropriate for them to use (upon reading the proposed label). For the remaining 28 subjects, whether the selection was correct or not could not be determined because the individual either did not provide a reason for their choice or left the site without completing the form. Following were the most common reasons for incorrect self-selection according to the label:

- 563 (93.4%) were either under a doctor's care for a continuing medical condition or they were taking other drugs,
- 58 (9.6%) either did not have sleep problem or had a chronic sleep problem,
- 47 (7.8%) either did not have pain or had chronic pain,
- 22 (3.6%) did not consult a physician or pharmacist prior to determining product suitability because they had benign prostatic hyperplasia (BPH).

Of the total 1308 subjects screened, 1016 (77.7%) were randomized into one of the four treatment groups:

- Placebo (N=174)
- 1 Advil PM Liqui-Gel (N=164)
- Advil PM Liqui-Gel (N=382)
- Tylenol PM (N=340)

Of these, 974 subjects took at least one dose of study medication and were included in the safety analysis. In total, 355 evaluable subjects (34.9% of all randomized subjects) treated a headache pain and sleeplessness the first night of study drug administration. In this sample, there were 63, 53, 122 and 117 subjects in the placebo, 1 Advil PM Liqui-Gel, 2 Advil PM Liqui-Gel, and 2 Tylenol PM groups, respectively.

Most subjects (68.2%) rated the severity of their headache pain prior to treatment as moderate, while 20.0% had mild pain, and 11.8% had severe pain. The treatment groups were comparable with respect to the pre-dose pain severity.

A summary of the efficacy results for subjects who treated a nighttime headache are presented in Table 3 below.

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

6.1 Indication

The proposed indication for Advil PM is for the relief of occasional sleeplessness when associated with — minor aches and pains.

7 INTEGRATED REVIEW OF SAFETY

The following sections of the Integrated Summary of Safety (ISS) are being updated with information not available at the time of the original NDA submission:

- Clinical Trials Conducted by Sponsor:
  - Study AE-01-11 is a market support study comparing the analgesic/sleep efficacy of the combination of ibuprofen/diphenhydramine to the combination of acetaminophen/diphenhydramine (as well as placebo).
  - Study AE-04-14A assessing the sleep efficacy of ibuprofen/diphenhydramine compared to ibuprofen alone.
  - The pharmacokinetic study AE-01-12 evaluating the pharmacokinetic profile of ibuprofen/diphenhydramine caplets compared to ibuprofen/diphenhydramine Liqui-Gels.
- Update of the Drug Abuse Warning Network (DAWN) database for Emergency Department Visits through 2002 and Medical Examiner data through 2002.
- AAPCC overdose data: 2001, 2002, and 2003.
- Sponsor-received adverse events for the period January 1, 2002– December 31, 2004.
- Update of the FDA Adverse Event Reporting System (AERS) database November 1, 1997 – March 31, 2004.
- Literature update for the single ingredients (January 1, 2000 – February 28, 2005) summarizing references on single-ingredient ibuprofen and references on single ingredient diphenhydramine.

This update includes three additional studies, AE-01-11, AE-01-12, and AE- 04-14a to the clinical database on ibuprofen and diphenhydramine reported in the original Integrated Summary of Safety for this NDA. The updated clinical trials database consists of 3066 subjects from 5 bioavailability studies (n=145), 8 single-dose efficacy trials (n=1947), and a maximum use safety and efficacy multiple-dose trial (n= 974). These numbers reflect an addition of 706 subjects to the original database presented in NDA 21-393. The original database consisted of 2360 subjects comprising 4 bioavailability studies (n=119), 6 single-dose efficacy trials (n= 1267), and a maximum safety and efficacy multiple-dose trial (n= 974). The safety of the proposed analgesic/sleep-aid dose of IBU 400 mg/DPH 50 mg is supported by data from a total of 14 clinical trials. For a list of those trials see section 4.2 of this review.

Brief description of the three clinical studies that contributed to the safety update:

- **Study AE-01-11**
  This was a randomized, stratified (by baseline pain and gender), inpatient, placebo-controlled, single dose, double-blind, parallel group, single-center study. The objective of the study was to evaluate the analgesic and sleep-aid efficacy of a single dose of 2 Advil PM Liqui-Gels (total dose = IBU 400/DPH 50) compared to 2 Tylenol PM (total dose = APAP 1000/DPH 50) and placebo. Three hundred fifty-one (351) males and females, 16 – 45 years of age underwent surgical extraction of 1 to 4 impacted molars (one of which must have been at least a partial bony mandibular impaction). Subjects continued their recovery at the inpatient unit where they were housed overnight. When at least moderate pain was experienced and it was between approximately 6:00 and 8:30 PM, subjects were randomized to receive either IBU 400/DPH 50, APAP 1000/DPH 50 or PBO (in a 4:4:1 ratio) in a double dummy fashion. Subjects were required to go to bed at least three hours before their normal bedtime and immediately after taking study medication. At specified intervals over the first 3 hours after dosing, a nurse observer determined whether or not the subject was asleep. At 90 and 120 minutes post-dose, subjects were awakened (if asleep) and interviewed to assess their pain severity and pain relief. Adverse experiences were recorded when they occurred. Subjects were discharged from the inpatient clinic the following morning.

- **Study AE-04-14A**
  This was a randomized, stratified (by baseline pain and gender), inpatient, single dose, double-blind, parallel group, single-center study. For the most part, the design of this study was similar to that for AE- 01-11 described above except subjects were not analyzed to assess pain. The study compared the efficacy and safety of IBU400/DPH50 to IBU400 alone. Total sleep time, measured objectively (using actigraph), was designated as the primary efficacy parameter. Adverse events were recorded when they occurred. Three hundred and twenty nine subjects (165 in the IBU/DPH group, 164 in the IBU group) participated in this study. All 329 subjects were included in the analysis of efficacy and in the analysis of safety.

- **Study AE-01-12**

This was a single-center, randomized (stratified by gender), open-label, single-dose, two-way crossover bioequivalence study, with a washout period of 7 days between treatments. The objective of the study was to evaluate the rate and extent of absorption of ibuprofen and diphenhydramine from Advil PM (ibuprofen/diphenhydramine 200/38 mg) Caplets compared to Advil PM (ibuprofen/diphenhydramine hydrochloride 200/25 mg) Liqui-Gels under fasted conditions. Twenty-six healthy male and female volunteers received a single dose of either 2 IBU/DPH Liqui-Gels or 2 IBU/DPH caplets under fasted conditions. Blood samples were drawn at periodic intervals over the following 36 hours post dose (the first 24 hours as an inpatient). One week later, the procedures were repeated with the alternate treatment. Twenty-six subjects were enrolled and 24 subjects completed the study.

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths reported during the three additional clinical studies. There are no reports of death with the use of therapeutic doses of the proposed combination drug product. Fatalities associated with the intentional overdose of ibuprofen and diphenhydramine are discussed in sections 7.1.16 and 7.1.17 of this review.

7.1.2 Other Serious Adverse Events

No serious AEs occurred during the three new studies: AE-01-11, AE-04-14A, and AE-01-12.

7.1.3 Dropouts and Other Significant Adverse Events

No subject discontinued due to an AE in study AE-01-11 and AE-04-14A.

One subject (Subject 58) discontinued due to an AE in Study AE-01-12. The subject called the site the day prior to Period 2 and reported taking a Cold Plus medication for a cold. The event (common cold) was rated mild, and considered unrelated to the study medication received by the subject in Period 1 (IBU/DPH caplets).

7.1.3.1 Overall profile of dropouts

The addition of the two studies AE-01-11 and AE-04-14A does not change the number of subjects who discontinued due to AEs from what was reported in the NDA database.

As reported in the original NDA 21-393, five subjects withdrew prematurely due to an AE during the duration of clinical efficacy and safety trials.

Subject No. 30196 (AE-98-01, IBU 400/DPH 50), a 21-year-old woman with a history of anxiety (indicated as not ongoing) became very agitated, calmed down, and insisted on leaving the trial 2

½ hours after dosing with the study medication. This event was evaluated as not related to the study drug.

Subject No. 40175 (AE-98-01, IBU 400 mg), a 21-year-old woman developed nausea prior to dosing and emesis ensued 7 minutes post-dosing, which was not related to study drug.

Subject No. 10014 (AE-98-02, PBO), an 18-year-old man, was withdrawn from the study when he developed a moderate headache for which he was given Lortab. The investigator rated the adverse event as remotely related to study drug.

Subject No. 10078 (AE-98-03, IBU 400/DPH 50), a 25-year-old man was discontinued from the study after developing bleeding at the surgical site that was considered possibly related to the study medication. The reaction resolved with packing. The subject also experienced an earache (remotely related), pharyngitis (unrelated), and a headache (possibly related). The subject was not treated for these three events and they all resolved spontaneously.

Subject No. 30070 (AE-98-03, IBU 400/DPH 50), a 31-year-old woman developed nausea and vomiting about one hour post dosing and was withdrawn from the study. Both events, considered to be possibly related to study medication, resolved spontaneously.

In addition to the five withdrawals due to AEs in the clinical efficacy trials, there are a total of two subjects (1.4%) who discontinued due to an adverse experience in the bioequivalence study database.

Subject No. 203 (AE-97-02, 2 IBU 400/DPH 50), a 25-year-old woman developed severe acute sinusitis that was considered unrelated to study medication. The event resolved with treatment.

Subject No. 58, (AE-01-12), Period 1 treatment assignment IBU/DPH caplets) called the site the day prior to Period 2 and reported taking a Cold Plus medication for a cold. The event (common cold) was rated mild and considered unrelated to the study medication received by the subject.

7.1.3.2 Adverse events associated with dropouts

Table 4 displays information on the seven subjects who withdrew early from the clinical trials.

Table 4. Adverse Events among Subjects who Withdrew from the Clinical Studies

Study #	Subject #	Drug Taken	Adverse Event	Relation to drug
AE-98-01	30196	IBU 400/DPH 50	Anxiety	Not related
AE-98-01	40175	IBU 400	Nausea	Not related
AE-98-02	10014	Placebo	Headache	Remotely related
AE-98-03	10078	IBU 400/DPH 50	Earache Pharyngitis Headache	Remotely related Not related Possibly related
AE-98-03	30070	IBU 400/DPH 50	Nausea & vomiting	Possibly related
AE-01-12	58	Prior to Treatment	Common cold	Not related
AE-97-02	203	IBU 400/DPH 50	Sinusitis	Not related

7.1.3.3 Other significant adverse events

Not applicable.

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

Historically, common (>1%) drug-related adverse events associated with ibuprofen use include the following reactions:

- Headache
- Dizziness
- Nervousness
- Rash
- Pruritus
- Abdominal pain or cramps
- Diarrhea
- Nausea
- Constipation
- Flatulence
- Epigastria/GI pain
- Heartburn
- Abdominal/GI distress
- Bloating
- GI fullness
- Anorexia/decreased appetite
- Fluid retention
- Edema
- Tinnitus

Safety of diphenhydramine has not been evaluated in controlled clinical trials. However, the most common drug-related adverse events for the first-generation antihistamines are well documented and include the following:

- Sedation
- Dizziness
- Tinnitus
- Lassitude
- Incoordination
- Fatigue
- Blurred vision
- Diplopia

- Euphoria
- Nervousness
- Insomnia
- Tremors
- Dryness of mouth and respiratory passages
- Urinary retention or frequency, and dysuria
- Rarely GI effects (distress, appetite disturbances, nausea, vomiting)

7.1.5.1 Eliciting adverse events data in the development program

Subjects in the two clinical trials (AE-01-11 and AE-04-14A) were observed by the study personnel during the entire duration of the study. Subjects were also observed over 24 out of 36 hours post-dosing in the bioequivalence study AE-01-12. Adverse events were observed or elicited by open-ended questions.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All adverse event reports observed during clinical studies were grouped by preferred terms using COSTART dictionary.

7.1.5.3 Incidence of common adverse events

Adverse events that occurred during the course of the three single-dose clinical studies are consistent with the known adverse event profile for ibuprofen and/or diphenhydramine. No single AE occurred at a rate >2% in the active treatment group.

7.1.5.4 Common adverse event tables

Tables 5 through 7 display adverse events reported during the three new clinical studies.

Table 5. Summary of Adverse Events Reported During the Study AE-01-11

Body System	COSTART Term	Placebo (N=38)	IBU/DPH (N=155)	APAP/DPH (N=158)
Total	No. of AEs	1	8	8
	No. of Subjects	1 (2.6%)	5 (3.2%)	6 (3.8%)
Body as whole	Headache	0 (0.0%)	1 (0.6%)	0 (0.0%)
Digestive	Nausea	0 (0.0%)	3 (1.9%)	3 (1.9%)
	Vomiting	0 (0.0%)	2 (1.3%)	2 (1.3%)
	Dysphagia	1 (2.6%)	0 (0.0%)	0 (0.0%)
	Gum hemorrhage	0 (0.0%)	0 (0.0%)	1 (0.6%)
Nervous	Dizziness	0 (0.0%)	1 (0.6%)	2 (1.3%)
Respiratory	Epistaxis	0 (0.0%)	1 (0.6%)	0 (0.0%)

Seventeen (17) AEs were reported by 12 (3.4%) subjects during Study AE-01-11: 2.6% in the PBO group, 3.2% in the IBU/DPH group, and 3.8% in the APAP/DPH group.

Table 6. Summary of Adverse Events Reported During the Study AE-04-14A

Body System	COSTART Term	IBU/DPH (400/50) (N=165)	IBU (400) (N=164)
Total	No. of AEs	5	6
	No. of Subjects	4 (2.4%)	4 (2.4%)
Digestive	Nausea	2 (1.2%)	4 (2.4%)
	Vomiting	1 (0.6%)	1 (0.6%)
Nervous	Dizziness	1 (0.6%)	1 (0.6%)
Special Senses	Conjunctivitis	1 (0.6%)	0 (0.0%)

Eleven (11) AEs were reported by 8 subjects, 2.4% in each treatment group during Study AE-14-04a. All were either mild or moderate in severity, and were rated as either not related, or remotely related to study medication. The most frequently reported event was nausea with a total of 6 reports, 2 (1.2%) in the IBU 400/DPH 50 group and 4 (2.4%) in the IBU 400 group.

Table 7. Summary of Adverse Events Reported During the Bioequivalency Study AE-01-12

Body System	COSTART Term	Advil PM Caplets (N=26)	Advil PM Liqui-Gels (N=24)
Total	No. of AEs	2	3
	No. of Subjects	2 (7.7%)	2 (8.3%)
Body as whole	Common cold	1 (3.8%)	0 (0.0%)
	Headache	0 (0.0%)	1 (4.2%)
Digestive	Nausea	0 (0.0%)	2 (8.3%)
Nervous	Dizziness	1 (3.8%)	0 (0.0%)

Five AEs (all rated mild) were reported by 4 subjects, which included common cold and dizziness with IBU/DPH caplets, and headache and nausea (2 occurrences) with IBU/DPH Liqui-Gels. All were considered either possibly, remotely, or not related to the study medication.

7.1.5.5 Identifying common and drug-related adverse events

None of the adverse events reported during the three clinical trials were rated as probably or definitely related to the treatment.

Study AE-01-11

- The only AE reported in the placebo group was rated as not related to the treatment.
- Advil PM group: three AEs (nausea, vomiting, and dizziness) were rated as possibly related, one (nausea) as remotely related, and one as unrelated to the treatment.
- Tylenol PM group: four AEs (nausea, two of vomiting, and dizziness) were rated as remotely related, and four as unrelated to the treatment.

Study AE-01-12

- In the Advil PM Caplet group two reported AEs were rated as unrelated to the treatment.
- In the Advil PM Liqui-Gels group, two adverse events (both nausea) were assessed as possibly related, and one (headache) remotely related to the treatment.

Study AE-04-14A

- In the IBU 400/DPH 50 group, only one AE (nausea) was rated as remotely related to the treatment. The remaining four AEs were not study drug related.
- In the IBU 400 group all the six reported AEs were assessed as unrelated to the treatment.

The most common adverse event in subjects taking the IBU/DPH combination was nausea. It was reported by a total of nine subjects. Only one of those nine reports was assessed as severe, four moderate, and four mild.

7.1.5.6 Additional analyses and explorations

There were no additional analyses or extrapolations performed by the sponsor. Discussion of this safety update in relationship to the original safety database is presented in sections 7.3 and 7.4 of this review.

7.1.6 Less Common Adverse Events

The population and the number of adverse events in the three clinical studies were too small to assess the incidence of less common adverse events.

7.1.7 Laboratory Findings

Except for the plasma concentration measurements for ibuprofen and diphenhydramine in the Study AE-01-12, no other laboratory tests were performed during the course of the three new clinical studies.

7.1.7.1 Overview of laboratory testing in the development program

Not applicable.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable.

7.1.7.3 Standard analyses and explorations of laboratory data

Not applicable.

7.1.7.4 Additional analyses and explorations

Not applicable.

7.1.7.5 Special assessments

Not applicable.

7.1.8 Vital Signs

The only study that monitored vital signs was the bioequivalency study AE-01-12. Blood pressure, heart rate, respiration, and oral temperature were measured at baseline and at the end of 36 hours of the study. There were no clinically significant changes in vital signs during the course of the study.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not done in the conducted clinical trials.

7.1.9.1 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

There are no known immunogenicity issues related to ibuprofen or diphenhydramine.

7.1.11 Human Carcinogenicity

There are no known carcinogenicity issues related to ibuprofen or diphenhydramine.

7.1.12 Special Safety Studies

There were no special safety studies requested or performed for this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

To evaluate a drug abuse potential, the sponsor had analyzed the data gathered by the Drug Abuse Warning Network (DAWN). There are two different data bases: Emergency Department (ED) Data and Medical Examiner Data, which are discussed separately below.

Emergency Department Data
At the time this update was prepared, DAWN had published ED estimates only for the period 1995-2002. These data provide estimates of drug abuse-related ED admissions (episodes) either induced by or related to drug abuse. The term, ED drug mention, refers to a substance that was mentioned in a drug abuse episode; alcohol is reported only for episodes in which at least one other drug is also mentioned. The data are derived from a representative sample of non-Federal, short-stay hospitals with 24-hour emergency departments in the coterminous U.S; facilities in Hawaii and Alaska are not included in the sample.

Trend data for seven product categories are shown in Table 8. The categories include: three, single-ingredient, analgesics: APAP, aspirin (ASA), and IBU; single-ingredient DPH products; two combination analgesic-sleep aid products, (APAP-DPH, ASA-DPH), and data for a

representative, "Major" substance of abuse, alcohol-in-combination. As defined by DAWN, the category alcohol-in-combination refers to episodes where alcohol is reported in combination with any other substance reported to DAWN. In a recent publication DAWN noted that of the 44,000 individuals who were admitted in 1999 for substance abuse treatment, less than 1% (600) of all subjects (total >78,000 admissions) seeking treatment for drug abuse were admitted for nonprescription, OTC, product abuse.[1]

Table 8. Estimates of Drug Abuse Related ED Admissions

	Mention frequency by reporting year							
	Total 1995	Total 1996	Total 1997	Total 1998	Total 1999	Total 2000	Total 2001	Total 2002
APAP	35,371	37,093	34,867	31,424	27,702	32,835	30,888	28,720
ASA	12,701	11,811	11,231	11,696	9,365	11,096	6,137	7,494
IBU	21,754	17,350	17,647	17,567	14,696	18,338	17,123	15,867
DPH	11,953	13,008	11,122	8,058	6,771	7,440	7,670	5,430
ASA-DPH	0	0	0	0	0	0	10	1
APAP-DPH	2,703	3,081	2,891	3,345	3,054	4,224	3,513	2,809
Alcohol-in-combination	166,897	166,166	171,894	184,989	196,178	204,500	217,940	207,395
Total Drug Abuse Episodes	513,429	513,841	526,671	542,250	554,570	601,392	638,345	670,307
Total Drug Abuse Mentions	899,977	906,078	941,627	981,286	1,013,688	1,098,915	1,165,148	1,209,938
Total ED Visits (in 1,000s)	88,548	91,189	89,720	89,683	91,100	96,163	100,518	102,810

Medical Examiner Data

At the time of preparing this review, data up to 2002 had been released by DAWN; hence only two reporting periods are included.

In 2001, 128 jurisdictions in 42 metropolitan areas voluntarily submitted medical examiner data to DAWN.[2] The 42 metropolitan areas ranged in size from Casper, WY, (population 66,798) to Chicago (population 8,342,190). The most common single drugs reported to DAWN by Medical Examiners were cocaine, heroin/morphine, narcotic analgesics, and marijuana. The most common drug combinations reported were: alcohol and cocaine; alcohol and heroin/morphine; cocaine and heroin/morphine; alcohol, cocaine, and heroin/morphine; heroin/ morphine and other narcotic analgesics; alcohol and narcotic analgesics (other than heroin/morphine); and amphetamines plus methamphetamine. Participating jurisdictions reported a number of prescription and over-the-counter drugs involved in drug abuse deaths; most involved overdoses of benzodiazepines or narcotic analgesics. Even though DPH ranked in the top 10 list of drugs for 19 cities, notably Detroit (71), Philadelphia (67), Phoenix (54), Baltimore (50), and Dallas

[1]Drug and Alcohol Services Information System. The DASIS Report. Characteristics of primary prescription and OTC treatment admissions: 2002. Available on-line at http://www.oas.samhsa.gov.

[2] Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Mortality Data From the Drug Abuse Warning Network, 2001.DAWN Series D-23, DHHS Publication No. (SMA) 03-3781. Rockville, MD. 2002.

(40), there were no mentions in the DAWN report of fatalities associated with the combination APAP-DPH or ASA-DPH. IBU was not mentioned in any of the top ten lists.

In 2002, Medical Examiners in 127 jurisdictions in 38 metropolitan areas voluntarily submitted data to DAWN.[3] The 38 metropolitan areas ranged in size from Fargo, ND (population 177,064) to New York, NY (population 9,411,687). The most common single-drug deaths reported to DAWN involved either cocaine, heroin/morphine, narcotic analgesics, or marijuana. However, the tendency for deaths involving multiple drugs was evident even among those involving cocaine, heroin/morphine, and other narcotic analgesics. The most common multiple-drug deaths involved 2- and 3-drug combinations of cocaine, heroin/morphine, other narcotic analgesics, and alcohol. The most common combinations included alcohol and cocaine; cocaine and heroin/morphine; alcohol and heroin/morphine; alcohol, cocaine, and heroin/morphine; heroin/morphine and other narcotic analgesics; cocaine and narcotic analgesics; and cocaine, heroin/morphine, and other narcotic analgesics. In eleven reporting areas, single ingredient diphenhydramine was mentioned in the top ten lists, typically ranking between fifth and tenth. For these same areas, alcohol-in-combination was ranked as one of the top three. IBU was not mentioned in any of the top ten lists nor was the combination product APAP-DPH mentioned in any of these lists.

Comments:
There is no known withdrawal phenomenon or abuse potential associated with the use of ibuprofen and diphenhydramine combination. Both, the ED and the Medical Examiner data suggest that IBU when combined with DPH is unlikely to possess an abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

There are no new reproduction or pregnancy data submitted to support this application. The proposed labeling carries an appropriate pregnancy warning for OTC drug products containing ibuprofen and diphenhydramine.

7.1.15 Assessment of Effect on Growth

There are no new data on effects on growth. Ibuprofen is approved for use in children down to six months of age. Diphenhydramine has also been used in children and infants as a single ingredient or as part of cough and cold combinations.

7.1.16 Overdose Experience

To evaluate overdose experience, the sponsor gathered data from the American Association of Poison Control Centers (AAPCC). Since an IBU – DPH combination product is not currently marketed in the U.S., the case selection strategy employed by AAPCC consisted of extracting all

[3] Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Mortality Data From the Drug Abuse Warning Network, 2002.DAWN Series D25, DHHS Publication No. (SMA) 043875, Rockville, MD, 2004.

cases for the years of interest where a single ingredient IBU product was reported to have been co-ingested with a single ingredient, DPH product. As shown in Table 9 (Appendix 10.3) the number of reports received by AAPCC for this combination over the four-year period ranged from 556 reports in 2001 to 619 in 2004.

Between January 1, 2001 and December 31, 2001 AAPCC recorded a total of 1,190,016 pharmaceutical exposures (44% of all substances). Between January 1, 2002 and December 31, 2002, AAPCC recorded a total 1,281,336 pharmaceutical exposures (44.8% of all substances) and a total of 1,336,209 pharmaceutical product exposures (46.1% of all substances) were received between January 1, 2003 and December 31, 2003. Relative to pharmaceutical products, the proportion of exposures associated with single ingredient forms of APAP, ASA, DPH and IBU, respectively, were, 4.7%, 1.4%, 2.4%, 5.1% during 2001 and 4.6%, 1.3%, 2.2%, and 5.1% during 2002. Similarly, during 2003, the proportion of exposures associated with single ingredient forms of APAP, ASA, DPH and IBU, respectively, were, 4.6%, 1.3%, 2.1%, and 5.3%. Although IBU and DPH are not marketed as a combination product, there were reports of the two single ingredient substances being used concomitantly (IBU/DPH category).

For the years between 2001 and 2004 a total of 77 unique event-coding terms were associated with the cases involving the concomitant ingestion of single ingredient DPH with IBU. The number of contacts received by AAPCC ranged from 556 in 2001 to 619 in 2004. Approximately one half of all exposures were intentional (i.e., suicide attempts). The remaining reports were classified as unintentional or accidental.

Over the four-year period, the search strategy used by AAPCC uncovered a total of seven fatalities where single ingredient IBU and single ingredient DPH were ingested together with multiple, additional drug products. Typically these cases were suicides and involved exposures to multiple drug products. None of the fatalities involved ingestion of just single ingredient IBU with single ingredient DPH.

In addition to the APCC data, the sponsor identified a subset of overdose cases from the FDA's AERS database. Cases involving overdose were selected using the following MedDRA terms: Accidental Overdose, Non-Accidental Overdose, Overdose or where the reported total daily dose exceeded the limits for OTC ibuprofen or for OTC diphenhydramine. Based on these criteria, a total of eight unique unduplicated cases satisfied the overdose search criteria. The most frequently mentioned outcome was hospitalization (5 mentions) followed by death (4 mentions), Required Intervention (2 mentions) and one mention of Life Threatening. Except for one case (3302749), all of the cases are complex since at least three or more medical products were reported. As a result it is very difficult to assess the role of either IBU or DPH or the combination in these cases.

In the one case where just IBU and DPH were ingested, (3302749), and based on electronic records, a 49-year-old female ingested two Motrin Sinus (ibuprofen, pseudoephedrine) caplets and 300 mg diphenhydramine (6 Benadryl tablets) over a 90-minute period. The reported outcome was Life Threatening.

Comments:
Based on the limited information submitted, and the proposed dosing directions, the possibility of unintentional accidental overdose with this combination product is unlikely. The overdose issues are addressed by warnings in different sections of the proposed OTC label. Fatalities due to ingestion of IBU and DPH occurred only in cases of an intentional overdose.

7.1.17 Postmarketing Experience

Postmarketing experience data submitted to this NDA comes from two different sources: sponsor's database and FDA AERS database.

Sponsor Database
Between January 1, 2002 and December 31, 2004 the Sponsor received a total of 31 spontaneously reported cases (including both medically confirmed and non-confirmed cases) documenting the use of IBU with DPH. Of these cases and with respect to the roles of IBU and DPH, four types were received: those where the reporter believed both IBU and DPH were related to the reported event(s) and outcome(s) – "suspect drugs", (IBU-S - DPH-S) (8 cases); cases where the reporter believed IBU and DPH were not related to the reported event(s) and outcome(s) – "concomitant drugs" (IBU-C - DPH-C) (14 cases); cases where IBU was classified as suspect and DPH was classified as concomitant (IBU-S - DPH-C) (7 cases) and two cases where IBU was classified as concomitant product and DPH was considered suspect (IBU-C - DPH-S). A tabular listing of all 31 cases is shown in Table 10 which can be found in Appendix 10.4.

Three cases were associated with a serious outcome: one fatality and two cases involving hospitalization. Narrative of the death case is presented below.

HQWYE114810OCT03: "...information [was] received from a literature source (2002 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance), regarding a 25-year-old patient who received ibuprofen (manufacturer and dosage form unspecified) therapy (indication, duration of therapy and dose regime was not provided); she took a drug overdose in a suicidal attempt and died. Additional suspect medication included diphenhydramine and pseudoephedrine (manufacturer and dosage form unspecified). Relevant medical history was not provided."

Comment:
The most serious cases reported to the sponsor involved either severe hypersensitivity reactions or consequences of an intentional overdose. Based on the review of cases contained in the sponsors' spontaneous report database no new safety-related concerns were uncovered for the proposed product.

AERS Database
FDA individual safety reports (ISRs, Medwatch forms) describing concomitant ingestion of an IBU-containing and a DPH-containing product were selected from Freedom of Information (FOI) extracts of the AERS database according to a four-step data extraction process:

1. Initially, all ISRs mentioning an IBU-containing product (ibuprofen reports) or DPH-containing product (diphenhydramine reports) were extracted.
2. Individual ISR numbers common to both the IBU reports and the DPH reports were collated and an initial, working dataset was created.
3. After isolating those cases where both IBU and DPH were mentioned together, Step III consisted of examining the reporter's role code assessment in order to identify cases where both IBU and DPH were believed to be related (suspect drug, interacting drug) to the reported event(s) and outcome(s).
4. After sub-setting just the cases where both an IBU-containing product (single ingredient or combination product) and a DPH-containing product (single ingredient or combination product) were assigned the role code of suspect drug, Step IV consisted of removing cases which had been included in a previous safety update or cases which had been transmitted by WCH as part of its periodic reporting requirements.

For 371 (80%) out of the 464 extracted cases, the reporter determined that the role of both IBU and DPH was concomitant; that is, neither IBU nor DPH were believed to have contributed to the reported event(s) and reported outcome(s). In 8% (39/464) of the found cases did the reporter believed that both IBU and DPH were suspected of being related to the reported event(s) and reported outcome(s).

The sponsor believes that ten cases have been stimulated by lawsuits associated with phenylproponolamine (PPA) withdrawal. Identification of these cases was based on: all individual reports were transmitted to FDA after PPA was withdrawn, yet for many of the cases the reported events occurred between 1996 and 2000; all cases mention multiple products including at least one PPA formulation; in eight of the cases the following MedDRA coding terms were used: Cerebrovascular Accident (NOS); and in four cases the MedDRA coding term, Hemorrhagic Stroke was employed. As a result the sponsor decided to exclude event and outcome information from these cases for the final analysis.

Finally, two duplicated fatality reports were uncovered based on the narratives presented.

Hence for the time period November 1, 1997 through March 31, 2004 only 23, and most likely only 20, cases were found in the AERS database where IBU and DPH were classified as suspect products. Of the 23 cases, 19 were classified as serious in nature. The number of reported cases ranged from one in 1998 to nine in 2003.

The sponsor did not provide tabular summaries or the number of cases associated with each body category; they concluded that no new safety issues were identified based on their review of reports identified by this search.

There were a total of ten fatality cases where both IBU and DPH were classified as suspect products. These complex cases typically involving poly-drug use and suicide attempts. Based on either the narratives presented in FOI-obtained copies of Form 3500A or information contained in electronic records, it was difficult to assess the role of either IBU or DPH or the combination in these cases. The sponsor states that, based on analysis of the events associated

with the cases found in the AERS database, no new safety-related concerns for the combination IBU-DPH product were uncovered.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The updated safety database comprised 3066 subjects. The distribution among the treatment groups in the updated safety database is shown in Table 11.

Table 11. Overall Distribution of Subject Population Included in Updated and Original Clinical Trial Safety Database

Type of Study	Total	IBU 400/ DPH 50	IBU 200/ DPH 25	IBU 400	DPH	PBO	APAP 1000 DPH 50
Multiple-dose							
Updated	974	323	158	0	0	167	326
(Original)	(974)	(323)	(158)	(0)	(0)	(167)	(326)
Single-dose							
Updated	1947	844	120	488	31	306	158
(Original)	(1267)	(524)	(120)	(324)	(31)	(268)	(0)
Bioavailability							
Updated	145	Cross-Over Studies					
(Original)	(119)						
Total							
Updated	3066						
(Original)	(2360)						

7.2.1.1 Study type and design/patient enumeration

A list of all clinical studies conducted by the sponsor to support the IBU/DPH combination is provided in Table 12.

Table 12. List of Clinical Studies Included in Safety Analysis

Study No.	Study Type/Design	Duration of Treatment Evaluation	Dose	No. of subjects
AE-97-01	Oral surgery, RA, I, PC, DB	Single dose	IBU400/DPH 76[1] IBU 400 DPH 76 Placebo	29 31 31 14
AE-97-05	Headache, RA, O, PC, DB	Single dose	IBU 400/DPH 76 IBU 400 Placebo	49 51 52
AE-98-01	Oral surgery, RA, I, PC, DB	Single dose	IBU 400/DPH 50 IBU 400 Placebo	122 119 40
AE-98-02	Oral surgery, RA, I, PC, DB	Single dose	IBU 400/DPH 50 IBU 400 Placebo	120 123 40
AE-98-03	Oral surgery, RA, I, PC, DB	Single dose	IBU 400/DPH 50 IBU 200/DPH 25 Placebo	123 120 41
AE-98-04	Tension headache, RA, I, PC, DB	Single dose	IBU 400/DPH 50 Placebo	81 81
AE-01-11	Oral surgery, RA, I, PC, DB	Single dose	IBU 400/DPH 50 APAP 1000/DPH 50 Placebo	155 158 38
AE-04-14A	Oral surgery, RA, I, DB	Single dose	IBU 400/DPH 50 IBU 400	165 164
AE-97-08	Maximum use safety, RA, O, PC, DB	10 days	IBU 400/DPH 50 IBU 200/DPH 25 APAP 1000/DPH 50 Placebo	323 158 326 167
WM-716	Bioequivalence, drug interaction, RA, OL, CO	Single dose	IBU 400/DPH 76 IBU 400 DPH 76	23
AE-97-02	Bioequivalence, food effect, RA, OL, CO	Single dose	IBU 400/DPH 50 IBU 400/DPH 50 fed IBU 400/DPH 50	27
AE-97-09	Bioequivalence, formulation effect, RA, OL, CO	Single dose	IBU 400/DPH 50 IBU 400 DPH 50 IBU 400	27
AE-00-10	Bioequivalence, RA, OL, CO	Single dose	IBU 400/DPH 50 IBU 400/DPH 76	42
AE-01-12	Bioequivalence, RA, OL, CO	Single dose	IBU 400/DPH 50 IBU 400/DPH 76	26
Total				3066

[1]diphenhydramine citrate; RA: randomized; I: inpatient; PC: placebo-controlled; O: outpatient; DB: double-blind; OL: open label; CO: cross-over

7.2.1.2 Demographics

The updated safety database comprised 3066 subjects, 1237 (40.3%) male and 1829 (59.7%) female. The population enrolled in the clinical trials consisted of 2453 (80.0%) Caucasian, 321

(10.5%) Black, 218 (7.1%) Hispanic, 47 Asian (1.5%), and 27 "Other" (0.9%) subjects. There were 2294 (74.8%) subjects <45 years old, 504 (16.4%) between 45-64 years, and 268 (8.7%) who were ≥65 years. Three hundred and seventy two (12.1%) were between the ages of 12 and 18 years. As can be seen in Table 13 the addition of the 705 subjects from the three trials did not significantly change the demographic profile of the overall population.

Table 13. Overall Safety Database: Demographic Profile

		Updated Database	Original Database
No. of Subjects		**3066**	**2360**
Gender	Male	1237 (40.3%)	897 (38%)
	Female	1829 (59.7%)	1463 (62%)
Race	Caucasian	2453 (80.0%)	1809 (76.7%)
	Black	321 (10.5%)	301 (12.8%)
	Asian	47 (1.5%)	34 (1.4%)
	Hispanic	218 (7.1%)	193 (8.2%)
	Other	27 (0.9%)	23 (1.0%)
Age	< 45 years	2294 (74.8%)	1589 (67.3%)
	45-65 years	504 (16.4%)	503 (21.3%)
	≥ 65 years	268 (8.7%)	268 (11.4%)

7.2.1.3 Extent of exposure (dose/duration)

Most of the subjects in the clinical trials were exposed to only one dose of the drug. The only safety trial (AE-97-08) had a 10-day treatment duration.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Safety data submitted from the literature is discussed in section 8.2 of this review.

7.2.3 Adequacy of Overall Clinical Experience

This is a supplemental application. The original submission of this NDA contained a full safety data for the combination. No safety issues were identified at the time of the original application review.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Animal or In Vitro data were not provided in this application.

7.2.5 Adequacy of Routine Clinical Testing

Not applicable for this supplemental safety data submission.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The sponsor has provided sufficient data to characterize the pharmacological profile of this combination product during the original submission of the NDA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

From a clinical safety perspective, there are no recommendations for further studies.

7.2.8 Assessment of Quality and Completeness of Data

From a clinical safety perspective, this application is adequate and complete.

7.2.9 Additional Submissions, Including Safety Update

On September 16, 2005, the sponsor submitted the last safety update which included information in accordance with 21CFR 314.50 (d) (5) (vi) (b). The following sections of the Integrated Summary of Safety (ISS) were updated with new information: clinical literature, drug abuse data, spontaneous adverse drug experience (ADE) reports received by the sponsor, and spontaneous ADE reports submitted to the FDA Adverse Experience Reporting System (AERS) but not to the sponsor. These additional data discussed in this section of the review.

Drug Abuse Network Data
This report contains DAWN Emergency Department (ED) data and Medical Examiner (ME) data for the last six months of 2003.

1. Emergency Department Data
Beginning in 2003 the format and content of the DAWN Emergency Department Report was revised, the ED data for 2003 were no longer directly comparable to previous reports issued by DAWN because of the following changes:

- The reason for a drug-related ED visit was assigned to one of the eight case types: suicide attempt, seeking detox, alcohol only (age < 21), adverse reaction, overmedication, malicious poisoning, accidental ingestion, and other.
- To characterize drug abuse/misuse, all ED visits were classified into three categories: Use of Illicit Drugs; Use of Alcohol, in combination with other drugs plus where appropriate, alcohol use alone in minors; and, Non-medical Use ("misuse") of Pharmaceutical Products, which included both prescription and OTC products.
- Unlike prior reports, the 2003 Annual Report did not contain mention frequency listings for individual drug products. Instead therapeutic categories according to the Multnum Lexicon system were used for data presentation. Within the Multnum system, ibuprofen is grouped in the major category, CNS agents and the subcategory, single ingredient NSAIDs. Aspirin (ASA) and aspirin combination products are classified within the

subcategory, Salicylates/combinations, of CNS agents, and acetaminophen is classified within the category, Miscellaneous analgesics/combinations, also under CNS agents. The primary classification for diphenhydramine (DPH) is Psychotherapeutic Agents, and the subcategory Anxiolytics, sedatives, and hypnotics.

Of the estimated total 52 million ED visits recorded in DAWN's sample during the third and fourth quarters of 2003, only 627,923 (1.2%) were classified by DAWN as drug-related. Approximately 105,401 visits (32%) were associated with Overmedication defined as taking more than the prescribed or recommended dose of either a prescription or OTC pharmaceutical. Over a half (52%) of the Overmedication ED visits (54,420) were associated with the category, Psychotherapeutic agents, and of those approximately 18.1% were associated with NSAIDs, (7,894). Of all the drug-related ED visits, (627,923) only 1.3% were associated with the non-benzodiazepine products, or 0.015% of all ED visits recorded by DAWN involved non-benzodiazepine Psychotherapeutic agents.

For the case types Adverse reaction, Accidental ingestion, Suicide attempt and Seeking detox, there were no mentions associated with the subsets to which IBU and DPH were assigned.

2. Medical Examiner Data
As with the ED data, the format and content of the annual 2003 DAWN ME report was changed from previous versions. The mortality data for 2003 were no longer comparable to the data from previous reports issued by DAWN. The most important change is that the 2003 report did not contain mention frequency listings for individual drug products. Diphenhydramine is included in the Miscellaneous anxiolytics category, and ibuprofen is a part of NSAIDs category. For both Miscellaneous anxiolytics and NSAIDs where fatalities were recorded, these cases involved multiple drug products. There were no Drug Misuse fatalities recorded for single-ingredient NSAIDs or Miscellaneous anxiolytics.

The data from 2003 DAWN ED and ME reports suggest that there is little abuse potential for the proposed combination product that would contain IBU and DPH.

Sponsor database
Since the last update submitted by the sponsor, a total of three adverse events reports were received documenting the use of IBU together with DPH between January 1, 2005 and June 30, 2005. In none of these cases did the reporter assign a role code to both IBU and DPH as suspect. In two non-serious reports, (dysuria and swelling face & pruritus), the reporter assigned the role code of IBU as suspect and assigned the role code for DPH as concomitant. In the third case, a serious report (intentional suicide), the reporter assigned the role codes for IBU and DPH as concomitant.

No new safety concerns for the proposed combination product, IBU and DPH, were identified from spontaneous report cases received by the sponsor over the first six months of 2005.

AERS Database
Individual safety reports (ISRs) received by FDA during the period April 1, 2004 through March 31, 2005 where both IBU and DPH were believed by the reporter as related to the reported event(s) and outcome(s) were analyzed for this safety update. The same methodology (discussed in section 7.1.17 of the review) was used for the screening and selection of pertinent cases.

A total of 48 unique MedDRA Preferred Terms were used to encode the 20 individual ISRs (for 13 cases), where IBU and DPH were classified as suspects. Eleven out of the 13 cases were deaths. All of them are complex cases typically involving multiple drug use and suicide attempts. Data are insufficient for assessing causality of IBU and DPH and the fatal outcome. There were no cases extracted documenting just the ingestion of IBU and DPH alone.

No reports were uncovered where IBU and DPH were used in children aged 12 years or younger.

Based on analysis of the events associated with the cases found in the AERS database, no new safety-related concerns for the combination IBU–DPH product were uncovered.

Literature Review
A literature search was performed on Pub Med using the terms "ibuprofen" and "diphenhydramine" for the period March 1, 2005 to August 31, 2005 to capture all pertinent safety references for this safety update. The search yielded 35 papers (32 on ibuprofen and 3 on diphenhydramine).

The updated literature did not reveal any unique adverse events that have not been reported previously or are not addressed in the proposed labeling for the combination product.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Eight single-dose studies evaluated a total of 1947 subjects, of whom 844 received IBU 400/DPH 50. Additionally, 120 subjects received IBU 200/DPH 25. The safety data from these studies were pooled and evaluated for safety signals. Table 14 displays the AEs grouped by COSTART term within each body system. For the purposes of this review, only the two IBU/DPH treatment groups and the placebo group data are presented.

Table 14. Number of Subjects with Adverse Experiences by Body System

Body System	COSTART Term	IBU/DPH			Placebo (n=306)
		Total (n=964)	400/50 mg (n=844)	200/25 mg (n=120)	
Body as a Whole	Headache	38 (3.9)	22 (2.6)	16 (13.3)	9 (2.9)
	Cellulitis	1 (0.1)	0 (0.0)	1 (0.8)	0 (0.0)
	Chest Pain	1 (0.1)	0 (0.0)	1 (0.8)	0 (0.0)
	Infection	2 (0.2)	1 (0.1)	1 (0.8)	1 (0.3)
	Pain	1 (0.1)	0 (0.0)	1 (0.8)	0 (0.0)
	Asthenia	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
	Chills	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Nervous	Paresthesia	4 (0.4)	0 (0.0)	4 (3.3)	2 (0.7)
	Dizziness	12 (1.2)	10 (1.2)	2 (1.7)	1 (0.3)
	Vertigo	1 (0.1)	0 (0.0)	1 (0.8)	0 (0.0)
	Abnormal Dreams	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
	Agitation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
	Anxiety	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.3)
	Hyperkinesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
	Insomnia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)
	Nervousness	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)
	Somnolence	5 (0.6)	5 (0.6)	0 (0.0)	0 (0.0)
Respiratory	Pharyngitis	10 (1.0)	3 (0.4)	7 (5.8)	2 (0.7)
	Epistaxis	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)
	Rhinitis	2 (0.2)	2 (0.2)	0 (0.0)	1 (0.3)
Digestive	Nausea	27 (2.8)	21 (2.5)	6 (5.0)	8 (2.6)
	Vomiting	14 (1.5)	11 (1.3)	3 (2.5)	4 (1.3)
	Abdominal Pain	2 (0.2)	2 (0.2)	0 (0.0)	1 (0.3)
	Constipation	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
	Diarrhea	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
	Dry Mouth	18 (1.9)	18 (2.1)	0 (0.0)	9 (2.9)
	Dyspepsia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Dysphagia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
	Glossitis	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
	Gum Hemorrhage	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Special Senses	Ear pain	2 (0.2)	1 (0.1)	1 (0.8)	0 (0.0)
	Conjunctivitis	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
	Taste Perversion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular	Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal	Bone Pain	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and Appendages	Sweating	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Of the 1947 subjects in the updated single-dose treatment groups, a total of 191 (9.8%) subjects reported at least one AE:

- 88 (10.4%) in the IBU.400/DPH 50 group,
- 35 (29.2%) in the IBU 200/DPH 25 group,
- 22 (4.5%) in the IBU 400 mg group,
- 3 (9.7%) in the DPH 50 mg group,
- 6 (3.8%) in the APAP 1000/DPH 50 group and
- 37 (12.1%) in the PBO group.

Four events accounted for most AEs: headache (2.7%), nausea (2.7%), dry mouth (1.4%), and vomiting (1.3%). No dose response was suggested as the higher IBU/DPH dose group tended to have a lower incidence when compared with the lower-dose group.

Table 15 presents the incidence of adverse events reported by ≥2% of subjects in any treatment group.

Table 15. Pooled Single-Dose Trials: Frequent AEs: Updated Safety Database

Body System	PBO N=306 (%)	IBU 200/DPH 25 N=120 (%)	IBU 400/DPH 50 N=844 (%)
Nervous	7 (2.3)	7 (5.8)	17 (2.0)
Dizziness	1 (0.3)	2 (1.7)	10 (1.2)
Paresthesia	2 (0.7)	4 (3.3)	0 (0.0)
Digestive	22 (7.2)	6 (5.0)	48 (5.7)
Nausea	8 (2.6)	6 (5.0)	21 (2.5)
Dry Mouth	9 (2.9)	0 (0.0)	18 (2.1)
Vomiting	4 (1.3)	3 (2.5)	11 (1.3)
Body as a whole	10 (3.3)	20 (16.7)	25 (3.0)
Headache	9 (2.9)	16 (13.3)	22 (2.6)
Cellulitis	0 (0.0)	1 (0.8)	0 (0.0)
Respiratory	3 (1.0)	7 (5.8)	7 (0.8)
Pharyngitis	2 (0.7)	7 (5.8)	3 (0.4)

These data are similar to the findings for the 1267 subjects in the single-dose treatment groups as reported in the original NDA.

The incidence of any AE as well as overall digestive and nervous system events were comparable in the two groups. The incidence was higher in the lower dose group for any AE, AEs within body as a whole, nervous and respiratory system, and the individual AEs headache, paresthesia and pharyngitis.

As mentioned earlier, there were a total of five crossover bioavailability studies conducted with the new product. A total 145 subjects were exposed to the new combination product, 119 during the trials of the original NDA and 24 subjects during study AE-01-12.

Overall, the incidence of AEs in the updated safety population is similar to those reported for the four bioavailability studies in the original NDA. Of the 145 subjects in the bioavailability studies, 41 (28.3%) had an AE: thirty-two (22.4%) subjects while on IBU 400/DPH 50 (liquigel or caplet), six (12%) subjects while on IBU 400 mg, and ten (21%) while on DPH 50 mg.

For the IBU 400/DPH 50 exposure, the nervous system (8.4%) accounted for the highest percentage of events followed by body as a whole (7.7%) and digestive (7.0%).

Table 16 shows the AEs with an incidence ≥ 2% for any treatment in both the original and updated safety databases.

Table 16. Pooled Bioavailability Trials: Frequent AEs: Updates Safety Database

Body System	IBU 400/DPH 50 N=143 (%)	IBU 400 N=50 (%)	DPH 50 N=48 (%)
Nervous	12 (8.4)	2 (4.0)	5 (10.4)
Somnolence	4 (2.8)	2 (4.0)	3 (6.3)
Dizziness	6 (4.2)	0 (0.0)	1 (2.1)
Incoordination	0 (0.0)	0 (0.0)	1 (2.1)
Digestive	10 (7.0)	1 (2.0)	3 (6.3)
Abdominal pain	3 (2.1)	0 (0.0)	2 (4.2)
Diarrhea	2 (1.4)	0 (0.0)	1 (2.1)
Nausea	5 (3.5)	1 (2.0)	2 (4.2)
Body as a whole	11 (7.7)	0 (0.0)	2 (4.2)
Headache	3 (3.1)	0 (0.0)	1 (2.1)
Pain	4 (2.8)	0 (0.0)	0 (0.0)
Infection	0 (0.0)	0 (0.0)	1 (2.1)
Cardiovascular	2 (1.4)	0 (0.0)	1 (2.1)
Syncope	2 (1.4)	0 (0.0)	1 (2.1)
Skin	1 (0.7)	1 (2.0)	1 (2.1)
Rash	1 (0.7)	1 (2.0)	1 (2.1)
Urogenital	0 (0.0)	2 (4.0)	0 (0.0)
Dysmenorrhea	0 (0.0)	1 (2.0)	0 (0.0)
Vaginitis	0 (0.0)	1 (2.0)	0 (0.0)
Vulvovaginitis	0 (0.0)	1 (2.0)	0 (0.0)

7.4.1.2 Combining data

The sponsor pooled all the original safety data and combined it with the safety update data, and analyzed it on how this additional safety data influenced the safety profile of the combination. There was no difference seen in the safety profile of the IBU/DPH combination product between the original and the updated database.

7.4.2 Explorations for Predictive Factors

Analyses of safety data were performed for patient-predictive factors such as age, gender, race and the presence of underlying allergy/asthma. Since most of the clinical studies were a single dose trials, no analyses based on dose, duration, or concomitant medication use were done.

7.4.2.1 Explorations for dose dependency for adverse findings

None of the additional studies were multiple dose studies. Therefore, the safety data for the multiple-dose subject population remains as originally reported in the NDA. Nervous system AEs are of particular clinical interest in this application. The three active treatments (2 IBU/DPH Liqui-Gels, 1 IBU/DPH Liqui-Gel, and 2 APAP/DPH caplets) were comparable in the incidence of nervous system AEs overall and for somnolence. All three active treatment groups had nervous system and somnolence incidence rates significantly higher than placebo. There appeared to be no increased risk due to the combination for somnolence among the active treatment groups. There were no differences among the active treatment groups in the number of subjects who discontinued due to somnolence.

7.4.2.2 Explorations for time dependency for adverse findings

The sponsor has not conducted additional multiple dose studies. The product is indicated for the relief of occasional sleeplessness when associated with — minor pain.

7.4.2.3 Explorations for drug-demographic interactions

Incidence of AEs by Age Group

- <18 Years (n=349)

The updated database added 173 subjects <18 years of age to the original database. The incidence of any AE was 5.4%, 50%, and 27.8% for IBU 400/DPH 50, IBU 200/DPH 25, and PBO, respectively. Only 4 subjects received IBU 200/DPH 25, 2 of whom reported an AE. The AE incidence rates in the updated database were similar to the original database. The incidence of any AE in those <18 years of age in the original database was 9.9%, 50%, and 31% for those who received IBU 400/DPH 50, IBU 200/DPH 25, and PBO, respectively.

- ≥65 Years

No additional subjects ≥65 years of age were enrolled. As reported in the original database, the only subject in this age group did not report an AE.

Incidence of AEs by Gender

There were 442 and 124 male subjects in the combined IBU/DPH and placebo groups, respectively. The corresponding number of female subjects was 522 and 182, respectively. As with the original database, a somewhat higher incidence of AEs were seen with females compared to males in the combined IBU/DPH groups for any AE, overall digestive and nervous system AEs as well as individual events vomiting, and dizziness; except for vomiting, similar trends were not seen in the PBO group.

Incidence of AEs by Race

The overall incidence of AEs within the Caucasian and non- Caucasian subgroups was compared for combined IBU/DPH groups and PBO group. Some statistically or marginally significant differences in the incidence were seen between the two subgroups for the combined IBU/DPH groups for dry mouth (2.3% in Caucasians vs. 0.0% in non-Caucasians), abdominal pain (0.0% in Caucasians vs. 1.1% in non-Caucasians), and somnolence (0.3% in Caucasians vs. 1.6% in non-Caucasians). These differences were not seen within the PBO group except for dry mouth where 3.4% of the Caucasians and 0.0% of the non-Caucasians also reported the event.

7.4.2.4 Explorations for drug-disease interactions

The only disease group evaluated in the original NDA was the asthma/allergy sub-population. The subjects enrolled in the single-dose studies were in general good health. In the updated database, there were 645 subjects in this disease group, 274, 35, 170, 13, 62 and 91 subjects in IBU 400/DPH 50, IBU 200/DPH 25, IBU 400, DPH, APAP 1000/DPH 50 and PBO respectively. In the original NDA database, there were 172, 35,124, 13, 0 and 79 subjects in the corresponding groups, respectively.

A side-by-side comparison of the updated database and the original database for the more frequent AEs is shown in Table 17.

Table 17. Pooled Single-Dose Trials: Frequent AEs in the Asthma/Allergy Subgroup

	IBU/DPH Groups		Placebo	
	Updated (N=309) N (%)	Original (N=207) N (%)	Updated (N=91) N (%)	Original (N=79) N (%)
Any AE	42 (13.6)	38 (18.4)	13 (14.3)	13 (16.5)
Nervous System	11 (3.6)	9 (4.3)	3 (3.3)	3 (3.8)
Dizziness	6 (1.9)	4 (1.9)	0 (0.0)	0 (0.0)
Paresthesia	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Digestive System	15 (4.9)	14 (6.8)	6 (6.6)	6 (7.6)
Nausea	12 (3.9)	11 (5.3)	2 (2.2)	2 (2.5)
Dry Mouth	1 (0.3)	1 (0.5)	2 (2.2)	2 (2.5)
Vomiting	4 (1.3)	4 (1.9)	1 (1.1)	1 (1.3)
Body as a Whole	17 (5.5)	16 (7.7)	4 (4.4)	4 (5.1)
Headache	16 (5.2)	15 (7.2)	4 (4.4)	4 (5.1)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory System	5 (1.6)	4 (1.9)	2 (2.2)	2 (2.5)
Pharyngitis	4 (1.3)	4 (1.9)	2 (2.2)	2 (2.5)

7.4.2.5 Explorations for drug-drug interactions

Not applicable for this application.

7.4.3 Causality Determination

The sponsor has not performed special causality assessment. Safety profiles for ibuprofen and diphenhydramine are well characterized. This safety data update did not reveal new safety signals.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

There were no new data submitted to this application on dose ranging. Whether the proposed dose of the combination product is acceptable for the proposed indication will be addressed by reviewers in the Division of Neuropharmacological Drug Products.

8.2 Drug-Drug Interactions

Similar to the single dose oral surgery studies submitted with the original NDA, these additional studies also did not allow concomitant medications (except for oral contraceptives and prophylactic antibiotics). Thus, no drug-drug interactions were evaluated in the original NDA, or in this safety update.

8.3 Special Populations

The proposed labeling has all the appropriate warnings for consumers of certain age categories, with underlying medical conditions, and for those taking interacting medications.

8.4 Pediatrics

The sponsor has been granted a waiver for studies in individuals under the age of 18 years.

There were no clinical studies conducted by the sponsor in the pediatric population. Two adverse event reports involving children were reported to the FDA AERS database between 1998 and 2003, where both IBU and DPH were considered suspect drugs. In the first report, submitted by a healthcare professional (Case ID 3129575), a 4-year-old male child was hospitalized after ingesting both DPH and IBU. The reported events were not considered related to the use of these products but were felt by the child's pediatrician to be more related to a viral etiology. In the second case (Case ID 3948144), the reported events (urticaria, rash, and erythema) were felt by the mother to be more related to the use of IBU than the combination of IBU and DPH.

Based on these two cases no new safety-related concerns were uncovered in children for the proposed combination of IBU and DPH.

8.5 Advisory Committee Meeting

No advisory committee meetings addressed this application.

8.6 Literature Review

For the purposes of this safety update, the sponsor performed a PubMed literature search utilizing the terms "ibuprofen," and "diphenhydramine" for the period January 1, 2000 to February 28, 2005 to capture any previously unsubmitted safety references. The search yielded 155 papers (124 papers pertaining to ibuprofen; 31 to diphenhydramine) distributed among various organ systems or subjects. Some of the data, such as AAPCC and ED reports have been discussed in the previous sections of the review. Reported clinical trials, epidemiological studies, or case reports, where safety of ibuprofen or diphenhydramine is discussed, are summarized below.

Summary of literature reports on ibuprofen:

- 21 articles addressed the risk of developing a gastrointestinal bleeding:
    - 13 citations (References 1-13) reported events associated with Rx doses of IBU and/or longer than 10-day treatment duration.
    - 8 articles (References 14-21) reported either clinical trials, where different NSAIDs were compared for their efficacy or safety; case control studies assessing the risk of GI bleeding for IBU, or endoscopic studies assessing effects of IBU on

GI mucosa. None of these studies revealed any new safety information. Ibuprofen is known for its' effects on GI tract. Dosing directions and warnings on the proposed label adequately address this safety issue.

- Two citations (References 22 and 23) assessed the association between IBU and inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease. There was no evidence found to show that ibuprofen induces relapse of IBD or increases severity of UC or Crohn's disease.
- 6 citations (References 24-29) were case reports of acute ingestion of large doses of ibuprofen. The overdose issue is discussed in section 7.1.16 of this review. No new safety information was gathered from these 6 references.
- Two citations reported 2 cases of liver toxicity (References 30 and 31), both associated with the use of prescription doses of ibuprofen.
- 14 articles addressed IBU interactions with other medications:
    - One case report (Reference 32) of hypoglycemia following concomitant use of IBU and sulfonurea (glibenclamide).
    - Three studies (References 33-35) addressed IBU effects on blood pressure in patients taking antihypertensives. Two out of the three studies did not reveal the interaction. The third (Reference 35) found an increase in systolic blood pressure but the doses of IBU used in the study population well exceeded the OTC dosing regimen.
    - Two reports on the concomitant use of IBU and aspirin showed conflicting results. Reference 36 suggested that IBU suppresses aspirin-induced platelet inhibition, but reference 37 showed no interaction. In addition reference 38 reporting population based cohort study suggesting an additive cardioprotection effect of NSAIDs when used concomitantly with aspirin. OTC ibuprofen labeling directs consumers to consult a health care professional before the use of ibuprofen if they are taking aspirin for cardioprotection.
    - One citation (Reference 39) reported results of population-based cohort study showing an additive risk of upper GI bleeding on concomitant use of NSAIDs and serotonin reuptake inhibitors. GI bleeding is addressed in the proposed labeling.
    - One citation reported a case (Reference 40) of increase in psychotic symptoms in schizophrenic patient on risperidone concomitantly taking ibuprofen. This interaction has not been reported in the past.
    - Two pharmacokinetic study reports evaluated IBU interactions with two drugs, naltrexone (Reference 41) and bazedoxifene (Reference 42), metabolized via glucuronidation. No clinically significant interactions were found.
    - One case of hyponatremia (Reference 43) in patient taking concomitantly desmopressin and ibuprofen, confirms ibuprofens' side effects on kidney, and is already addressed by warning in OTC labeling.
    - One citation reported a case of intraabdominal bleeding in patient with a history of alcohol abuse taking high doses of IBU (Reference 44). An alcohol warning is already present on the IBU OTC label.
    - A case of intracranial bleeding was reported (Reference 45) in patient taking IBU on a chronic basis concomitantly with ginkgo-biloba. Reported dosing regimen for IBU exceeds the one proposed for the IBU-DPH product.

- Five references (References 46-51) reported acute allergic reactions associated with the use of IBU. Hypersensitivity reactions caused by IBU are well known and are already addressed by several warnings in the OTC label.
- Four references (References 52-55) reported IBU effects on fertility. Ibuprofen effects when used during pregnancy are well known and already adequately addressed by pregnancy warning on all OTC ibuprofen-containing drug products.
- Aseptic meningitis has been reported in four cases (References 56-59) after the use of IBU. It is not clear what the association with IBU in those cases is and whether it could be prevented. Three of the reported patients recovered and the outcome of the fourth patient was not known.
- One case report of dementia (Reference 60) occurred with prescription doses of IBU.
- One study showed no effect of OTC doses of IBU on a complex memory and cognition task in young adults (Reference 61).
- Two citations addressed the IBU effect on bleeding time (Reference 62-63). IBU effects on clotting and bleeding are well known and documented. They are also addressed by warnings on OTC labeling.
- One case of transient leucopenia (Reference 64) was reported with prescription doses of IBU.
- 15 citations (References 65-79) reported results of various comparative trials or surveys where IBU was compared to the other non-steroidal anti-inflammatory drugs (aspirin, APAP, celecoxib, ASA, naproxen, diclofenac, or lumiracoxib). There were no new safety issues reported in patients treated with ibuprofen.
- Two citations (References 80-81) reported possible association of IBU use and serious streptococcal infections. All cases were observational and it is not clear if infection was associated with the use of ibuprofen or preexisted prior to its use.
- Fourteen references addressed prescription and OTC doses of IBU effects on kidney (References 82-95). Ibuprofen is known for its' renal effects. Dosing directions and warnings on the proposed label adequately address this safety issue.
- Four references (96 through 99) reported results of studies evaluating the IBU effects on bone structure or metabolism. No safety or other concerns were discovered for ibuprofen.
- Twelve citations (References 100-111) reported data related to IBU effects on cardiovascular system. None of the studies used ibuprofen dosing regimen as proposed for the combination drug product label.
- One case report of transient eosinophilic pneumonia (Reference 112) associated with the use of unknown dose of IBU for 7 days on two different occasions, could possibly be related to the hypersensitivity.
- The final reference (Reference 113) reported a case control study assessing the association between ASA and other NSAIDs and the risk of adult glioblastoma multiforme (GBM). The study failed to show the association between IBU and GBM.

There were 31 references in the DPH search distributed as follows:

- The largest number of citations (References 114-124) discussed issues related to drug abuse and intentional or accidental overdose. The symptoms related to the overdose of

DPH are well documented: sedation, anticholinergic signs, delirium, hallucinations, cardiac dysrythmias, seizures, and rhabdomyolysis. The overdose issue is already addressed by several warnings on the proposed OTC label.

- The second largest group of articles (References 125-130) reported comparative clinical studies where DPH was used in one of the treatment arms. No new safety issues related to the DPH use were reported.
- Six references reported clinical studies in healthy adults (References 131-136) evaluating DPH effects on psychomotor and cognitive functions in healthy adults.
- Four citations (References 137-140) reported effects of DPH on elderly population. These effects are well known, and are already addressed by warnings in the proposed label.
- A case of neonatal depression was reported (Reference 141) after a prolonged use of DPH during pregnancy. The proposed label carries an appropriate pregnancy warning.
- DPH interactions with other medications (acetaminophen, debrisoquine, and prolintane) were reported in three articles (References 142-144).

The majority of the references pertain to the known effects of DPH on sedation and psychomotor skills. In most of these studies, diphenhydramine was used as the positive control. The other references did not provide any previously unknown information pertaining to the safety profile of DPH.

The literature review for each ingredient in the combination did not reveal any unique adverse events that have not been reported previously.

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan.

8.8 Other Relevant Materials

There are no other relevant materials submitted for the review.

9 OVERALL ASSESSMENT

9.1 Conclusions

Experience with the already approved ibuprofen and diphenhydramine HCl does not suggest an unusual pattern of toxicity, either in terms of frequency or severity of adverse reactions reported. The safety profile of IBU/DPH combination is acceptable for OTC use. Therefore, this application is approvable from a clinical safety standpoint.

9.2 Recommendation on Regulatory Action

The proposed ibuprofen 200 mg/ diphenhydramine HCl 25 mg has an acceptable safety profile for the OTC marketing, therefore, it is approvable from the safety stand point. Final approvability depends on the outcome of the clinical efficacy study AE-04-14A, which is being reviewed by the reviewers in the Division of Neuropharmacological Drug Products.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No special post-marketing risk management activities are recommended.

9.3.2 Required Phase 4 Commitments

No special Phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

The proposed label is presented below. The labeling review is being done by an interdisciplinary scientist in the Office of Nonprescription Products. The sponsor incorporated all the important warnings for ibuprofen as well as diphenhydramine. It is acceptable from the clinical point of view.

3 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

__✓ § 552(b)(4) Draft Labeling

10 APPENDICES

10.1 Review of Individual Study Reports

Not applicable. The only pivotal study reports AE-14-04a is being reviewed by reviewers in the Division of Neuropharmacological Drug Products.

10.2 Line-by-Line Labeling Review

An interdisciplinary scientist in the Office of Nonprescription Products is reviewing the proposed labeling for the product.

Labeling should not state th

Labeling should also state that this product should not be used by those who suffer sleeplessness without a pain.

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10.3 Appendix I.

Table 9. Selected Exposure and Outcome Data from the AAPCC 2002, 2003, 2004 Annual Report for: APAP, ASA, DPH, IBU, and Concomitant Use of DPH with IBU

Substances	No. of Exposures				Ingestion Category								Outcome Category							
					Intentional				Unintentional				Major[1]				Death			
	2001	2002	2003	2004	2001	2002	2003	2004	2001	2002	2003	2004	2001	2002	2003	2004	2001	2002	2003	2004
APAP[2]	56,516	58,377	61,902	NI[5]	20,002	19,905	20,113	NI	35,705	37,643	40,835	NI	829	902	916	NI	120	119	147	NI
ASA[3]	17,075	17,201	17,337	NI	9,593	9,277	9,143	NI	7,023	7,413	7,651	NI	341	332	367	NI	66	60	59	NI
DPH[4]	28,263	28,133	28,092	NI	9,468	9,563	9,776	NI	17,945	17,464	17,418	NI	459	458	455	NI	26	34	38	NI
IBU / DPH[4]	556	607	600	619	362	394	403	433	177	179	181	167	22	18	19	17	1	3	2	1
IBU	60,304	65,726	71,043	NI	16,610	17,051	17,280	NI	42,510	47,357	52,346	NI	228	253	275	NI	20	12	13	NI
Total Pharma-ceuticals	1,190,016	1,281,336	1,336,269	NI	354,473	376,847	387,190	NI	778,311	839,757	881,481	NI	22,931	25,373	25,584	NI	1,730	2,130	2,054	NI
Total non-pharma-ceuticals	1,365,471	1,407,184	1,378,990	NI	65,216	69,604	69,961	NI	1,268,293	1,304,548	1,274,757	NI	4,536	4,678	4,423	NI	316	369	371	NI
Totals	2,718,201	2,858,564	2,894,173	619	473,724	502,641	513,866	433	2,149,964	2,254,361	2,274,687	167	29,346	32,014	32,039	17	2,279	2,727	2,684	1

[1] A major outcome as defined by AAPCC is where the patient exhibited signs or symptoms as a result of the exposure that were life threatening or resulted in significant residual disability or disfigurement.

[2] The exposure of all subcategories (adult formulation, pediatric formulation and unknown formulation) as shown in the published report were summed for this summary; NI: no information

[3] The exposure data for Rx and OTC products as shown in the published report were summed.

[4] Data purchased from AAPCC. Case selection was performed by AAPCC and involved reports in which a single ingredient IBU product was concomitantly ingested with a single ingredient DPH product.

[5] At the time this report was authored a pre-print for the AAPCC 2004 Annual Report was unavailable; these data will be updated when the final safety update is prepared in response to the approvable letter.

10.4 Appendix II.

Table 10. Summary Clinical Information for Adverse Event Cases Where IBU and DPH were Co-Administered

Manufacturer Control Number	Gender Age	Reporting Products	MedDRA Coding Terms	If Serious, reported Outcome	Concomitant Products
HQWYE114810OCT03	Unknown 25	Advil (Ibuprofen) Dimetapp 12-Hour Non-Drowsy (Pseudoephedrine,Diphenhydramine)	Intentional Overdose Completed Suicide	Death	Unknown
DEWYE649418MAR04	Female 21	Tavor (Lorazepam) Diphenhydramine, Ibuprofen, Dominal (Prothipendyl HCl), Paracetamol	Intentional Overdose Somnolence	Hospitalization	Unknown
HQWYE948005AUG04	Female 15	Advil (Ibuprofen) Benadryl (Diphenhydramine HCl)	Overdose	Non-serious	Unknown
HQ3937823AUG2002	Female Unknown	Advil (Ibuprofen), Unisom Sleepgels (Diphenhydramine HCl)	Intentional Overdose Coma	Other	Unknown
HQWYE701215SEP03	Female Unknown	Advil (Ibuprofen), Diphenhydramine	Abdominal Pain Drug Interaction	Non-serious	Unknown
HQWYE177623SEP04	Female 22	Advil (Ibuprofen), Benadryl (Diphenhydramine HCl)	Heart Rate Increased	Non-serious	Unknown

Table 10. (Cont.) Summary Clinical Information for Adverse Event Cases Where IBU and DPH were Co-Administered

WYE040816DEC04	Female 66	Advil (Ibuprofen) Tylenol PM (Diphenhydramine / Paracetamol)	Hypersensitivity Pruritus Urticaria Swelling Face	Other	Lopresor (Metoprolol Tartrate), Adalat CC (Nifedipine), Prilosec (Omeprazole), Premarin (Conjugated Estrogens), Centrum (Multivitamin / Multimineral), Vitamin E (Tocopherol), Hydrochlorothiazide, Flonase (Fluticasone Propionate), Diovan (Valsartan), Hydroxyzine, Doxepin
HQWYE877509FEB04†	Female 2	Robitussin Pediatric Cough† (Dextromethorphan / HBr) Benadryl (Diphenhydramine HCl)	Glossodynia Drug Interaction	Non-serious	None
HQ4072505SEP2002	Female 45	Norplant System (Levonorgestrel)	Breast Cancer	Hospitalization	Allegra (Fexofenadine HCl), Flonase (Fluticasone Propionate), Tylenol PM (Diphenhydramine, Paracetamol), Motrin (Ibuprofen) Decongestants and Antiallergics
HQ1762112APR2002	Female Unknown	Enbrel (Etanercept) Methylphenidate HCl	Grand Mal Convulsion	Other	Loratadine (Loratadine) Ibuprofen (Ibuprofen) Diphenhydramine
HQWYE755814OCT04	Female 33	Novantrone (Mitoxantrone HCl)	Cardiomyopathy Arthralgia	Other	Ibuprofen (Ibuprofen), Tylenol PM (Diphenhydramine/Paracetamol), Baclofen
HQWYE783410MAY04	Female 45	Effexor XR (Venlafaxine HCl)	Drug Withdrawal Syndrome, Pain in Jaw, Oedema Peripheral, Mood Swings Paraesthesia, Anger, Feeling of Despair, Bruxism, Crying	Non-serious	Fiorinal with Codeine (Acetylsalicylic Acid / Butalbital / Caffeine / Codeine Phosphate/ Phenacetin), Advil Cold and Sinus (Ibuprofen/Pseudoephedrine), Benadryl (Diphenhydramine HCl)
HQWYE850212MAY04	Female 55	Caltrate + Soy (Calcium Carbonate/ Soy Isoflavins/ Vitamin D)	Hypothyroidism	Non-serious NHP	Synthroid (Levothyroxine Sodium), Benadryl (Diphenhydramine HCl), Ibuprofen, Acetylsalicylic Acid, Zocor (Simvastatin) Toprol XL (Metoprolol Succinate)

Table 10. (Cont.) Summary Clinical Information for Adverse Event Cases Where IBU and DPH were Co-Administered

HQWYE633907OCT04	Female 74	Synvisc (Hylan GF 20)	Ill-defined Disorder Arthralgia Joint Swelling Condition Aggravated	Non-serious	Ultram (Tramadol HCl), Premarin (Conjugated Estrogens), Ocuvite (Multivitamin/Multimineral), Fosamax (Alendronate Sodium), Duragesic (Fentanyl), Detrol (Tolterodine L-Tartrate), Calcium, Benadryl (Diphenhydramine HCl), Vitamin B12 (Cyanocobalamin), Glucosamine, Chondroitin Sulfate, Ibuprofen, Multivitamins, Plain
HQ4018430AUG2002	Female 83	Caltrate 600 + Vitamin D (Calcium Carbonate/ Vitamin D)	Bunion Condition Aggravated	Non-serious	Advil (Ibuprofen), Tylenol PM (Diphenhydramine / Paracetamol), One-A-Day (Ascorbic Acid / Cyanocobalamin / Ergocalciferol / Nicotinamide / Pyridoxine HCl / Retinol / Riboflavin / Thiamine Mononitrate), Unspecified Antihypertensive Agent
HQ2876619JUN2002	Female 67	Fibercon (Calcium Polycarbophil)	Loose Stools Condition Aggravated	Non-serious	Neurontin (Gabapentin), Advil (Ibuprofen), Tums (Calcium Carbonate/Magnesium Carbonate / Magnesium Trisilicate)
HQWYE480705JUN03	Female 41	Alavert (Loratadine)	Condition Aggravated	Non-serious	Lisinopril (Lisinopril), Motrin (Ibuprofen), Benadryl (Diphenhydramine HCl)
HQ2312714MAY2002	Male 45	Protonix (Pantoprazole)	Toxicologic Test Abnormal Laboratory Test Interference	Non-serious	Albuterol (Salbutamol), Benadryl (Diphenhydramine HCl), Lopressor (Metoprolol Tartrate), Motrin (Ibuprofen)
HQ3038701JUL2002	Male Unknown	Centrum (Multivitamin/ Multimineral)	Dermatitis Burning Sensation	Non-serious	Benadryl (Diphenhydramine HCl), Tylenol (Paracetamol), Ibuprofen, Triple Antibiotic (Bacitracin / Neomycin Sulfate / Polymyxin B Sulfate)
HQWYE309821MAY03	Female Unknown	Caltrate Plus (Calcium Carbonate/VitaminD/ Zinc)	Myalgia Constipation Night Sweats	Non-serious	Advil (Ibuprofen), Diovan (Valsartan), Tylenol PM (Diphenhydramine/Paracetamol)
HQWYE047013MAR03	Female 49	Alavert (Loratadine)	Headache Drug Ineffective Abdominal Pain	Non-serious	Advil (Ibuprofen), Paxil (Paroxetine HCl), Benadryl (Diphenhydramine HCl)
HQ1992522APR2002	Female 35	Enbrel (Etanercept)	Bronchitis Migraine Drug Ineffective	Non-serious	Methotrexate, Diphenhydramine / Acetaminophen, Ibuprofen, Paroxetine, Methylphenidate, Medroxyprogesterone, Albuterol (Salbutamol)

Table 10. (Cont.) Summary Clinical Information for Adverse Event Cases Where IBU and DPH were Co-Administered

HQWYE995112MAR03	Female 31	Advil (Ibuprofen)	Overdose Drug Ineffective	Non-serious	Triamcinolone, Effexor (Venlafaxine HCl), Unspecified Antidepressant, Benadryl (Diphenhydramine HCl), Unspecified Pain, Aciphex (Rabeprazole), Azulfidine (Sulfasalazine)
HQWYE646629APR04	Female 7	Junior Strength Advil (Ibuprofen)	Swelling Face Eye Swelling	Non-serious	Benadryl (Diphenhydramine HCl), Unspecified Asthma Medication
HQWYE496604SEP03	Male 2.5	Children's Advil (Ibuprofen)	Respiratory Arrest Depressed Level of Consciousness Hypotonia	Other	Benadryl (Diphenhydramine HCl)
HQWYE129627OCT04	Female 6	Children's Advil (Ibuprofen)	Hypersensitivity, Swelling Face, Swollen Tongue, Urticaria	Other	Benadryl (Diphenhydramine HCl)
HQ0776220FEB2002	Female 11	Children's Advil (Ibuprofen)	Hypoventilation Feeling Abnormal	Non-serious	Albuterol (Salbutamol), Benadryl (Diphenhydramine HCl), Centrum Kids Complete (Multivitamin/Ascorbic Acid/Multimineral)
HQWYE306331MAR04	Male 72	Advil (Ibuprofen)	Rash Pruritic Rash Erythematous Skin Warm	Non-serious	A Benadryl (Diphenhydramine HCl), Hydrocortisone, Theragran-M (Minerals NOS / Vitamins NOS), Adalat (Nifedipine), Androgel (Testosterone), Zestril (Lisinopril), Zocor (Simvastatin)
HQWYE422726JUL04	Female 64	Advil Migraine (Ibuprofen)	Drug Ineffective	Non-serious	Benadryl (Diphenhydramine HCl), Dramamine (Dimenhydrinate), Diltiazem, Diazepam,, Coumadin (Warfarin Sodium), Hydrocodone W / Acetaminophen (Hydrocodone Bitartrate / Paracetamol)
HQWYE906411FEB04	Female Unknown	Robitussin (Guaifenesin) Tylenol PM (Diphenhydramine / Paracetamol)	Overdose Dizziness Medication Error	Non-serious	Advil (Ibuprofen), Duratuss (Guaifenesin/ Pseudoephedrine HCl)
HQWYE146618MAR03	Male 41	Diphenhydramine HCl	Urticaria	Other	Advil (Ibuprofen), Activase (Alteplase), Coumadin (Warfarin Sodium), Epogen (Epoetin Alfa), Heparin, Ancef (Cefazolin Sodium), Lidocaine, Paxil (Paroxetine HCl), Phoslo (Calcium Acetate), Proamatine (Midodrine HCl), Renagel (Sevelamer), Venofer (Ferric Hydroxide)

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Daiva Shetty
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MEDICAL OFFICER

Charles Ganley
11/4/2005 11:19:26 AM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Drug Products

To: Charles Ganley MD
Division Director
Division of Nonprescription Clinical Evaluation, HFD-560

To: Bob Rappaport MD
Division Director
Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170

From: Russell G. Katz MD
Division Director
Division of Neurological Drug Products, HFD-120

John Feeney III MD
Team Leader
Division of Neurological Drug Products, HFD-120

D. Elizabeth McNeil MD
Clinical Reviewer
Division of Neurological Drug Products, HFD-120

Date: 15 September 2005

Subject: Consult on Advil PM, NDAs 21-393, 21-394

EXECUTIVE SUMMARY

Background

Wyeth developed ibuprofen/diphenhydramine 200/25 mg liquigels as a combination analgesic/sleep-aid. Prior to initiation of study AE-04-14, the sponsor had performed two partial-factorial studies (AE-98-01 and AE-98-02) using a oral surgery model with sleep phase advance, which compared 1) the analgesic efficacy and 2) the sleep efficacy of ibuprofen/diphenhydramine 400/50 mg liquigels to that of ibuprofen 400 mg and that of placebo. According to the sponsor these studies, which have been previously submitted to the Agency, demonstrated the following:

- Ibuprofen was the primary component contributing to sleep latency
- The ibuprofen/diphenhydramine 400/50 mg combination was statistically superior to ibuprofen for sleep duration.

Upon review of studies AE-98-01 and AE-98-02, the Agency expressed the following key concerns:

- The protocols called for patient awakenings at 90 and 120 minutes post-dose to assess analgesic efficacy. These forced awakenings may have biased the sleep duration measurement.
- The data from AE-98-02 showed that ibuprofen alone was, numerically, superior to the ibuprofen/diphenhydramine 400/50 mg combination for sleep latency.

In previous communications with the agency, the sponsor was told that sleep efficacy should be measured objectively as well as subjectively. By previous agreement between the Agency and the Sponsor, total sleep time objectively measured by actigraphy, was to be the primary efficacy parameter in Study AE-04-14A: Advil PM Oral Surgery Study Using Actigraphy To Objectively Measure Sleep Efficacy.

Efficacy findings:

The sponsor has adequately shown, using a oral surgery model with sleep phase advance, that the combination product, IBU/DPH 400/50 mg, provides a longer total sleep time than IBU 400 mg alone. The demonstrated difference was 72 minutes, which is clinically and statistically significant.

Conclusions and recommendations

In this study, the combination product, IBU/DPH 400/50 mg, provided a longer total sleep time than IBU 400 mg alone.

As seen in the previous studies, on measures of sleep latency the combination product appears to offer no significant benefit over ibuprofen alone. The benefit from use of the combination product comes from an effect on sleep maintenance with a decrease in wake time after sleep onset (WASO): a decrease of 2.3 hours in the combination group as compared to 3.6 hours in the ibuprofen alone group.

We, in DNDP, currently believe that there are three sleep related problems that may be affected by a (prescription) hypnotic agent, i.e. 1) sleep onset, 2) sleep maintenance and

3) early morning awakenings. A given hypnotic agent may be effective in the treatment of one or more of these problems. In the indication section of the recently approved hypnotics, we have attempted to clarify the expected problem that may be treated by the agent in question and do away with the 'duration of sleep' language which can obscure which type of problem is actually going to be treated.

The combination product, IBU/DPH 400/50 mg, has no benefit over ibuprofen in the treatment of a sleep onset difficulty. It does appear to improve sleep maintenance as demonstrated by the WASO results. It may be fairly stated that this combination product may be expected to increase the duration of sleep not by aiding faster onset of sleep but rather by decreasing the time spent awake after one has fallen asleep.

CONSULT EFFICACY REVIEW:

Study AE-04-14A: Advil PM Oral Surgery Study Using Actigraphy To Objectively Measure Sleep Efficacy

Objective:
To objectively, via actigraphy, and subjectively evaluate the sleep efficacy of ibuprofen/diphenhydramine hydrochloride 400/50 mg (IBU/DPH) compared to ibuprofen 400 mg (IBU) in subjects with sleeplessness associated with oral surgery pain

Study design
A randomized, stratified (by gender and baseline pain), inpatient, single-dose, double-blind, parallel group single-center study to be conducted in 320 subjects who had a post-operative baseline score consistent with moderate-to-severe post-operative pain, as determined by a score of >50 mm on a VAS scale. The study participants were required to take a dose of study medication and go to bed > 3 hours earlier than their usual bedtime, i.e. between 18:30 and 20:00, in this phase advance model of transient insomnia.

Study population and procedures
Study duration
Each participant was to be studied for 19-24 hours.

Entry criteria
Inclusion criteria

1. Healthy male or females, 16 to 45 years old
2. Subjects were to be examined by the site-affiliated dentist or physician and medically cleared to participate in the study. In general, the subjects were to have been in good health and have had no contraindications to any of the study medications
3. Subjects were to be outpatients scheduled to undergo surgical removal of 1 to 2 impacted third molars, one of which had to be at least a partial bony mandibular impaction (Note: up to 4 molars may have been extracted as long as no more than 2 were impacted)
4. Subjects who had received the following pre-operative anesthetic regimen: a short-acting local anesthetic (lidocaine or mepivacaine) with or without vasoconstrictor and nitrous oxide
5. Subjects who had not taken any form of medication or dietary supplements within 3 days of entry (except for oral contraceptives and prophylactic antibiotics) and agreed not to take any medication (other than that provided) throughout the study.
6. Subjects who had not consumed alcoholic beverages or foods and beverages containing xanthines for 2 hours prior to surgery and agreed not to consume any of these foods or beverages throughout the evaluation period
7. Subjects had to be capable of understanding and willing to sign the consent form
8. Subjects under 18 years of age had to have parent/guardian consent

Exclusion criteria

1. Known hypersensitivity to ibuprofen, any other NSAID, acetaminophen, diphenhydramine or any other antihistamine (gastric intolerance was not to be considered sensitivity.)
2. Presence of a serious medical condition (e.g. poorly controlled hypertension, poorly controlled diabetes, significantly impaired cardiac, renal, or hepatic function, poorly controlled hyper- or hypothyroidism)
3. Presence of a chronic breathing problem such as asthma, emphysema, sleep apnea or chronic bronchitis (productive cough not attributable to other causes on most days for at least 3 months over 2 consecutive years
4. Presence or history (within 2 years of enrollment) of peptic ulcer disease
5. Presence or history of bleeding disorder
6. Presence of symptomatic benign prostatic hyperplasia or urethral stricture
7. Glaucoma
8. Acute local infection at the time of surgery that could confound the post-surgical evaluation
9. Use of a prescription or non-prescription drug with which the administration of ibuprofen or any other NSAID is contraindicated (e.g. coumarin-type anticoagulants, thiazides, furosemide, probenecid)
10. Use of a prescription or non-prescription drug with which diphenhydramine or any other antihistamine is contraindicated (e.g. other antihistamines, tranquilizers or sedatives)
11. Use of any investigational drug within 30 days of screening
12. Use of antihistamines prior to study entry for the following time periods:
    - Non and low-sedating oral antihistamines (e.g. Claritin, Allegra, Zyrtec, Semprex): 72 hours
    - Hismanal (astemizole), if regular use was > 3 days: 72 hours
    - All other oral antihistamines: 48 hours
    - Nasal and ocular antihistamines (e.g. asrelin, Livostin, levocabastine: 72 hours
    - Intramuscular administration of any antihistamine: 72 hours
13. Pregnancy or lactation
14. Females of child-bearing potential or who are post-menopausal for less than 2 years who were not using one of the medically approved methods of contraception listed in the protocol
15. History of regularly going to bed earlier than 11 pm
16. Habituation to analgesic drugs, i.e. routine use of oral analgesics 5 or more doses/week
17. Sleep schedule changes required by night or shift work
18. Had flown across greater than 3 time zones within the 7 days prior to screening
19. History of restless leg syndrome
20. History treatment of depression within the previous 6 months
21. Use of any psychotropic agent (including St. John's wort) in the past 6 months
22. Use of nicotine transdermal patches, spray or gum
23. History of alcoholism or substance abuse or regularly consumes 3 or more alcoholic drinks/day

24. Previous participation in this study
25. Member or relative of either study staff or sponsor directly involved in the study

Study medications

- 2 x IBU/DPH HCl 200 mg/25mg blue liquigels
- 2 x IBU 200 mg blue liquigels

Study procedures

Study flow chart

			Post-Dosing time Point												
Procedure	**Screening**	**Surgery**	**0***	**10**	**20**	**30**	**40**	**50**	**60**	**75**	**90**	**120**	**150**	**180**	**Next Morning**
Surgical Consult/Informed Consent	X														
Medical History	X														
Surgical Procedure (between ~3-4pm)		X													
Surgical Trauma Scale		X													
Randomization			X												
Dosing			X												
Pain Evaluations:															
Cat. Pain Severity Rating Scale[a]			X												
VAS Pain Severity Rating Scale[a]			X												
Sleep Evaluations:															
Observed sleep latency				X	X	X	X	X	X	X	X	X	X	X	
Duration of sleep[b]															X
ACTIGRAPHY			→	→	→	→	→	→	→	→	→	→	→	→	→
Subjects taking a rescue medication during this time will be considered:			← Discontinued →							← Treatment Failures →					

*Must be between approximately 6:30 – 8:00 p.m.
a To be completed within 5 minutes prior to the administration of study medication.
b If rescue occurs prior to waking the next morning, assessment of duration will be completed at the time rescue medication is taken.

Oral surgery was to be performed between 15:00 and 16:00. The entire surgery was not to exceed 30 minutes. During the recovery period, subjects were to sit quietly but not sleep until they were given study medication and sent to retire for the evening.

A baseline assessment of the patient's post-operative pain was to be comprised of a 4-point categorical rating scale as well as a 100-mm visual analog pain severity rating scale. When patients begin to experience at least moderate pain, assuming that this occurred between 18:30 and 20:00, subjects were to be randomized to one of two treatment arms.

Sleep latency, as determined by an observer, was to be assessed at 10-, 20-, 30-, 40-, 50-, 60-, 75-, 90-, 120-, 150- and 180 minutes post-dose.

Sleep duration was to be defined as the subject's assessment of the number of hours slept (to the nearest 15 minutes). This estimate was to be obtained upon awakening in the morning or at the time of rescue.

Once 60 minutes from the initial dose had elapsed, rescue medication was permissible. If a patient were to receive rescue medication, the subsequent elapsed time until they arose from bed was to be coded as awake.

Upon arrival at the study site, the patient was to have a Actigraph placed on his/her nondominant wrist. The patient was to be required to wear the actigraph until the morning following surgery. The actigraph was to be programmed to sample the patient's movements at a constant rate of 10 Hz with a data storage epoch of 60 seconds. Data was to be downloaded on the morning after surgery and sent to for review.

Efficacy parameters

Primary efficacy variable

- Total sleep time as measured by actigraph

Secondary efficacy variables

- Wake after sleep onset as measured by actigraph
- Sleep efficiency as measured by actigraph
- Subjective sleep duration
- Sleep latency as measured by actigraph
- Sleep latency, based on observation
- Time to rescue medication
- Percentage requiring rescue medication

Statistical analysis

The power calculations were based upon data from a similarly designed pilot study in which a between-subject variability of 2.9545 hours was noted for actigraph derived sleep time. A similar variability was assumed for this study, and 140 subjects per treatment group was estimated to provide 80% power to detect a one hour difference in total sleep time between the IBU/DPH 400/50 group and the IBU 400 mg group. The sample size was increased to 160/group to account for potential missing data associated with technical difficulties.

The primary efficacy analysis was to be performed upon the intent-to-treat population, defined as all randomized subjects who dosed with study product including those who took rescue prior to one hour. The sponsor also planned a secondary analysis on the per-protocol population.

was to derive the following sleep parameters: TST, total awake time in bed, WASO, sleep efficiency and sleep latency. The time of dosing was

considered the bedtime. The time that the call bell was pressed in the morning was considered the time of arising. WASO was to be derived by subtracting sleep latency from the total time in bed awake. In the case of a patient who took rescue medication, the time between the pressing of the call button to request rescue medication until time of arising was to be manually adjusted as "awake." If the time that the call button was pressed for rescue medication was missing but the time of taking rescue was available, the latter time would be used in the sleep scoring. For those patients who did not take rescue medication, if the time of arising was missing but the sleep assessment time was available, the latter would be used for arising time. If the time to rescue medication was less than the Actigraphic measurement of sleep latency, the sleep latency was to be considered censored at 3 hours or 15 minutes plus the longest observed sleep latency for the entire subject sample, whichever was later.

Total sleep time, wake after sleep onset, and sleep duration were to be analyzed using an ANOVA model with treatment, baseline pain severity rating (PSR) and gender terms. The treatment by baseline PSR and gender interactions would be assessed in separate models.

The sponsor planned to declare a statistically significant treatment difference if $p \leq 0.05$. A marginally significant difference was to be declared if $0.05 \leq p \leq 0.10$. A difference in sleep duration of 40 minutes or more and/or a difference of 20 minutes or more in sleep latency were to be considered clinically significant.

No interim analysis was planned.

Changes to the planned statistical analysis
The only change made was to clarify the method for derivation of wake after sleep onset (WASO). The protocol originally stated that WASO was to be derived by subtracting sleep latency (time to sleep onset) from the total time in bed awake. The sponsor later noted that the sleep scoring algorithm defined sleep onset as the first sleep episode of at least 20 minutes in duration and therefore, "a subject could potentially have shorter sleep episodes prior to sleep latency (study report page 43, section 6.8)."

The sponsor altered the derivation of WASO "to more accurately reflect the total wake time after sleep onset during the study night (study report page 43, section 6.8)." The modified derivation (done via actigraph software) calculated WASO from the time of sleep onset until sleep offset, i.e. the time of rescue or the time of morning awakening for those patients who did not require rescue.

Study results
Trial characteristics
This study began in November 2004 and ended in March 2005. The plan was to enroll 320 patients. The final ITT and safety population had 329 subjects, with 165 in the IBU/DPH group and 164 in the IBU group. The per-protocol population (PP) had 322 patients. One subject in each treatment group did not provide actigraph data due to technical difficulties with the equipment.

Demographics

Table 1: Demographics

	IBU/DPH group N=165	IBU group N=164
Age (years) Mean (SD)	18.7 (2.4)	19.0 (3.1)
Sex		
Male	81 (49.2%)	81 (49.4%)
Female	84 (50.8%)	83 (50.6%)
Ethnicity		
White	149 (90.3%)	151 (92.1%)
Black	2 (1.2%)	1 (0.6 %)
Asian	2 (1.2%)	4 (2.4%)
Hispanic	11 (6.7%)	6 (3.7%)
Other	1 (0.6%)	2 (1.2%)

A total of 7 patients did not complete the study:

Ibuprofen 400 mg group

- Subject 10076 protocol violation
- Subject 30015 protocol violation 13.9 hours from dosing
- Subject 30016 protocol violation
- Subject 30017 protocol violation 12.7 hours from dosing
  Hypothyroidism medication was discontinued 5 days prior to surgery
- Subject 40008 protocol violation 12.6 hours from dosing

Ibuprofen/Diphenhydramine 400 mg/50 mg group

- Subject 20001 subject left — 1.2 hours from dosing
- Subject 30033 protocol violation 13.7 hours from dosing
  "Mandibular third molar was a soft tissue"

There were no statistically significant demographic differences at baseline between the treatment groups. A marginally significant difference in the mean duration of the surgical procedure was seen (6.3 minutes for IBU/DPH vs. 5.7 minutes for IBU, p=0.052).

A slightly higher proportion of patients in the IBU group had 3 teeth (3.7% vs. 1.2% in the IBU/DPH group) or 4 teeth (2.4% vs. 1.2% in the IBU/DPH group) extracted. The treatment groups had no other differences in their surgically related parameters or in their baseline pain scores.

Protocol violations

As shown above there were 6 patients who were noted to have protocol violations that rendered them ineligible to complete the study. Details of the violations were provided for two of those patients. Those two patients did not have violations that would affect the study results.

Additionally, protocol deviations were noted in a total of 16 patients in the Ibuprofen 400 mg group and a total of 16 patients in the Ibuprofen/Diphenhydramine 400 mg/50 mg group:

- Inclusion/exclusion deviations
  - Regular bedtime before 2300 (specifically 22:30 or 22:45)
    - 9 in the Ibuprofen/Diphenhydramine 400 mg/50 mg group
    - 12 in the Ibuprofen 400 mg group
  - History of substance abuse (marijuana)
    - 5 in the Ibuprofen/Diphenhydramine 400 mg/50 mg group
    - 1 in the Ibuprofen 400 mg group
  - Medication use (non-confounding)within 3 days of study entry
    - 1 in the Ibuprofen/Diphenhydramine 400 mg/50 mg group
    - 4 in the Ibuprofen 400 mg group

- Study procedure deviation
  - Baseline measurement before 6:15 pm
    - 1 in the Ibuprofen/Diphenhydramine 400 mg/50 mg group

A given patient could have more than one protocol deviation though each patient was only counted once in the overall total for the treatment arm.

The protocol deviations seen would not affect the validity of the study results.

Efficacy endpoints
The sponsor reports that since the usual parametric assumptions were not satisfied for WASO and were questionable for objective and subjective assessments of sleep duration, additional analyses using the CMH test stratifying by gender and baseline pain severity rating were performed.

The sponsor further reports that the interaction effects of treatment-by-baseline pain and treatment-by-gender were not found to be significant.

Primary endpoint
The primary endpoint for this study was total sleep time (TST) as measured by actigraph.

> There was a significant treatment effect when Ibuprofen/Diphenhydramine (IBU/DPH) 400 mg/50 mg was compared to Ibuprofen (IBU) 400 mg.

Table 2: TST-ITT population

	IBU/DPH N=165	IBU N=164
Mean (hours)	9.29	8.09
Standard deviation	3.2	3.5
Median	10.28	8.88
Range		
Treatment difference (95% CI)	1.2 (0.49, 1.92)	
p-values		
Treatment[a]	0.001	
Treatment (CMH test)[b]	<0.001	
Treatment*base interaction[c]	0.707	
Treatment*gender interaction[d]	0.146	

[a]p-value based upon the ANOVA model with treatment, baseline pain scale rating (PSR) and gender terms (this represents the primary model)
[b]p-values using the Cochran-Mantel-Haenzel test with modified ridit scores, controlling for both gender and PSR.
[c]p-value from the addition of treatment-by-baseline PSR interaction to the primary model
[d]p-value from the addition of treatment-by-gender interaction to the primary model
This table is a modification of table B.2 in the study report for AE-04-14.

Secondary endpoints

- Wake after sleep onset (WASO) as measured by actigraph

There was a significant treatment effect when Ibuprofen/Diphenhydramine (IBU/DPH) 400 mg/50 mg was compared to Ibuprofen (IBU) 400 mg.

Table 3: WASO- ITT population

	IBU/DPH N=165	IBU N=164
Mean (hours)	2.28	3.64
Standard deviation	2.9	3.5
Median	0.78	1.84
Range		
Treatment difference (95% CI)	- 1.35 (-2.05, -0.66)	
p-values		
Treatment[a]	<0.001	
Treatment*base interaction[b]	0.547	
Treatment*gender interaction[c]	0.362	

[a]p-value based upon the ANOVA model with treatment, baseline pain scale rating (PSR) and gender terms (this represents the primary model)
[b]p-value from the addition of treatment-by-baseline PSR interaction to the primary model
[c]p-value from the addition of treatment-by-gender interaction to the primary model
This table is a modification of table B.4 in the study report for AE-04-14.

- Sleep efficiency as measured by actigraph

There was a significant treatment effect when Ibuprofen/Diphenhydramine (IBU/DPH) 400 mg/50 mg was compared to Ibuprofen (IBU) 400 mg.

Table 4: Sleep efficiency-ITT population

	IBU/DPH N=165	IBU N=164
Mean (measured as %)	75.87	65.73
Standard deviation	24.9	27.5
Median	88.35	76.28
Range		
Treatment difference (95% CI)	0.27 (0.15, 0.38)	
p-values		
Treatment[a]	<0.001	
Treatment*base interaction[b]	0.268	
Treatment*gender interaction[b]	0.318	

[a]p-value based upon the Cochran-Mantel-Haenzel test with modified ridit scores, controlling for both gender and PSR.
[b]p-values were computed using the pseudo-homogeneity test
This table is a modification of table B.4 in the study report for AE-04-14.

- Subjective sleep duration

There was a significant treatment effect when Ibuprofen/Diphenhydramine (IBU/DPH) 400 mg/50 mg was compared to Ibuprofen (IBU) 400 mg.

Table 5: Subjective sleep duration-ITT population

	IBU/DPH N=165	IBU N=164
Mean (hours)	7.94	6.90
Standard deviation	3.0	3.3
Median	8.50	7.00
Range		
Treatment difference (95% CI)	1.04 (0.36, 1.73)	
p-values		
Treatment[a]	0.003	
Treatment (CMH test)[b]	0.005	
Treatment*base interaction[c]	0.578	
Treatment*gender interaction[d]	0.053	

[a]p-value based upon the ANOVA model with treatment, baseline pain scale rating (PSR) and gender terms (this represents the primary model)
[b]p-values using the Cochran-Mantel-Haenzel test with modified ridit scores, controlling for both gender and PSR.
[c]p-value from the addition of treatment-by-baseline PSR interaction to the primary model
[d]p-value from the addition of treatment-by-gender interaction to the primary model
This table is a modification of table B.3 in the study report for AE-04-14.

- Sleep latency as measured by actigraph

There was no significant treatment effect when Ibuprofen/Diphenhydramine (IBU/DPH) 400 mg/50 mg was compared to Ibuprofen (IBU) 400 mg.

Table 6: Sleep latency- ITT population

	IBU/DPH N=164	IBU N=163
Median (minutes)	23.3	22.5
Range		
Treatment difference (95% CI)	1.04 (0.83, 1.29)	
p-values		
Treatment[a]	0.731	
Treatment*base interaction[b]	0.709	
Treatment*gender interaction[c]	0.523	

[a]p-value based upon the proportional hazards model with treatment, baseline pain scale rating (PSR) and gender terms (this represents the primary model)
[b]p-value from the addition of treatment-by-baseline PSR interaction to the primary model
[c]p-value from the addition of treatment-by-gender interaction to the primary model
This table is a modification of table B.4 in the study report for AE-04-14.

- Sleep latency, based on nurse observation

There was no significant treatment effect when Ibuprofen/Diphenhydramine (IBU/DPH) 400 mg/50 mg was compared to Ibuprofen (IBU) 400 mg.

Table 7: Sleep latency based on observation- ITT population

	IBU/DPH N=165	IBU N=164
Median (minutes)	17.6	17.6
95% CI (Median)	(17.00, >180.0)	(20.00, 30.0)
Treatment difference (95% CI)	1.04 (0.83, 1.29)	
Hazard ratio		
p-values		
Treatment[a]	0.751	
Treatment*base interaction[b]	0.535	
Treatment*gender interaction[c]	0.403	

[a]p-value based upon the proportional hazards model with treatment, baseline pain scale rating (PSR) and gender terms (this represents the primary model)
[b]p-value from the addition of treatment-by-baseline PSR interaction to the primary model
[c]p-value from the addition of treatment-by-gender interaction to the primary model
This table is a modification of table B.5 in the study report for AE-04-14.

- Time to rescue medication

There was a significant treatment effect when Ibuprofen/Diphenhydramine (IBU/DPH) 400 mg/50 mg was compared to Ibuprofen (IBU) 400 mg.

Table 8: Time to rescue medication- ITT population

	IBU/DPH N=165	IBU N=164
Median (minutes)	>720	>720
p-values		
Treatment[a]	0.020	
Treatment*base interaction[b]	0.483	
Treatment*gender interaction[c]	0.179	

[a]p-value based upon the proportional hazards model with treatment, baseline pain scale rating (PSR) and gender terms
[b]p-value from the addition of treatment-by-baseline PSR interaction
[c]p-value from the addition of treatment-by-gender interaction
This table is a modification of table B.6 in the study report for AE-04-14.

- Percentage requiring rescue medication

  A significantly higher proportion of the IBU group required rescue medication (40% vs. 29%, p=0.031)

Summary of key results

Table 9: Summary table

Parameter	Summary Statistic	IBU 400/ DPH 50 (n=165)	IBU 400 (n=164)	Δ
Sleep duration				
Sleep Duration- Actigraph	Mean (hr)	9.3	8.1	1.2*
Sleep Duration - Subject	Mean (hr)	7.9	6.9	1.0*
Wake after sleep onset (WASO)				
WASO-Actigraph	Mean (hr)	2.3	3.6	-1.3*
Sleep Latency				
Sleep Latency - Actigraph	Median (min)	23.3	22.5	1.04
Sleep Latency - Observer based	Median (min)	17.6	17.6	1.04

Δ= IBU 400/DPH 50 - IBU 400 difference (observed); for parameters showing medians it is the hazard ratio of IBU 400/DPH 50 vs IBU 400.
* IBU 400/DPH 50 group was significantly better than the IBU 400 group; $p \leq 0.05$.

(This table is a modification of Table S.1 found on p. 14 of the study report for study ae-04-14)

Conclusions and recommendations

Wyeth developed ibuprofen/diphenhydramine 200/25 mg liquigels as a combination analgesic/sleep-aid. Prior to initiation of this study AE-04-14, the sponsor had performed two partial-factorial studies (AE-98-01 and AE-98-02) using a oral surgery model with sleep phase advance, which compared 1) the analgesic efficacy and 2) the sleep efficacy

of ibuprofen/diphenhydramine 400/50 mg liquigels to that of ibuprofen 400 mg and that of placebo. According to the sponsor these studies, which have been previously submitted to the Agency, demonstrated the following:

- Ibuprofen was the primary component contributing to sleep latency
- The ibuprofen/diphenhydramine 400/50 mg combination was statistically superior to ibuprofen for sleep duration.

Upon review of studies AE-98-01 and AE-98-02, the Agency expressed the following key concerns:

- The protocols called for patient awakenings at 90 and 120 minutes post-dose to assess analgesic efficacy. These forced awakenings may have biased the sleep duration measurement.
- The data from AE-98-02 showed that ibuprofen alone was, numerically, superior to the ibuprofen/diphenhydramine 400/50 mg combination for sleep latency.

The sponsor states that study AE-04-14 was performed to confirm the results of studies AE-98-01 and AE-98-02 and demonstrate that IBU/DPH 400/50 mg provided better sleep efficacy (as measured by sleep duration) compared to IBU 400 mg alone in a phase advance model utilizing patients who had undergone oral surgery. The Agency and the sponsor had previously agreed that the combination was effective as an analgesic. Since the previous studies had demonstrated that both the combination and Ibuprofen alone were both superior to placebo on all pain and sleep parameters assessed, no negative control was incorporated into this study.

In previous communications with the agency, the sponsor had been told that sleep efficacy should be measured objectively as well as subjectively. By previous agreement between the Agency and the Sponsor, total sleep time objectively measured by actigraphy, was to be the primary efficacy parameter.

The sponsor notes that, in their determination, standard parametric assumptions were not adequately satisfied for Wake time After Sleep Onset (WASO), actigraphic assessment of sleep duration or subjective assessment of sleep duration so they analyzed those parameters via the CMH test using modified ridit scores with stratification by baseline pain severity and gender. An assessment of the parametric assumptions as well as the evaluation of the CMH test findings was performed by Dr. Yongman Kim of the Office of Biometrics II, FDA. While a detailed review of the statistical issues may be found in his review, I will provide a summary of his preliminary findings here:

- He is in agreement with my findings on the primary and secondary efficacy variables.
- He was able to reproduce the sponsor's results except for p-value for treatment comparison of '0.001' rather than '<0.001' which does not affect the conclusion.
- He agrees with the analysis plan proposing a non-parametric method of CMH with modified ridit score as well as ANOVA approach in order to check the sensitivity of violation of ANOVA assumptions on study results. ANOVA and CMH lead to the same conclusions in those analyses using both methods so the

violation of the ANOVA assumptions did not have much impact on the conclusion.

In my interpretation of the data, the sponsor has adequately shown that the combination product, IBU/DPH 400/50 mg, provided a longer sleep duration than IBU 400 mg alone. The protocol had specified a treatment of 40 minutes in total sleep time, as measured by actigraph, as a "clinically meaningful" difference. The demonstrated difference was 72 minutes, representing a clinically and statistically meaningful difference.

I would note that the subjective sleep duration data mirrored the objective total sleep time data though it did not duplicate it. The subject assessment showed a mean sleep duration of 7.9 hours with the combination as opposed to 6.9 hours with ibuprofen alone. The sponsor determined that there was a correlation coefficient of 0.8, $p<0.001$.

As seen in the previous studies, on measures of sleep latency the combination product appears to offer no significant benefit over ibuprofen alone. The benefit from use of the combination product comes from an effect on sleep maintenance with a decrease in wake time after sleep onset (WASO): a decrease of 2.3 hours in the combination group as compared to 3.6 hours in the ibuprofen alone group.

For prescription hypnotics, we currently believe that there are three sleep related problems that may be affected by a hypnotic agent, i.e. 1) sleep onset, 2) sleep maintenance and 3) early morning awakenings. A given hypnotic agent may be effective in the treatment of one or more of these problems. In the indication section of the recently approved hypnotics, we have attempted to clarify the expected problem that may be treated by the agent in question and do away with the 'duration of sleep' language which can obscure which type of problem is actually going to be treated.

The product under consideration has no benefit over ibuprofen in the treatment of a sleep onset difficulty. It does appear to improve sleep maintenance as demonstrated by the WASO results. It may be fairly stated that this combination product may be expected to increase the duration of sleep not by aiding faster onset of sleep but rather by decreasing the time spent awake after one has fallen asleep.

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/s/

Dawn McNeil
9/30/2005 04:58:56 PM
MEDICAL OFFICER

John Feeney
10/20/2005 11:12:46 AM
MEDICAL OFFICER
Concur with Dr.McNeil. Of additional note, Dr.Kim (statistician) performed sensitivity analyses based on use of rescue medication. Among other analyses, a sub-group analysis incl. only pts who did not use rescue meds was also positive.

Russell Katz
10/21/2005 08:08:09 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Russell Katz, M.D., Division Director
Attn. Robbin Nighswander, Chief Project Manager
Division of Neuropharmacology, HFD-120

FROM:
Curt Rosebraugh, M.D., Acting Division Director
Leah Christl, Project Manager; 301-827-2248; christll@cder.fda.gov
ONP, Division of Nonprescription Clinical Evaluation, HFD-560

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 15, 2005		21-393, 21-394	NDA Class 2 resubmission	June 27, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Advil PM (200 mg ibuprofen/25 mg diphenhydramine)	HIGH	NSAID 5030300	October 15, 2005

NAME OF FIRM: Wyeth Consumer Healthcare

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

- **COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:** NDA 21-393 and 21-394 were originally received October 16, 2001. The applications have received 2 approvable actions and have gone through formal dispute resolution. The most recent approvable action issued December 18, 2003 conveyed to the sponsor that the original studies (AE 98-01 and AE 98-02) did not adequately support the efficacy of the product and failed to provide and unbiased determination of the effect of the combination product versus IBU alone on the endpoint of sleep duration. The sponsor was also informed of our concerns of whether forced/artificial awakenings bias results of the studies in favor of the combination over IBU alone. The sponsor was told that an additional trial was necessary to establish adequate evidence of an effect of DPH in the combination on sleep duration.
- The June 27, 2005 submission contains the final study report for an additional trial conducted by Wyeth with sleep duration as the primary endpoint and no artificial awakenings. Please review study AE-04-14A entitled "Advil PM Oral Surgery Study Using Actigraphy to Objectively Measure Sleep Efficacy" intended "to objectively and subjectively evaluate the sleep efficacy of IBU/DPH 400/50 mg compared to IBU 400 mg in subjects with sleeplessness associated with oral surgery pain". Please provide your evaluation of the study results with particular attention to demonstration of sleep duration and sleep latency.
- The June 27, 2005 submissions can be found at: \\CDSESUB1\N21393\N_000\2005-06-27 and \\CDSESUB1\N21394\N_000\2005-06-27
- Per instruction from Parinda Jani, CPMS HFD-170, we request that Elizabeth McNeil be assigned as the clinical reviewer for this consult request, if possible.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
	☒ DFS ☒ EMAIL ☐ HAND

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Leah Christl
7/15/05 08:51:31 AM

Curtis Rosebraugh
7/15/05 09:04:25 AM

Office Director Memorandum
Office of Drug Evaluation V

NDA 21-393
NDA 21-394

Sponsor: Wyeth Consumer Healthcare

Drug Product:

NDA 21-293 ibuprofen 200mg/diphenhydramine HCL 25 mg liquigel
NDA 21-394 ibuprofen 200mg/diphenhydramine citrate – caplet

Proposed Indication: Pain Reliever/Nighttime Sleep Aid

Date: December 18, 2003

Background

This re-submission consists of new analyses of data generated in trials AE 98-01 and AE 98-02 and other information deemed by the sponsor as relevant to the concerns of the Agency and the approvability for this combination product. It purports to respond to the deficiencies of the approvable action of August 8, 2003 and the recommendations of the Center Director's dispute resolution review of this application. It is noted that the sponsor had prior dispute resolution at the level of Office of Drug Evaluation V and the Office of New Drugs. These appeals were denied.

These analyses as well as information submitted in the sponsor's overview do not adequately answer the Agency's concerns of the Action letter of August 8, 2002. These re-analyses of subgroups do not provide compelling evidence of efficacy for the contribution of diphenhydramine to the endpoint of sleep duration. The sponsor's analyses and choice of time-points do not adequately address the acknowledged deficiencies. There is also concern that these subsets chosen for analyses may not be representative of the population for which this product would be used. It must be noted that it is unlikely that these concerns can be answered by data from the existing NDA database due to the significant design limitations of these studies.

Conclusion of Office Review of Action Package

The Office is in concurrence with the determination by the Divisions that the sponsor has failed to provide adequate evidence for regulatory approval for demonstration of efficacy for this combination product for the proposed indication.

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/s/

Jonca Bull
12/19/03 12:04:27 PM
MEDICAL OFFICER

CLINICAL REVIEW

Advil PM

NDA 21-393 (Ibuprofen 200 mg/Diphenhydramine HCl 25 mg Liquigels)
NDA 21-394 (Ibuprofen 200 mg/Diphenhydramine Citrate 38 gm Caplets)

Medical Officer Review (HFD-550)

Submission Date:	June 30, 2003
Received Date:	July 3, 2003
Review Date:	December 8, 2003
Drug Name:	Advil PM Liqui-Gels Advil PM Caplets
Generic Name:	Ibuprofen 200 mg/Diphenhydramine HCl 25 mg Liquigels Ibuprofen 200 mg/Diphenhydramine Citrate 38 gm Caplets
Chemical Name:	
Name:	Ibuprofen
Chemical name:	2-(4-isobutylphenyl)-propionic acid
Name:	Diphenhydramine hydrochloride
Chemical name:	2-(Diphenylmethoxy)-N N-dimethylethylamine monocitrate
Applicant:	**Wyeth Consumer Healthcare**
Related IND:	IND 44,767 IND 56,521 (Advil PM Liquigels) IND – (Advil PM Caplets)
Relate NDA:	NDA 20-402 (Advil Liquigels) NDA 18-989 (Advil Tablets)
Related Reviews:	Medical (original, HFD-550)-Lucious Lim, M.D. Medical (original, HFD-120)-Paul Andreason, M..D. Medical (original, HFD-560)- Rosemarie Neuner, M.D. Statistical-Laura Lu, Ph. D. Biopharm –Jang-IK Lee, Ph.D. Chemistry –Bart Ho, Ph.D.

CLINICAL REVIEW

	Pharmacology –Maria Rivera, Ph.D.
Pharmacologic category:	NSAID/antihistamine
Proposed Indication:	Analgesic/nighttime sleep-aid
Dosage forms and route:	Oral liquid filled capsule Oral capsule-shaped tablets
Submission type:	Original NDA
Medical reviewer:	Tatiana Oussova, M.D., M.P.H.

Table of Contents

Clinical Review for NDA 21-393 and NDA 21-394

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The current submission of new analyses of data from pivotal trials AE 98-01 and AE 98-02 does not adequately answer the deficiencies of the approvable letter from August 8, 2002 and therefore does not provide the evidentiary basis needed for a favorable regulatory action

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There is not enough of substantial evidence that diphenhydramine (DPH) contributes to the effect of a combination on sleep duration, therefore phase 4 study is not appropriate at this time.

II. Summary of Clinical Findings

In response to the approvable letter from August 8, 2002 the Sponsor submitted new analyses of data from clinical investigations that had not been previously reviewed by the review division.

In summary, the Sponsor analyzed the effect of awakening patients at 120 minutes on the sleeping status of the same subset of patients at 150 minutes, but did not explore the effect of awakening patients at 90 minutes on their sleeping status at 120 minutes. Even with both results, the question 'whether awakening subjects leads to bias in comparing sleep duration' can not by fully answered due to the limitation of the trial design. The Sponsor also analyzed sleep duration among

patients who were asleep at 150 minutes. Since sleep duration covered the whole night period, not just the period after 150 minutes, it was influenced by both awakening and drug effect. Therefore, it is not possible to dissect the awakening effect from any drug effect based on these analyses. It is noted that this wakening may potentially favor the particular pharmacokinetics of DPH, allowing more patients in this treatment arm to fall back to sleep, which then may artificially lengthen the apparent duration of sleep in those receiving DPH.

No new data on safety, dosing, or the use in special population were provided in this most recent submission by the Sponsor.

Clinical Review

I. Regulatory history

Original NDA 21-393 and 21-394 (referred to as Advil PM) were submitted on October 16, 2001 under 505 (b) (1).

Original NDAs were reviewed by three Divisions: DAAODP, Neuropharm, and OTC.

Approvable letter was issued on August 8, 2002.
Clinical deficiencies noted in approvable letter were:

1. Inconsistencies in the results of the primary endpoints, sleep latency and sleep duration. For sleep latency, ibuprofen (IBU) was numerically superior to a combination; combination was superior to IBU in sleep duration.
2. Awakening subjects at 90 min. and 120 min. could have a negative impact on the measure of sleep duration
3. The effect of diphenhydramine (DPH) in the combo product has not been established
4. Additional well-designed study is needed to evaluate sleep duration and sleep latency

The Sponsor responded by filing a formal dispute resolution request (FDRR) on December 10, 2002 to be reviewed by ODE V.

The conclusion of this review was to uphold the approvable action.

The second FDRR was submitted to OND on February 5, 2003 and responded to by Dr. Jenkins.

Deficiencies noted in Dr. Jenkins review were:

1. Problems with the study design , data collection on sleep duration and analysis of data

2. No statistically or clinically significant effect on sleep latency (primary endpoint) was demonstrated for the combination compared to IBU alone
3. Numerical advantage of IBU alone over the combination for sleep latency raises question whether DPH adversely impacts on the beneficial effect of IBU on sleep latency
4. Apparent effect of DPH in the combination on sleep duration may be an artifact of the forced awakening
5. Pivotal studies were unable to adequately demonstrate a positive effect of DPH on sleep duration

Approvable action was upheld, and Dr. Jenkins recommendation was:
" Substantial evidence of an effect of DPH in the combination on sleep duration from an adequate and well-controlled study designed with sleep duration as a primary endpoint, in addition to the data presented in the original NDA, would be sufficient for approval."

Third appeal was submitted to Dr. Woodcock on April 23, 2003
Per Sponsor's request, the meeting was held on May 20, 2003.
During this meeting, the Sponsor presented new analysis of data from pivotal clinical trials that had not been submitted to the NDA and was not previously reviewed by the review divisions.

The Sponsor was then asked to submit these new data to the NDA for review as part of a complete response to the approvable letter (Dr. Woodcock letter form June 16, 2003).

For additional information, please, see original reviews

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Please, see original reviews

III. Human Pharmacokinetics and Pharmacodynamics

Please, see original reviews

IV. Description of Clinical Data and Sources

1. New analyses of data from pivotal trials AE 98-01 and 98-02 submitted by the Sponsor in its June 30 submission, were reviewed.
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In addition to that, the following materials were consulted:

2. Meeting minutes
3. Dr. Jenkins letter from February 5, 2003
4. Original clinical reviews
5. Proposed labeling

V. Clinical Review Methods

This review concentrates only on the current submission of analyses of data that were not submitted to the original NDA. It does not duplicate original reviews.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

In summary, additional analyses of data from pivotal trials AE 98-01 and 98-02 were submitted by the Sponsor in support of its statement that artificial awakening has no effect on sleep duration, and that DPH contribution to sleep duration is a real finding and not an artifact of the design of awakening subjects.

This re-analysis provided little new information to address the impact that awakening may have had on sleep duration and does not answer the question whether or not awakening patients at different times (i.e. 90 and 120 minutes) affected their overall sleep duration.

Analysis suggested again that the apparent benefit of DPH in the combination on sleep duration may be an artifact of the forced awakening.

B. General Approach to Review of the Efficacy of the Drug

The Sponsor's primary hypothesis regarding addition of DPH was that its primary contribution to the claimed effects of the combination would be a positive effect on sleep latency. Sleep latency was the primary pre-specified end-point in trials AE 97-01, 98-01, 98-02, 98-03, and 98-04. "It was only after the Sponsor had failed to demonstrate an effect of DPH on sleep latency in other studies, including 98-01, that a decision was made to elevate sleep duration, one of several pre-specified secondary sleep endpoints in each of these studies, to be a second primary endpoint in study 98-02...While the design of the phase 3 pivotal studies was adequate for assessment of sleep latency and pain, it was significantly flawed with regard to assessment of sleep duration. An important flaw was the awakening of patients at specified intervals during the first 2-3 hours after administration of study drug in order to assess pain. These forced awakenings could have altered the sleep pattern that would otherwise have been observed in patients had the awakenings not occurred and could have induced an artificial benefit that would not have been seen in un-awakened patients...It is possible that the DPH in the **combination allowed patients to return to sleep more rapidly** than those patients who did not receive DPH; i.e., the ibuprofen and placebo treatment groups...In other words, the apparent benefit of DPH in the combination may be an artifact of the forced awakening" (Dr. Jenkins letter from February 26, 2003).

I. Study design issues

To address this concern, the Sponsor submitted two additional analyses of the data from trials AE 98-01 and AE 98-02 to show that the overall finding that DHP contributes to sleep duration is a real finding and not an artificial result of the design of awakening subjects.

1. Data analysis for studies AE 98-01 and 98-02 of the number of patients that were awakened at 120 minutes and then were asleep at 150 minutes was submitted.

Table 1. Subjects awakened at 120 minutes and then asleep at 150 minutes.

AE 98-01	**Awakened at 120 minutes**	**Sleep resumed at 150 minutes (%*)**
IBU-DPH (n=122)	61	57 (93%)
IBU (n=118)	54	48 (89%)
AE 98-02		
IBU-DPH (n=119)	95	87 (92%)
IBU (n=123)	72	64 (89%)

*Based on those awakened at 120 minutes

(Sponsor's submission Table #1).

Based on this analysis, the Sponsor concluded that awakening patients at specific intervals had no effect on their continuing sleep because the percentage of subjects who went back to sleep and were asleep at 150 minutes was similar between ibuprofen and the combination groups. Therefore, the Sponsor concluded that any difference in sleep duration that occurred after the subjects went back to sleep could only be contributed to by either drug.

Reviewer's comments:

- *This limited re-analysis provided little new information to address the impact that awakening may have had on sleep duration and does not answer the question whether or not awakening patients at different times (i.e. 90 and 120 minutes) affected their overall sleep duration. In trial 98-01 the proportion of patients who were awakened at 120 minutes was slightly higher than 50% in the each group. It is unknown what happened to the remainder of the patients. Were these patents awake from the beginning of the study, or from being awakened at 90 min.? Only a subset of patients that were awakened at 120 min. and went back to sleep at 150 min.(roughly half sample size) was included into the estimation of sleep duration after 150 min.*
- *The re-analysis does not explore the sleep latency at 120 min. among the subjects awakened at 90 min. This analysis was performed by a statistician*

(See statistical review by Dr. Laura Lu) and showed that proportion of patients who were awakened at 90 minutes and then were asleep at 120 minutes is different between treatment groups. It favors the combination group and suggest again that the apparent benefit of DPH in the combination on sleep duration may be an artifact of the forced awakening and may favor the particular pharmacokinetics of DPH.

2. The sleep duration was then analyzed for those subjects who were asleep at 150 minutes which suggested to the Sponsor that the combination group performed better than the ibuprofen group.

AE 98-01	Sample Size	Mean Duration of Sleep *	p-value
IBU-DPH (n=122)	76	3.62	
IBU (n=118)	67	2.97	0.03
AE 98-02			
IBU-DPH (n=119)	97	2.96	
IBU (n=123)	78	2.37	0.03

(Sponsor's submission Table #2).

Reviewer's comments:

- *Results came from a partial dataset (those patients who were asleep at 150 min.). It is not clear which time point is counted as the starting point of sleep by patients (before or after being awakened); therefore the assessment of sleep duration may be influenced by both awakening effect and drug effect.*

- *These re-analyses do not allow one to answer the primary question of whether awakening had an effect on sleep duration that favored one group over the other based on the existing study data. To do this, one would have to compare groups of patients randomized to either be awakened or not awakened and assess the effect awakening had on overall sleep duration.*

II. Categorical data

The second concern raised by Dr. Jenkins was that "the methods utilized by the Sponsor for collecting data on sleep duration and the methods for data analysis were flawed. The Agency would normally expect that patient-reported data on sleep duration would be captured as the number of hours (including partial hours) slept expressed and analyzed as a continuous variable. WCH chose instead to capture the data in arbitrary categories (e.g., <5 hours of sleep, 5 to 6 hours, 6+ to 7 hours). This transformation of continuous data into categories has the potential to result in data analysis that are not meaningful or interpretable."

In response to that statement the Sponsor further partitioned the <5 hour sleep category into hourly categories using the time to rescue medication as an indication of when a subjects sleep ended and the sleep latency time (as observed by the nurse) as an indication of when it began. Sleep duration was then estimated as the duration between these two times.

Reviewer's comments:

- *While this approach seems to be acceptable, it does not help to address the question of whether the method of data analysis impacted the final conclusions regarding sleep duration.*

D. Efficacy Conclusions

The Sponsor failed to demonstrate significant contribution of DPH component to the efficacy of the proposed combination product in both pivotal studies. The re-analyses did not provide the substantial evidence of the contribution of DPH to sleep duration.

The Sponsor's most recent submission did not resolve the questions whether or not artificial awakening of subjects lead to bias in comparing sleep duration, and therefore the concern remains that the apparent benefit of DPH in the combination may be an artifact of the forced awakening.

VII. Integrated Review of Safety

There is no new safety data.
See original clinical reviews

VIII. Dosing, Regimen, and Administration Issues

See original clinical reviews

IX. Use in Special Populations

See original clinical reviews

X. Conclusions and Recommendations

A. Conclusions

Submitted analyses of data from two pivotal trials AE 98-01 and 98-02 do not answer the deficiencies of the approvable letter and does not eliminate possible bias introduced by the study design.

The main remaining concern is whether or not artificial awakening biases results of both studies favoring the combination over ibuprofen alone.

Another concern is related to the study population that did not have sleeplessness, but pain, therefore may not be representative of the population for which the drug is intended to be used. It is currently unclear what would be considered a clinically meaningful increase in sleep duration in such a population without sleeplessness problems.

To put these re-analyses in proper perspective, it is important to remember that the original reviews by primary reviewers, the consults, and Dr. Jenkins indicate that sleep duration is not the only concern that needs to be addressed. One of the other concerns is whether DPH decreases the noted analgesic effects of ibuprofen. However, the Sponsor does not address this concern in their current submission.

1. The combination performed statistically significantly worse in a pain endpoint than ibuprofen alone in AE-98-02 and numerically worse in AE-97-01 though the difference was not significant from a clinical standpoint.

2. The combination failed the sleep latency endpoint (AE-97-01) and cumulative percentage of subjects who were asleep at 60 minutes was numerically worse for the combination than for ibuprofen in AE-98-01 and AE-98-02.

The results support the concern that the combination is worse than ibuprofen alone. This was commented on in Dr. Jenkins' letter noting that "Such an unexpected

result, if repeated in the requested additional study, would raise serious questions regarding whether the addition of DPH adversely impacts on the beneficial effect of ibuprofen on sleep latency in its population of patients. This is a valid regulatory concern, given that 21 CFR 330.10(a)(4)(iv) clearly states that a combination of two or more active ingredients should not decrease the safety or effectiveness of one or more of the active ingredients."

B. Recommendations

- Based upon the evaluation by this reviewer, the submitted analysis of data from trials AE 98-01 and 98-02 does not provide an evidentiary basis needed for a favorable regulatory action.

- Additional study with the sleep duration as a primary endpoint is a study design which could generate data to support the Sponsor's proposed claims; artificial awakening could introduce bias. The study could be designed as a partial factorial and include three arms: ibuprofen, combination and a placebo.

- Since there are ongoing concerns that DPH may adversely impact the analgesic characteristics of ibuprofen, sleep latency (viewed as a surrogate for pain relief) needs to also demonstrate a treatment response consistent to that for sleep duration

- A dental model could be acceptable despite the lack of sleeplessness in that population.

- Sponsor is strongly encouraged to discuss the study design with the Division prior to proceeding with the study.

Tatiana Oussova, M.D., M.P.H.

James Witter, M.D., Ph.D.

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ON ORIGINAL

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/s/

Tatiana Oussova
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MEDICAL OFFICER

James Witter
12/11/03 03:34:24 PM
MEDICAL OFFICER
Concur

Brian Harvey
12/12/03 09:52:45 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: 7 August 2002

FROM: Lee S. Simon, M.D., Division Director, HFD-550

SUBJECT: NDA 21-393 and NDA 21-394 (ibuprofen 200mg/diphenhydramine 25mg fixed combination)

INDICATION: Relief of occasional sleeplessness when associated with — — minor aches and pain

People who suffer pain occasionally suffer sleeplessness. This sleeplessness is more common with accompanying nighttime pain. Conditions such as muscle soreness, sprains, strains, arthritis, headaches, and outpatient surgical procedures are typically painful events that may interfere with sleep. Analgesics usually ameliorate the painful conditions; however, either residual pain or recurring pain may still be a factor leading to sleeplessness. Since ibuprofen's pharmacokinetic/pharmacodynamic profile is indicative of fast pain relief, there is reason to believe that fast pain relief would shorten the time to falling asleep (latency). OTC antihistamines, including diphenhydramine, take time to reach peak plasma concentrations thus, they are most effective when taken in anticipation of sleeplessness. It is not unreasonable that diphenhydramine in combination with ibuprofen would be beneficial and would increase sleep duration. Consequently a fixed combination of ibuprofen 200mg and diphenhydramine HCl 25mg, typically dosed as 2 pills intended for use at bedtime was developed and has been evaluated in a clinical program.

There is a large experience with both ibuprofen and diphenhydramine, which have been marketed throughout the world as single-ingredient products. Ibuprofen is marketed worldwide as a pain reliever and is available OTC in most countries. Diphenhydraminine is marketed globally primarily as an antihistamine for symptoms of allergy, and secondarily, as a sleep aid. Its regulatory status varies (RX or OTC) depending on the country. Ibuprofen in combination with diphenhydramine has not been marketed either domestically or outside the United States.

The submitted studies in NDA 21-393 and NDA 21-394 demonstrate no new safety concerns for the use of ibuprofen 400mg/diphenhydramine 50mg fixed combination medication (2X 200 mg ibuprofen/ diphenhydramine 25 mg) in the relief of occasional sleeplessness when associated with — minor aches and pain. However, the submitted studies in NDA 21-393 and NDA 21-394 are not sufficient to establish efficacy for the use of ibuprofen 400mg

ibuprofen/diphenhydramine 50mg fixed combination medication in relieving occasional sleeplessness when associated with minor aches and pain: specifically the difference in effect on sleeplessness of the fixed combination compared to ibuprofen monotherapy is not statistically and clinically significant. Neither Study AE-97-01, AE-98-01, nor AE-98-02 demonstrates a statistically nor a clinically significant contribution of the diphenhydramine component of the proposed combination drug product in the oral surgery acute pain model.

The totality of the evidence suggests that this product is approvable with the requirement for one study to demonstrate the benefit of the combination product over ibuprofen alone on both sleep latency and sleep duration. Suggestions for a trial design are included in the approvable letter.

cc:
Archival /NDA 21-393
HFD- 550/Div. Files

Initialed by: lls
Final: lls/August 7, 2002
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/s/

Jane Dean
8/7/02 12:15:22 PM
CSO

Lee Simon
8/7/02 12:43:37 PM
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Division Director Memo

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

Date: August 7, 2002

From: Charles J. Ganley, M.D.
Director, Division of Over-the-Counter Drug Products (HFD-560)

To: NDA #21-393 and #21-394

Subject: Advil PM Liquigels [NDA #21-393] (ibuprofen 200 mg/diphenhydramine HCl 25 mg)
Advil PM Caplet [NDA #21-394] (ibuprofen 200 mg/diphenhydramine citrate – mg)

Sponsor: Wyeth Consumer Healthcare (WH) [formerly Whitehall Robbins (WR)]

Summary

1. The sponsor has demonstrated that the combination product and ibuprofen alone are significantly better than placebo for the sleep latency and duration endpoints.
2. Study 98-01 failed to establish that the combination is superior to ibuprofen alone for the primary endpoint of cumulative percentage of subjects asleep at one hour (sleep latency).
3. In study 98-02, the primary endpoint for sleep latency trends strongly in the wrong direction ($p = 0.1$ in favor of the ibuprofen component) which is inconsistent with the original hypothesis of this study. This result cannot be ignored and impacts on how the sleep duration endpoint should be interpreted. Ibuprofen/DPH is better than ibuprofen for sleep duration ($p = .009$ using the CMH modified ridit method).
4. The only study to evaluate DPH alone (study 97-01) does not suggest any benefit of DPH for sleep and pain endpoints compared to placebo in this population of subjects.
5. The results for the sleep duration endpoint appear to be consistent, except for the magnitude of effect, for study 98-01 and 98-02.
6. The pivotal study (98-02) does not convincingly demonstrate that the observed improvement in sleep duration for the combination product over ibuprofen can be attributed to the diphenhydramine (DPH) component. Taking into account the results of the sleep latency endpoint, the results for sleep duration could also be explained by a bias attributable to the waking of patients to assess pain at 90 and 120 minutes after ingestion. The contribution of DPH may only be apparent when a subject is awoken from sleep (it helps them get back to sleep). It is difficult to exclude this as a reason for the results observed in the study. Consequently, the sponsor has failed to provide adequate evidence that the combination product is significantly better than the individual ibuprofen component.
7. The sponsor submitted a bioequivalence study comparing the Advil PM Liquigel to the Advil PM caplet. The clinical efficacy studies were conducted with the Liquigel formulation. The comparative bioavailability of the DPH component does not appear to be a concern. The Tmax for the ibuprofen component in the caplet is 2.2 hours compared to approximately 1 hour in the liquigel. The clinical implication of this difference requires further discussion in view of the results for the sleep latency and sleep duration endpoints.
8. There do not appear to be any safety issues related to the combination of these ingredients.

9.

10. If ibuprofen is superior to ibuprofen/DPH for primary sleep endpoints, then ibuprofen/DPH should not be considered an appropriate combination for OTC marketing.

Recommendations

1. The sponsor should conduct a randomized, double-blind, multi-center, single dose, parallel arm, placebo controlled trial in subjects with pain who are unable to sleep.
   - The study should demonstrate that the combination is more effective than the individual components for duration of sleep.
   - The measure of sleep duration should provide for some mechanism to validate the accuracy of the measurement.
   - Subjects should not be awoken during the study to assess pain.
   - Sleep latency and other sleep endpoints should be measured. It is not necessary to measure pain.
   - The Division of Neuropharm should be involved in discussions of the protocol design.
   - When evaluating this study, the results for sleep duration should not be inconsistent with the results for other sleep endpoints [1], especially the measure of sleep latency.
   - If the sponsor is able to successfully conduct this study within the parameters outlined above, then the data in the current submission would serve as supportive information.
2. Before embarking on another trial, additional analysis should be conducted on the data in study 98-02 to further assess why there are inconsistencies in the results of the sleep endpoints.

Background

Wyeth Consumer Healthcare submitted NDA # 21-393 (liquigel) and 21-394 (caplet) for an analgesic and sleep aid combination product containing ibuprofen and diphenhydramine. The PDUFA goal date is August 16, 2002. The sponsor had numerous meetings with the agency [2] dating back to 1996. The interactions with the sponsor led to various recommendations by the agency on the development program.

- Two adequate and well-controlled trials were necessary. They had to show that the combination beats the two individual components and each component contributes to the combination. A full factorial trial needed to be conducted in the target population. [7/8/96]
- The relative efficacy of different combinations of the ingredients needs to be conducted. Studies should be conducted in patients with aches and pains and another in a post-operative pain or dental pain model. [6/23/97]
- After completion of a pilot factorial study, it was decided that a partial factorial trial was acceptable to show that the combination performed better than ibuprofen alone for sleep in patients with pain. Sleep latency, duration of sleep and sleep quality are the efficacy parameters to be evaluated. The agency preferred two studies to clearly establish efficacy. The transient insomnia model with phase advancement is not considered reliable but the agency recognized there might be no other way to evaluate sleep and pain. [8/4/98]
- In a letter from WH to the agency [1/13/99], they note that the following agreement were reached:
  - A partial factorial study is recommended to show that the combination performs better than ibuprofen alone (studies 98-01 and 98-02);
  - The agency would prefer two studies but would consider one strong dental pain study and data from the pilot study;
  - The primary endpoints in all efficacy studies are the cumulative proportion of subjects asleep at 60 minutes for sleep efficacy and SPRID at 120 minutes for pain efficacy. Sleep latency, duration of sleep and quality of sleep are secondary parameters;
  - A dose response study was needed (2 Advil PM vs. 1 Advil PM);
  - —
  - Bioavailability studies were needed.

[1] They could show no difference or trend in the same direction
[2] HFD-550 and HFD-560

Discussion of Results

Safety

In reviews by Dr. Neuner and Dr. Karwoski, there do not appear to be any significant safety issues related to the co-use of the ingredients. There were no specific recommendations for labeling outside of the current labels for each ingredient.

Efficacy

The primary studies to evaluate efficacy were studies 97-01, 98-01 and 98-02. They were conducted in that order. Study 97-01 was a full factorial, pilot study. Although it is not explained in the past minutes of meetings and teleconferences between WR and the agency, at some point it was decided that a partial factorial study was acceptable to establish that the combination was superior to ibuprofen alone. There was no longer a necessity to compare the combination to diphenhydramine for any of the sleep parameters.[3] All three studies were single dose using an oral surgery pain model. There were dual primary efficacy endpoints specified in the original protocols, one for sleep latency (proportion asleep at 60 minutes) and one for pain (SPRID [4]). As noted previously in the background information, the agency also wanted an evaluation of sleep duration and quality of sleep. They were included as secondary endpoints.

In study 97-01, it is worth noting that DPH alone did not show any effect on the sleep and pain endpoints. In fact, for some endpoints it performed numerically worse than placebo. The sleep latency endpoint is interesting in that there is no difference between ibuprofen and ibuprofen/DPH for the percentage of subjects asleep at 180 minutes. For the median sleep latencies, however, there are numerical differences that favor ibuprofen (25 minutes) over ibuprofen/DPH (36 minutes) with placebo (30 minutes) coming in somewhere in-between.[5]

The results from study 98-01 caused the sponsor to reconsider the wisdom of the primary sleep endpoint of sleep latency for study 98-02. The results of study 98-01 showed that ibuprofen/DPH was not different from ibuprofen alone for the primary endpoint of sleep latency defined as the cumulative percentage of subjects asleep at 60 minutes (ibuprofen/DPH 63.9% vs. ibuprofen 64.4%, $p = 0.915$). The results for sleep duration, however, suggested a significant difference in the sleep duration en dpoint in favor of ibuprofen/DPH compared to ibuprofen alone (mean sleep score 2.25 for ibuprofen vs. 2.83 for ibuprofen/DPH, $p = .042$ using the Cochran Mantel Haenzel using modified ridit). Study 98-02 was already completed but the data had not been unblinded. In an amendment to the IND, the duration of sleep endpoint was elevated from a secondary endpoint to a primary endpoint for study 98-02. [6] The new analysis specified a sequential test that analyzed the sleep duration endpoint before the sleep latency endpoint.

The results for study 98-02 show a favorable effect of the combination over ibuprofen alone for sleep duration (mean sleep score 2.61 for ibuprofen/DPH vs. 1.98 for ibuprofen, $p = .009$ Cochran Mantel Haenzel using modified ridit). The cumulative percentage of subjects asleep at 60 minutes was not significantly different but trends strongly in favor of ibuprofen alone (75.6% for ibuprofen vs. 66.4% for ibuprofen/DPH, $p = 0.11$). The pain primary endpoint also significantly favored ibuprofen over ibuprofen/DPH ($p = 0.05$) but the actual scores (7.03 for ibuprofen/DPH vs. 7.81 for ibuprofen) are similar and are markedly different from placebo (0.26).

It is important to note that the sleep duration endpoint was not a measured value. Subjects were simply asked how long they slept and there was no attempt to validate the accuracy of their estimate. According to Dr. Andreason, this historically has been an accepted methodology for measuring this endpoint. This measurement, however, is different from other sleep studies in that subjects were awoken (if they were asleep) at 90 and 120 minutes after receiving medication for the assessment of pain. It is unclear how waking the subject impacted on their ability to get back to sleep and then maintain sleep. So, it is unclear what bias if any this had on the results of this endpoint.

The development program evolved from one attempting to establish that ibuprofen/DPH is superior to the individual components for sleep latency to one where each component contributes

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[3] Presumably this was decided based on the results from 97-01. Diphenhydramine performed miserably relative to placebo and the active treatments for the sleep and pain endpoints.

[4] Sum of PRID (pain relief scores combined with categorical pain intensity difference scores) scores

[5] no p value was calculated

[6] At the request of the agency, WH submitted information on 5/8/02 regarding the blinding of data, data access prior to unblinding, process for unblinding the data and the assignment of treatment codes to the data. Everything appears to have been done in an acceptable manner. The only aspect that is bothersome is the failure to recalculate the sample size based on a projected treatment effect for sleep duration. In not doing so, the sponsor took on a risk that seems unwarranted under the circumstances.

something for different facets of sleep (i.e. sleep latency and sleep duration). In the new development scheme, ibuprofen contributes to sleep latency and sleep duration and DPH contributes to sleep duration. The sponsor would have to establish that the combination is superior to the DPH for sleep latency and superior to ibuprofen for sleep duration. Under this construct, the comparison of ibuprofen/DPH to ibuprofen for sleep latency and to DPH for sleep duration should be null or trend in favor of ibuprofen/DPH. This would be acceptable if the contribution of each component relative to the combination was demonstrated. Unfortunately, the inconsistency of the results within study 98-02 lead to serious concerns about the contribution of DPH. The sleep latency results in study 98-02 trend strongly in favor of ibuprofen over ibuprofen/DPH. In view of this finding, the results from the sleep duration endpoint are surprising. It suggests that although subjects on ibuprofen alone were able to get to sleep more readily relative to the combination, they were not able remain asleep [7]. It may be that the contribution of DPH is only observed on this endpoint because the subjects were awoken from sleep at 90 and 120 minutes. DPH helped them get back to sleep. It is not evident that the effect would be observed had the subjects been allowed to continue sleeping. There is no other sleep endpoint that supports the contribution of DPH. The inconsistency of the results of the primary endpoints is a sufficient basis for not granting approval of the application and requiring that another trial be conducted.

There were some issues raised during the review of study 98-02 related to the analysis and measurement of the sleep duration endpoint. First, a Chi Square test or CMH test using general association was considered but is less desirable because it does not take advantage of the ordering of the categories. Second, there was a concern that the truncation of the data in the extreme categories could introduce bias into the test. This is a concern because of the number of subjects in each of the extreme categories. A simulation test to assess this possibility suggests that this type of transformation can inflate type I error. This is a hypothetical situation and it is difficult to determine the impact on the current situation. The fact that study 98-01 and 98-02 both showed similar results makes this hypothetical less likely but it should be reevaluated in designing future studies. Third, the accuracy of the measurement of sleep duration cannot be validated. This was a secondary endpoint initially. Because there was some expectation at the start of the study that there would be some consistency in the results of the endpoints, this should not be to be an issue. The fact that it is now the primary measure for determining the approval of the application (without any other supporting endpoints) it is reasonable to raise this issue for further discussion.

Other Studies

Study 98-03 suggests a possible dose response for ibuprofen 400 mg/DPH 50 mg versus 200/25 mg for the endpoint of sleep duration. This data needs to be analyzed with the CMH using modified ridit scores. There was no difference between treatment groups in the cumulative percentage asleep at 60 minutes.

For study 98-04 (subjects with tension headache),

The sponsor conducted a bioequivalence study (AE-00-10) to support the caplet formulation application (#21-394). The Cmax for DPH with the caplet formulation was higher than the liquigel formation resulting in the 90% confidence interval falling outside the upper limit of acceptability (127%). It is unlikely that this has any impact the safety and efficacy of the caplet relative to the liquigel formulation. The Cmax and AUC for ibuprofen were within the accepted limits for bioequivalence. The Tmax for ibuprofen differed for each formulation (2.18 hr. for the caplet vs. 0.95 hr. for the liquigel). Normally, this would not be of any concern when assessing the efficacy or safety of the products. In this

[7] In study 98-02, approximately 75% of ibuprofen subjects were asleep at 60 minutes but 34% slept < 5 hours. The < 5 hour category is where the ibuprofen and ibuprofen/DPH separate out. The fact that ibuprofen looks better than ibuprofen/DPH (strong trend but not statistically different) for sleep latency makes it surprising that they are so different for the < 5 hour category.

case, however, the sponsor attributes the difference in sleep latency between ibuprofen/DPH and ibuprofen alone observed in study 98-02 to the difference in Tmax between those two products. Consequently, if Tmax influences the sleep latency efficacy endpoint, it is unclear that the caplet would have the same clinical effect on the sleep latency endpoint as the liquigel. Thus, it is not clear they can be considered bioequivalent.

Sponsor Response to Issues

The sponsor submitted material dated May 17, 2002 and July 9, 2002 to address concerns raised in discussions with the sponsor during the review process. Their comments were taken into consideration in the writing of this memo. I will only address the opinions expressed by Dr. and Dr. Ph.D.[9] included in the July 9th submission.

- The discussion of the data provided by Dr. does not address the inconsistency in the results of the sleep latency endpoint and sleep duration endpoint for study 98-02. Consequently, it adds little to the decision process regarding the approval of the application.
- The information provided by Dr. does little to assuage any concerns regarding the duration of sleep endpoint. In his report, Dr notes that it is rare to have "some sleep less than 4 – 5 hours". In a population based study, less than 5% of subjects report sleeping less than 5 hours and less than 5% report sleeping more than 9 hours. In the 98-02 study, greater than 20% of both drug groups had less than 5 hours of sleep. Greater than 10% of the ibuprofen alone group had greater than 9 hours of sleep. Consequently, it is unclear that the measure of sleep duration used in previous sleep studies provides a precise valid measure in the dental pain studies.

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/s/

Charles Ganley
8/7/02 10:37:43 AM
MEDICAL OFFICER

NDA 21-393

Neuropharmaceutical Addendum to Review

MEMORANDUM

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

DATE: August 5, 2002

FROM: Paul J. Andreason, M.D.
Medical Officer, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 21-393, for Advil PM (ibuprofen 200 mg/diphenhydramine 25 mg) as a nighttime sleep aid and analgesic

TO: File, NDA 21-393
[Note: This memo should be filed with the 10-16-01 original submission of this application.]

This memo is an addendum to my original review of this application, and the reader is referred to that document for my more complete comments. In my review, I reported a p-value for study 98-02 that I subsequently learned was incorrect.

I had reported a p-value of 0.242 for the comparison of the IB/DPH combination to IB alone on the variable "sleep duration." Dr. Kun Jin, the statistical team leader reported corrected p-values for this contrast in a 6-5-02 memo. In particular, both the CMH test and a simple chi-square test gave a p-value of 0.10. He argued in his memo that the protocol specified CMH row mean test, which gave a p-value of 0.009, is not appropriate because of the potential for bias. Even the corrected p-values do not reach the usual level of significance needed to declare this finding positive, and so my conclusion about this study is unchanged. Further, even if the study had been positive on this outcome, it was one of two primary endpoints for that trial, the second being sleep latency. IB alone actually was numerically superior to IB/DPH (76% vs 66%).

Thus I do not change the conclusions of my original review.

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/s/

Paul Andreason
8/5/02 03:58:59 PM
MEDICAL OFFICER

Thomas Laughren
8/6/02 08:36:09 AM
MEDICAL OFFICER

MEDICAL OFFICER GLOBAL SAFETY REVIEW
Division of Over-The-Counter Drug Products

NDA: 21-393 and 21-394

NAME: Advil PM Liqui-Gels; Advil PM Caplets

SPONSOR: Wyeth Consumer Healthcare

TYPE OF SUBMISSION: Commercial Pharmaceutical

DATE OF SUBMISSION: October 16, 2001

DATE OF REVIEW: May 10, 2002

REVIEWER: Rosemarie Neuner, MD,MPH

Executive Summary

Wyeth Consumer Healthcare, the manufacturer of Advil Liqui-Gels and Caplets (ibuprofen 200 mg) has filed these NDAs in the hope of obtaining marketing approval for two formulations of a combination analgesic/sleep-aid product comprised of 200 mg ibuprofen with 25 mg diphenhydramine that are to be called Advil PM Liqui-Gels (ibuprofen 200 mg/ diphenhydramine HCL 25 mg liquid filled capsule) and Advil PM Caplets (ibuprofen 200 mg/diphenhydramine citrate 38 mg tablet). Although ibuprofen was introduced to the OTC analgesic market in this country in 1984 via the NDA review process, diphenhydramine is a Category I monograph product whose marketing oversight has been provided by 21 CFR Part 338 since 1989. These proposed combination sleep-aid/analgesic products would have the following dosing directions for adults 12 years and older: 2 liquigels/caplets as needed for the relief of occasional sleeplessness associated with , minor aches and pains

Safety information, from the clinical safety database generated from 4 biopharmaceutical studies, 106 citations identified from a worldwide literature search including drug overdose and abuse potential data obtained from the Drug Abuse Warning Network (DAWN) and the American Association of Poison Control Centers (AAPCC), and postmarketing adverse event reports as related to the individual drug ingredients of the proposed combination product collected by both the sponsor's and the FDA's drug monitoring safety databases are reviewed and discussed in this global safety review. Additionally, there is a consultative safety review dated April 4, 2002 that was done at the request of this reviewing division by the Office of Drug Safety's Division of Drug Risk Evaluation (HFD-430) which assessed the potential risk for drug-drug interactions occurring when diphenhydramine and ibuprofen are concomitantly administered. Based on the safety information listed above and the safety database generated by the 6 single-dose and 1 multi-dose clinical efficacy studies discussed by the medical reviewer from HFD-550 in the review dated March 6, 2002 that were submitted in support of these applications by the sponsor, no new or unexpected adverse events associated with the use of diphenhydramine and ibuprofen alone or in combination were identified.

Final Recommendation:

Review of the global safety database submitted by the sponsor in support of this combination sleep-aid/analgesic product's safety profile was consistent with what is already known about diphenhydramine and ibuprofen, and did not reveal any new or unexpected adverse events or drug-drug interactions for this combination drug product. Although analysis of the drug abuse overdose data also did not identify the existence of major risk for both abuse/misuse of this combination product, the potential for such problems could rise due to increased accessibility once it is introduced to the OTC market. Based on the information reviewed, the current consumer safety warnings for both diphenhydramine and ibuprofen are appropriate and do not need to be changed or updated for this combination sleep-aid/analgesic product.

II. Table of Contents

I. Introduction and Background

This medical officer review is a global safety profile of the combination drug products Advil PM Liqui-Gels (ibuprofen 200 mg /diphenhydramine HCL 25 mg liquid filled capsule) and Advil PM Caplets (ibuprofen 200 mg/diphenhydramine citrate 38 mg tablet) that was done as part of the Agency's overall review of Wyeth Consumer Healthcare's submissions, NDAs 21-393 and 21-394 respectively for which the sponsor has requested the indication of analgesic/sleep-aid. (Note: The sponsor of these NDAs was formerly known as Whitehall Robins Healthcare.) Ibuprofen, a member of the nonsteroidal anti-inflammatory class of drugs, has been available in the U.S. as an over-the-counter (OTC) analgesic since 1984. It is indicated for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for the reduction of fever. The recommended dose of OTC ibuprofen is 200 mg tablets/caplets every 4-6 hours. If symptoms persist, 2 (400 mg) tablets/caplets may be taken. The maximum total daily dosage of OTC ibuprofen is 1200 mg, or 6 tablets/caplets in a 24-hour period. Diphenhydramine, a first generation member of the ethanolamine class of antihistamines, has been marketed as an OTC sleep aid product in this country under 21 CFR Part 338 the Final Monograph for Nighttime Sleep-Aid Drug Products for OTC Human Use (publication date February 14, 1989). Products containing diphenhydramine are labeled to help a consumer to fall asleep if the individual has difficulty falling asleep. The recommended dose for diphenhydramine hydrochloride is 50 mg at bedtime if needed or as directed by a physician.

In support of this application, the sponsor has submitted for Agency review the following safety information much of which was contained in a safety update submitted to the pending NDA applications by the sponsor on March 21, 2002:

1. The safety database containing 2,360 subjects generated from 4 biopharmaceutical studies, 6 single-dose and 1 multi-dose efficacy studies and 2 ancillary studies contained in these combined submissions (Study Numbers: WM-716, AE-97-02, AE-97-09, AE-00-10, AE-97-01, AE-97-05, AE-98-01, AE-98-02, AE-98-03, AE-98-04, AE97-08, CRD 85-31, and AE-95-01).
2. The results of a worldwide literature search of published clinical safety reports utilizing MEDLINE, EMBASE, EMBASE Alert, Biosis Previews, Derwent Drug File and SciSearch Cited References as follows:
    a. Diphenhydramine citrate/hydrochloride in adults only for the period from 1966 through December 2000.
    b. Ibuprofen for the period from 1995 through December 2000.
3. Reports of potential drug abuse and overdose obtained from the following sources:
    a. Drug Abuse Warning Network (DAWN) Emergency Department Reports for the period from 1994 through 1999.
    b. Drug Abuse Warning Network (DAWN) Medical Examiners for the period from 1996 through 1999.
    b. American Association of Poison Control Center (AAPCC) for the period from 1995 through 1999.
4. A summary of postmarketing surveillance reports collected by the following sources for both single ingredients contained in this proposed compound, diphenhydramine and ibuprofen and when :
    a. Whitehall-Robins Product Safety Surveillance Department for the period of August 1982 through October 1996 for diphenhydramine and from February 1,1999 to February 28, 2001 for ibuprofen.
    b. FDA's Spontaneous Reporting System (SRS) for the period of January 1, 1968 through October 31, 1997 for diphenhydramine.
    c. FDA's Adverse Event Reporting System (AERS) for the period of November 1, 1997 through September 30, 2000 for diphenhydramine and from May 22, 1999 through September 30, 2000 for ibuprofen.

d. Whitehall-Robins Product Safety Surveillance Department's database for case reports of adverse events attributed to co-administration of both ingredients (time period undefined).

Since a review of the clinical trial safety database generated from the 6 single-dose and 1 multi-dose efficacy studies is contained in the medical officer's review dated March 6, 2002 by Dr. Lucious Lim of HFD-550, this global safety will focus on the clinical data generated by the 4 biopharmaceutical studies, the 2 supportive ancillary studies, and the remaining 3 sources of safety data as listed above.

II. Safety database generated from the 4 biopharmaceutical studies (WM-716, AE-97-02, AE-97-09, and AE-00-10) and the 2 supportive ancillary studies (CRD 85-31 and AE-95-01).

II.A. Description of Patient Exposure:

The overall safety database submitted in support of this application was generated from the 2,360 subjects enrolled in clinical studies that were conducted by the sponsor. [Note: The sponsor did not include the patients enrolled in the 2 ancillary studies (Studies CRD 85-31 and AE-95-01) when they calculated this number since Study CRD 85-31 was conducted by another sponsor and did not have complete data sets, while patients enrolled in Study AE-95-01 were only exposed to ibuprofen or placebo but not to the combination product under review.) The following table, Sponsor's Table 1, shows the distribution by drug exposure of these 2,360 subjects.

Sponsor's Table 1 – Distribution of Clinical Studies Safety Database Study Population by Drug Exposure

Type of Study	Total	2 IBU/DPH	1 IBU/DPH	IBU 400	DPH	Placebo	Tylenol PM
Multiple-dose	974	323	158	0	0	167	326
Single-dose	1267	524	120	324	31	268	0
Bioavailability	119	Cross-Over Studies					
Total	2360						

IBU= ibuprofen; DPH= diphenhydramine

The safety data generated from the 2,241 patients who were enrolled in the 1 multi-dose and 6 single-dose clinical efficacy studies was discussed and commented on by the medical officer who reviewed these studies, and thus will not be repeated here. (Refer to medical officer's review by Dr. Lucious Lim dated March 6, 2002.) The remaining 119 patients were enrolled in the 4 bioavailability studies. All 4 of these studies were dual-phased, crossover studies in which 117 subjects received a single dose of the combination of ibuprofen 400 mg/diphenhydramine 50 mg, 50 subjects received a single dose of ibuprofen 400 mg, and 48 patients received a single dose of diphenhydramine 50 mg. Table 2 shown below lists the disposition of these pooled study subjects. (Note: A further description and the agency's analysis of the data generated from these pharmacokinetic studies can be found in the review by the Division of Biopharmaceutics [HFD-780] of this application).

Table 2 – Disposition of Pooled Subjects Enrolled in the 4 Pharmacokinetic Studies (WM-716, AE-97-02, AE-97-09, and AE-00-10)

	All Subjects	
	Number	Per Cent
All Subjects Randomized	121	100%
Subjects Lacking Study Data	2	1.7%
Subjects Included for Safety	119	98.3%
Subjects Who Completed Both Phases of the Studies	113	93.4%
Discontinued Subjects	6	5.0%
Reason for Discontinuation:		
Adverse Event	1	0.8%
Voluntarily Withdrew	1	0.8%
Lost to Follow-Up	4	3.3%

II.B. Pooled Demographic Profile

The following table, Table 3, lists the demographic characteristics of the 119 subjects enrolled in the pooled pharmacokinetic studies

Table 3 – Demographic Summary of the Subjects Enrolled in the Pooled 4 Pharmacokinetic Studies (WM-716, AE-97-02, AE-97-09, and AE-00-10)

	All Subjects (N=119)	
	Number	Per Cent
Gender: Male	59	49.6%
Female	60	50.4%
Race: Caucasian	69	58.0%
Black	41	34.5%
Hispanic	8	6.7%
Other	1	0.8%
Age (yrs.): Mean	29.7	
Standard Deviation	7.8	
Median	28.0	
Range	(18, 45)	

Medical Reviewer's Comments *: Review of the demographic parameters for the population from the pooled pharmacokinetic studies reveals a skewed mean age of 28.0 years which is typical of these types of studies since they routinely use healthy, normal volunteers. The target population that would most benefit from this combination analgesic/sleep aid are older individuals with nighttime pain from arthritis. In order to generate the safety data necessary for this target subgroup population, the multidose study (Study AE-97-08) was designed to include an enriched population of patients over the age of 65 years. Two hundred sixty-seven (267) patients out of the total 974 (27.4%) entered in the multidose study were 65 years or older. Further discussion of this subgroup's adverse event experience while participating in Study AE-97-08 can be found in the medical officer's clinical study efficacy and efficacy review dated March 6, 2002.*

II.C. Safety Findings

II.C.1. Deaths and Serious Adverse Events

No deaths, serious adverse events, or hospitalizations were reported to have occurred in any of the 4 pharmacokinetic studies.

II.C.2. Dropouts Due to Adverse Events

Only 1 out of the 119 subjects (0.8%) enrolled in the 4 pharmacokinetic studies dropped out due to an adverse event while participating in the study. (Refer to the preceding table, Table 2.) The individual (Subject Number AE-97-02) was a 25 year old female who developed acute sinusitis after receiving ibuprofen 400 mg/diphenhydramine 50 mg which resolved without treatment. The adverse event was deemed unrelated to the study medication by the investigator.

II.C.3. Other Significant Adverse Events

A total of 37 out of the 119 subjects (31.1%) enrolled in the 4 biopharmaceutical studies reported having an adverse event. The highest incidence of adverse events was reported to have occurred by 28 individuals who took ibuprofen 400 mg/diphenphydramine 50 mg, followed by 10 subjects who took diphenhydramine 50 mg (21%), and 6 subjects who took ibuprofen 400 mg (12%). The following table, Sponsor's Table 4, lists in tabular format the most commonly reported adverse events which occurred at incidences of $\geq$ 2% in association with any of the 3 treatments during either phase of the 4 pooled pharmacokinetic studies.

Sponsor's Table 4 – Tabular Summary of the Most Commonly Reported Adverse Events With Incidences ≥ 2% Reported During Either Phase of the 4 Pooled Biopharmaceutical Studies.

Body System	Ibuprofen 400 / Diphenhyramine 50 (n=117)	Ibuprofen 400 (n=50)	Diphenhydramine 50 (n=48)
Nervous	11(9.4%)	2(4.0%)	5(10.4%)
Somnolence	4(3.4%)	2(4.0%)	3(6.3%)
Dizziness	5(4.3%)	0(0.0%)	1(2.1%)
Incoordination	0(0.0%)	0(0.0%)	1(2.1%)
Digestive	8(6.8%)	1(2.0%)	3(6.3%)
Abdominal Pain	3(2.6%)	0(0.0%)	2(4.2%)
Diarrhea	2(1.7%)	0(0.0%)	1(2.1%)
Nausea	3(2.6%)	1(2.0%)	2(4.2%)
Body as a Whole	9(7.7%)	0(0.0%)	2(4.2%)
Headache	2(1.7%)	0(0.0%)	1(2.1%)
Pain	4(3.4%)	0(0.0%)	0(0.0%)
Infection	0(0.0%)	0(0.0%)	1(2.1%)
Cardiovascular	2(1.7%)	0(0.0%)	1(2.1%)
Syncope	2(1.7%)	0(0.0%)	1(2.1%)
Skin	1(0.9%)	1(2.0%)	1(2.1%)
Rash	1(0.4%)	1(2.0%)	1(2.1%)
Urogenital	0(0.0%)	2(4.0%)	0(0.0%)
Dysmenorrhea	0(0.0%)	1(2.0%)	0(0.0%)
Vaginitis	0(0.0%)	1(2.0%)	0(0.0%)
Vulvovaginitis	0(0.0%)	1(2.0%)	0(0.0%)

** Cross-over designed trials wherein a subject could have AEs in different phases of treatment

As demonstrated in Sponsor's Table 4, the majority of the reported adverse events were related to the nervous system followed by the digestive system, body as a whole, cardiovascular system, skin, and urogenital system. The most frequently reported adverse events reported by subjects treated with ibuprofen 400 mg/diphenhydramine 50 mg were dizziness (4.3%), somnolence (3.4%), pain (3.4%), and abdominal pain (2.6%). In subjects treated with dihphenhydramine 50 mg the most frequently reported adverse events reported were somnolence (6.3%), abdominal pain (4.2%), and nausea (4.2%). For the ibuprofen 400mg treated subjects, the most frequently reported adverse event was somnolence (4.0%). (Note: A complete listing of all adverse events is shown in Sponsor's Table 14 which can be found in Appendix I at the end of this review.)

Sponsor's Table 5, shown below, lists the adverse events which were most frequently reported to have occurred during the biopharmaceutical studies by severity. Although the majority of adverse events for all 3 treatment groups were classified as mild to moderate in severity, the ibuprofen 400 mg/diphenhydramine 50 mg group had the highest number (5 reports) of severe adverse events which included 2 reports of syncope and 1 report of nausea as compared to the 2 other treatment groups which had none. (Refer to Sponsor's Table 5 listed below.) (Note: The other 2 severe adverse events reported by subjects treated with ibuprofen 400 mg/diphenhydramine 50 mg were dyspepsia [0.9%] and sinusitis [0.9%].) All of the severe adverse events reportedly resolved without further problems.

Sponsor's Table 5 - Tabular Summary of the Most Commonly Reported Adverse Events With Incidences ≥ 2% Reported During Either Phase of the 4 Pooled Biopharmaceutical Studies Listed by Severity of Event.

	2 Advil PM Liqui-Gels (n=117)			Ibuprofen 400 mg (n=50)			Diphenhydramine 50 mg (n=48)		
Adverse Experience	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Any	30	4	5	7	0	0	12	2	0
Headache	2	0	0	0	0	0	1	0	0
Pain	2	2	0	0	0	0	0	0	0
Infection	0	0	0	0	0	0	0	1	0
Abdominal Pain	3	0	0	0	0	0	2	0	0
Diarrhea	2	0	0	0	0	0	1	0	0
Nausea	2	0	1	1	0	0	2	0	0
Somnolence	4	0	0	2	0	0	3	0	0
Dizziness	3	2	0	0	0	0	1	0	0
Incoordination	0	0	0	0	0	0	1	0	0
Syncope	0	0	2	0	0	0	0	1	0
Rash	1	0	0	1	0	0	1	0	0
Dysmenorrhea	0	0	0	1	0	0	0	0	0
Vaginitis	0	0	0	1	0	0	0	0	0
Vulvolvaginitis	0	0	0	1	0	0	0	0	0

Medical Reviewer's Comments: *Examination of the above summarized data does not reveal any potential signal or new information regarding the safety profile of ibuprofen 400 mg/diphenhydramine 50 mg. In addition, it is similar to what was seen in the safety review of the clinical efficacy studies. (Refer to medical officer's safety review dated March 6, 2002 by Dr. Lucious Lim of HFD-550.) Although the 3 syncopal case reports were not provided to this medical officer for review, syncope is an adverse reaction that has been reported with the use of diphenhydramine. The current labeling warnings for diphenhydramine containing products carry multiple warning statements regarding the central nervous system effects of this drug.*

II.D. Ancillary Studies:

In support of this product's safety profile, the sponsor submitted summarized data of limited nature from 2 ancillary studies. The first trial, CRD 85-31, was a single-dose, double blind, placebo controlled, 4-arm, parallel group study conducted by another sponsor. This study was designed to evaluate the effectiveness of the combination of ibuprofen 200 mg/diphenhydramine 50 mg as a treatment for individuals with both pain and sleep disorders versus ibuprofen 200 mg, diphenhydramine hydrochloride 50 mg, and placebo. Since the sponsor of this NDA did not conduct this study, the protocol, data and case reports generated from it were unavailable. However, the sponsor did include the following table, Sponsor's Table 6, which lists the 7 adverse events reported by patients who participated in this study.

Sponsor's Table 6 – Tabular Listing of Reported Adverse Events From Study CRD 85-31

Patient Number	Treatment	Adverse Experience
Number 3	Diphenhydramine 50 mg	Chills; Fever
Number 54	Combination	Saw faces on closing eyes; Felt scared
Number 74	Ibuprofen 200 mg	Hallucinations
Number 88	Diphenhydramine 50 mg	Tachycardia
Number 211	Placebo	Generalized itching (after taking Percocet)

The second ancillary study, AE 95-01, was a multidose, placebo controlled study in 30 patients that was undertaken to define what effects, if any, ibuprofen has on sleep as measured by subjective and sleep laboratory polysomnography. (Note: Due to the paucity of information

submitted, i.e., the lack of a protocol, data sets, and case reports, little can be said about this study.) The sponsor reports in their narrative summary that there were only 3 adverse events all classified as mild in nature in the ibuprofen treatment group as follows: 1 case of skin irritation reported by 1 patient, and 1 case of abdominal pain and chest pain reported by another study subject.

Medical Reviewer's Comments: *The few adverse events seen in these ancillary studies are consistent with the adverse event profile of both diphenhydramine and ibuprofen.*

III. Published clinical adverse event reports and drug safety studies for:
A. Diphenhydramine citrate/hydrochloride in adults only for the period from 1966 through December 2000
B. Ibuprofen for the period from 1995 through December 2000

In support of this combination product's safety profile, the sponsor submitted a narrative summary comprised of 64 citations for the individual ingredients, diphenhydramine and ibuprofen, that they identified via a worldwide literature search utilizing the following 6 sources: MEDLINE, EMBASE, EMBASE Alert, Biosis Previews, Derwent Drug File and SciSearch Cited References. A listing of these references can be found at the end of this review in Appendix II.

III.A. Diphenhydramine citrate/hydrochloride :

Although diphenhydramine has been available on the OTC market for nearly 50 years, the sponsor's worldwide literature search yielded a total of 40 references in adults for the period from 1966 through December 2000. Since 4 of these citations (References 88-90, and 96) are case reports that discuss issues related to drug abuse and overdose situations due to diphenhydramine, they will be discussed with associated data submitted for review on these areas later in this review. References 1 through 6 described case reports of various dermatological disorders such as fixed drug eruptions, eczema, and contact dermatitis that were reported to have occurred following the use of either systemic or topical diphenhydramine containing products. Case reports of a variety of central nervous system effects such as tardive dyskinesia, dystonic reactions, and acute psychosis associated with the use of diphenhydramine were discussed in References 7, 12-14, and 17. References 8-11 and 15-16 reported the findings of clinical studies which evaluated the effects that diphenhydramine alone or in combination with alcohol had on psychomotor functioning and cognitive skills as compared to terfenadine, a variety of H1-antagonists, loratadine, and placebo. Ten articles (References 18-27) described various drug-drug interactions (i.e., potentiation of anticholinergic effects, and inotropic and chronotrophic effects on the heart) and pharmacokinetic reactions that involved diphenhydramine and the following drugs: para-aminosalicylic acid, antidepressants, oral contraceptives, pentaerythitol tetranitrate, nonsteriodal anti-inflammatory agents, warfarin, and metoprolol. There were also 2 articles (References 35 and 36) which described the results from double blind, placebo-controlled studies that evaluated the effects that diphenhydramine alone or in combination with quinidine, had on cardiac function as measured via EKGs and the QTc interval.

Seven (7) additional articles (References 28-34) were included in this section which described the findings from retrospective studies in clinical reproductive medicine and on lactation which investigated the association between birth defects and diphenhydramine. Diphenhydramine has been classified as a Category I drug under the monograph process since 1989. Thus, further discussion of these 7 articles is unwarranted since all predate the publication of the monograph.

Medical Reviewer's Comments: *Review of the above cited case reports and safety studies (References 1-27, 35, and 36) failed to reveal any new information regarding the safety profile of diphenhydramine. The most common side effects associated with this drug are related to the central nervous system (i.e., sedation, sleepiness, dizziness, disturbed coordination, etc...). Label warnings to consumers regarding anticholinergic and multiple central nervous system side effects associated with the use of diphenhydramine are a regulatory requirement for all products*

containing this drug. Based on these citations from the worldwide literature, there is no evidence to support changing or adding to the currently required consumer labeling warnings for diphenhydramine.

III.B. Ibuprofen

The sponsor's worldwide literature search yielded a total of 28 references for the period from 1995 through December 2000 concerning the use of OTC ibuprofen in adults. Since 10 of these citations (References 97-106) are case reports that discuss issues related to drug abuse and overdose situations due to ibuprofen, they will be discussed with associated data submitted for review on these areas later in this review. Another ten of these citations (References 42-48, 56, and 59-60) will not be discussed further since they are either abstracts (References 45 and 46) or involved non-OTC doses of ibuprofen (References 42-44, 47-8, 56 and 59-60). Another 4 citations (Reference 44, 53-5) which described allergic reactions in patients with histories of allergies to ibuprofen or other nonsteroidal anti-inflammatory drugs will not be discussed further since all OTC products containing ibuprofen are required to carry an allergy warning. Of the remaining 14 citations, References 37-41 described 5 studies which either directly (i.e., endoscopically) or indirectly (i.e., retrospective case or database reviews) assessed the risk for developing a gastrointestinal bleed while using OTC doses of ibuprofen as compared to other nonsteriodal anti-inflammatory drugs such as aspirin, naproxen and diclofenac. Another article (References 43) describe a case of leukocytoclastic vasculitis that occurred following the ingestion of OTC doses of ibuprofen. The sponsor also included 3 citations (References 49, 50, and 52) which reported drug interactions that occurred in patients who took OTC doses of ibuprofen and ciprofibrate (renal failure), tacrine (delirium), and gentamicin (renal failure and vestibular toxicity in a patient with cystic fibrosis.) Another citation (Reference 51) reported the results of a pharmacokinetic study that demonstrated that 1g of telmisartan did not interfere with the pharmacokinetic profile of ibuprofen when given at OTC doses. References 57 and 58 describe 2 cases of hepatotoxicity associated with the use of OTC-doses of ibuprofen.

The remaining 4 articles describe pharmacovigilance studies (References 61-4), 3 of which (References 61-2, and 64) demonstrated that the incidence of gastrointestinal adverse events associated with the use of low-dose ibuprofen was less frequent as compared to paracetamol, aspirin, diclofenac, or naproxen, or comparable to that of placebo. Reference 63 was an overall safety review of OTC ibuprofen in which the authors calculated that an adverse reaction to this drug occurs once for every 5 million (United Kingdom) to 25 million (United States) tablets sold, while 1 death occurs for every 23 billion tablets sold.

Medical Reviewer's Comments: *Review of the above cited case reports and safety studies failed to reveal any new information regarding the safety profile of ibuprofen. The most common side effects associated with this drug are related to the gastrointestinal system. The current label for ibuprofen products contains a consumer warning regarding the risk for gastrointestinal bleeds, and the concomitant use of alcohol, other analgesics, and medications with ibuprofen. Based on these citations from the worldwide literature, there is no evidence to support changing or adding to the currently required consumer labeling warnings for ibuprofen.*

IV. Drug Abuse Potential and Overdose

In support of this combination product's drug abuse potential and overdose profile, the sponsor submitted data from the following sources:

1. Drug Abuse Warning Network (DAWN) Emergency Department (ED) Reports for the period from 1994 through 1999.
2. DAWN Medical Examiner (ME) Reports for the period from 1994 through 1999
3. American Association of Poison Control Center (AAPCC) for the period from 1995 through 1999.
4. Search of the worldwide literature as described previously.

5. Postmarketing reports of drug abuse and overdose collected by the FDA's Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS).

Both ingredients will be discussed separately for drug abuse potential followed by overdose event profile.

IV.1.A. Diphenhydramine Drug Abuse Potential

As per 21 FR 338 the Final Monograph for Nighttime Sleep-Aid Drug Products for OTC Human Use (publication date February 14, 1989), the agency stated there was no potential for abuse/misuse of diphenhydramine as an OTC drug product based on the data submitted for review under the monograph process. Due to technical advances in drug delivery, the first liquigel formulations containing 50 mg of diphenhydramine were introduced for marketing in the U.S. in 1994. In 1997, a 50 mg diphenhydramine single-ingredient liquigel formulation reverted to prescription status in the United Kingdom because of abuse issues in that country. The sponsor of this submission maintains that there is no abuse potential when diphenhydramine is combined with an analgesic. This conclusion is based on data generated from DAWN Emergency Department (ED) Reports. The following table, Sponsor's Table 7, is a comparative listing of 5 categories of medicinal products including OTC sleep-aids that were compiled from reports of drug abuse-related emergency department admissions during 1994-99.

Sponsor's Table 7- DAWN Emergency Department (ED) Reports for Drug Abuse Mentions for the Period 1994-99.

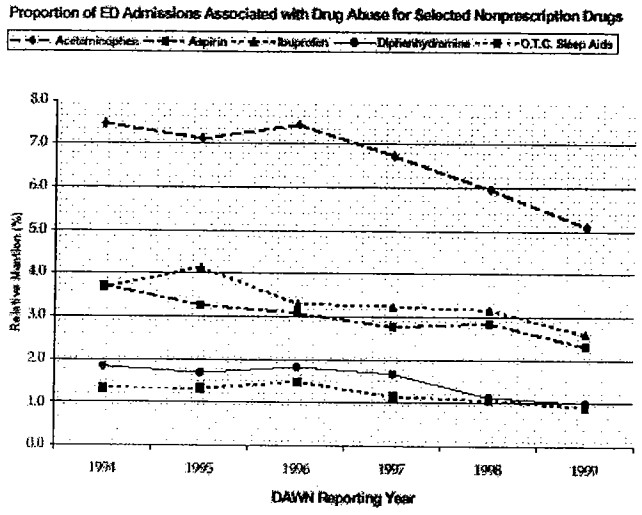
	Mention frequency by reporting year					
Substance	1994	1995	1996	1997	1998	1999[1]
Alcohol-in-combination	160,744	166,925	166,185	171,982	185,002	196,277
Acetaminophen	38,674	36,563	38,265	35,448	32,257	28,258
Aspirin	19,358	16,729	15,854	14,623	15,457	12,815
Ibuprofen	9,031	21,250	16,979	17,070	17,146	14,400
O.T.C. Sleep Aids[2]	6,890	6,794	7,628	6,084	5,750	4,986
Total	518,521	513,633	514,347	527,058	542,544	554,392

[1] The latest available DAWN report from the Substance Abuse and Mental Health Services Administration

[2] Enumerated in the detailed tables as: Sominex, Unisom and Nytol.

Sponsor's Table 7 shows that the number of Emergency Department drug abuse-related admissions for OTC sleep aids is much lower as compared to alcohol-in-combination, or 3 popular OTC analgesics. This is supported by the graphic presentation of the data from Sponsor's Table 7 as shown below in Sponsor's Graph 8.

Sponsor's Graph 8 – DAWN Emergency Department Report: Frequency of Emergency Department Admissions Due to Drug Abuse of Selected OTC Drugs.



According to the sponsor, prior to the initial marketing of liquigel formulations the relative frequency of Emergency Department admissions in 1992 due to overdoses with diphenhydramine was 1.81% as compared to 1.62% for OTC sleep-aids. Marketing of the liquigel formulation of diphenhydramine did not result in an increase in abuse admissions as demonstrated by Sponsor's graph 8 (six-year mean frequency of Emergency Admissions for diphenhydramine 1.5% versus 1.2 % for OTC sleep-aids).

The following table, Sponsor's Table 9, lists both "raw" and "consistent panel" drug abuse data collected by the DAWN Medical Examiner (ME) Reports that was generated from reports by voluntary medical examiners who judged case fatalities to be either drug-induced or drug-related. (Note: The "consistent panel" is made up of 134 medical examiners from 39 metropolitan areas who reported to DAWN for at least 10 months per year each year from 1996 through 1999. Since the participants from both sections vary from year to year, and do not included rural areas, a cross year comparison of the annual data displayed in Sponsor's Table 9 should not be undertaken.)

Sponsor's Table 9 – DAWN Medical Examiner (ME) Reports: Drug Mentions by Medical Examiners

	Mention Frequency by reporting year					
Substance	1994	1995	1996	1997	1998	1999
Raw Data						
Alcohol-in-combination	3,145	3,613	3,509	3,546	3,723	3,916
Acetaminophen	309	367	353	403	401	427
Aspirin	80	105	107	92	101	104
Ibuprofen	36	26	32	40	31	35
Diphenhydramine	319	458	431	522	504	641
Total	8,426	9,216	9,484	9,743	10,123	11,651
Consistent Panel Data						
Acetaminophen	–	–	342	392	395	425
Aspirin	–	–	103	87	98	104
Ibuprofen	–	–	NM[†]	NM	NM	NM
Diphenhydramine[‡]	–	–	424	517	502	640
OTC-Sleep-Aid	–	–	1	0	1	1

† NM signifies zero mentions

‡ The brand name Benadryl was cited in the detailed table

Sponsor's Table 9 demonstrates that for the "raw" data diphenhydramine overdoses are second to only alcohol-in-combination in terms of numbers of drug mentions by medical examiners in case fatalities followed by acetaminophen, aspirin and ibuprofen. Only 3 overdose cases were attributed to combination OTC sleep-aid products as noted by the "consistent panel" data (refer to Sponsor's Table 9 found above) which supports the sponsor's conclusion that the abuse potential for diphenhydramine in combination with an analgesic is minimal.

A query by the sponsor of the FDA's SRS and AERS Databases for case reports of abuse of diphenhydramine yielded a total of 17 cases as shown in the table below, Sponsor's Table 10. Although the number of cases of diphenhydramine abuse is higher as compared to other OTC drugs with no abuse potential (i.e., acetaminophen, aspirin and ibuprofen), it is markedly lower than drugs with high abuse potential such as tramadolol and alprazolam.

Sponsor's Table 10 – Drug Abuse Reports Obtained From Case Reports Collected by the FDA's SRS (October 1969 to October 1997) and AERS Databases (November 1997 to September 2000).

Substance Name(s)	SRS Database		AERS Database[1]	
	Number of ISR found	% (of abuse reports)	Number of ISR found[2]	% (of abuse reports)
ACETAMINOPHEN	8	0.09	5	0.001
ACETAMINOPHEN – DIPHENHYDRAMINE	0	0	1	0.0002
ACETYLSALICYCLIC ACID	5	0.05	0	0
DIPHENHYDRAMINE	17	0.19	0	0
IBUPROFEN – Advil	3	0.03	0	0
IBUPROFEN – Motrin	7	0.08	1	0.0002
IBUPROFEN – unspecified	1	0.01	2	0.0004
NICOTENE (Smoking Cessation products)	1,243	14.6	2	0.0004
ALPRAZOLAM	743	8.7	40	0.008
TRAMADOL HCL	299	3.5	204	0.04
Total Records (ISR) contained in database	1,486,927		498,723	

[1] Data are presented only for reports in which the medicinal product was encoded as "Primary Suspect"
[2] Only reports noted as "initial" are included.

For completeness, the sponsor submitted summaries of 3 case reports of dihphenhydramine abuse which were identified during their search of the worldwide literature (References 88-90). (Note: The parameters used by the sponsor to do the literature search are described in the preceding section, Section II.) In 2 of the articles (References 88 and 90), the subjects took diphenhydramine concomitantly with other psychoactive drugs for the purpose of getting high, while only 1 subject was taking the drug chronically at high doses (1,600 mg/day) for its intended purpose (i.e., sleep) [Reference 89]. Three of the subjects who abused diphenhydramine had histories of schizophrenia (References 89 and 90), one of whom become a chronic abuser of the drug and was subsequently detoxed 3 times without permanent sequelae (Reference 90).

IV.1.B. Ibuprofen Drug Abuse Potential

The sponsor maintains that review of the data contained in the preceding tables and graph, Sponsor's Tables and Graph 7-10, fails to demonstrate any data that would suggest ibuprofen could potentially be abused. In support of this conclusion, they have also cited the annual reports from 1994 through 1999 of the Substance Abuse and Mental Health Services Administration (SAMHSA), and the1990 report by the National Institute on Drug Abuse (NIDA) which did not include ibuprofen on their lists of potentially addictive or abused drugs. Review of their internal postmarketing safety database system failed to identify any reported cases of ibuprofen drug abuse using the MedDRA terms abuse, drug abuse, or drug dependence. The sponsor query of the FDA's AERS database system for the time period described in Section IV identified using these same MEDDRA terms yielded 3 case reports.

Medical Reviewer's Comments: *Based on the limited and highly variable data reviewed above, this medical officer concurs with the sponsor that the risk for potential abuse of a combination diphenhydramine-ibuprofen OTC product is low although it could potentially rise due to the increase accessibility of the combined product on the OTC market.*

IV.2.A. Diphenhydramine Drug Overdose

In support of diphenhydramine's safety profile, the sponsor submitted overdose data obtained from the American Association of Poison Control Centers (AAPCC) for the period of 1995-99. This data is displayed in the following table, Sponsor's Table 11. This table shows that during the 5 year period spanning 1995-99 there were a total of 122,894 reported overdoses with single-ingredient prescription and nonprescription diphenhydramine products, out of which there were only 65 fatalities. Approximately a third of all these overdoses were intentional (i.e., suicide attempts) while the remainder were classified as unintentional or accidental overdoses. (Refer to Sponsor's Table 11 shown below.)

Sponsor's Table 11 – Selected Exposure and Outcome Data From the 1995-99 AAPCC Reports for Both Single-Ingredient Prescription and OTC Diphenhydramine and Acetaminophen/Diphenhydramine Preparations.

			Ingestion category		Outcome classification	
Year	Substance	No. of Exposures	Unintentional*	Intentional†	Major‡	Death
1999	Diphenhydramine	23,900	16,099	7,198	289	38
	Acetaminophen / Diphenhydramine, All Exposures§	10,364	3,580	6,530	199	12
	Acetaminophen / diphenhydramine without Concomitants§	6,858	2,663	4,064	97	4
1998	Diphenhydramine	24,611	15,970	7,999	260	16
	Acetaminophen / Diphenhydramine, All Exposures	9,220	3,107	5,913	157	11
	Acetaminophen / diphenhydramine without Concomitants	6,246	2,378	3,745	80	5
1997	Diphenhydramine	26,862	17,574	8,540	250	14
	Acetaminophen / Diphenhydramine, All Exposures	9,441	3,583	5,619	124	4
	Acetaminophen / diphenhydramine without Concomitants	5,650	2,181	3,358	52	1
1996	Diphenhydramine	34,456	14,797	9,009	208	11
	Acetaminophen / Diphenhydramine, All Exposures	8,124	2,708	5,123	82	6
	Acetaminophen / diphenhydramine without Concomitants	5,506	2,099	3,270	39	4
1995	Diphenhydramine	23,065	13,892	8,549	193	4
	Acetaminophen / Diphenhydramine, All Exposures	7,145	2,380	4,563	74	10
	Acetaminophen / diphenhydramine without Concomitants	4,921	1,894	2,900	39	3
Totals	Diphenhydramine	122,894	78,373	41,295	1,209	65
	Acetaminophen / Diphenhydramine, All Exposures	44,294	15,358	27,748	636	43
	Acetaminophen / diphenhydramine without Concomitants	29,181	11,214	17,337	307	17

Unintentional ingestion as defined by the authors includes: therapeutic error, unintentional misuse, suspected suicide attempt

† *Intentional ingestion as defined by the authors includes: intentional misuse, intentional abuse, and suicide attempt*

‡ Major outcome as defined by the authors includes: signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability.

§ Sum of reported exposures for single ingredient, adult, pediatric and unknown formulations.

¶ Data purchased from AAPCC

Additionally, the sponsor identified a subset total of 220 adverse event reports from the FDA's combined SRS and AERS databases for the time period as described in the following section, Section IV, which were attributed to either accidental or intentional overdoses of diphenhydramine. One hundred seventy-four (174) of these 220 overdose cases were classified as serious in nature, with hospitalization as the most frequently reported outcome. (Note: The sponsor did not list the number of cases that resulted in death due to diphenhydramine overdose from this source of information.) The sponsor also submitted a summarized case series article involving 3 patients who were successfully treated with intravenous sodium bicarbonate for EKG changes that were described as wide-complex tachycardia following overdoses of diphenhydramine (Reference 96).

IV.2.B. Ibuprofen Drug Overdose

In support of ibuprofen's safety profile, the sponsor submitted overdose data obtained from the AAPCC for the same period of time (i.e.,1995-99). This data is displayed in the following

table, Sponsor's Table 12. This table shows that during the 5 year period spanning 1995-99 there were a total of 250,231 reported overdoses with both single-ingredient prescription and nonprescription ibuprofen products, out of which there were only 25 fatalities. Approximately a fourth of all these overdoses were intentional (i.e., suicide attempts) while the remainder were classified as unintentional or accidental overdoses. (Refer to Sponsor's Table 12 shown below.)

Sponsor's Table 12 - Selected Exposure and Outcome Data From the 1995-99 AAPCC Reports for Both Single-Ingredient Prescription and OTC Acetaminophen, Aspirin, and Ibuprofen Preparations.

			Ingestion category		Outcome classification	
Year	Substance	No. of Exposures	Unintentional*	Intentional†	Major‡	Death
1999	Acetaminophen**	61,092	43,293	17,122	740	85
	Aspirin	13,854	6,236	7,226	251	45
	Ibuprofen	54,643	41,986	11,678	105	3
1998	Acetaminophen	66,885	47,544	18,671	723	70
	Aspirin	14,263	6,062	7,822	222	33
	Ibuprofen	52,751	39,397	12,425	97	4
1997	Acetaminophen	72,580	51,665	20,063	566	65
	Aspirin	15,648	7,072	8,158	162	44
	Ibuprofen	51,738	37,434	13,203	95	6
1996	Acetaminophen	72,947	51,037	21,063	533	52
	Aspirin	15,426	6,373	8,675	146	46
	Ibuprofen	51,738	37,434	13,203	96	6
1995	Acetaminophen	72,889	51,450	20,730	501	55
	Aspirin	15,548	6,220	8,924	164	48
	Ibuprofen	39,361	24,815	13,639	80	6
Totals	Acetaminophen	346,393	244,989	97,649	3,063	328
	Aspirin	74,739	31,963	40,805	945	216
	Ibuprofen	250,231	181,066	64,148	473	25

Unintentional ingestion as defined by the authors includes: therapeutic error, unintentional misuse, suspected suicidal

† *Intentional ingestion as defined by the authors includes: intentional misuse, intentional abuse*

‡ Major outcome as defined by the authors includes: signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability.

** Sum of reported exposures for single ingredient, adult, pediatric and unknown formulations.

Additionally, the sponsor identified a subset of 229 adverse event reports from the FDA's AERS database for the time period as described in the following section, Section IV, which were attributed to either accidental or intentional overdoses of ibuprofen. One hundred forty-three (143) of these 229 overdose cases were classified as serious in nature, with hospitalization as the most frequently reported outcome. (Note: The sponsor did not list the number of cases that resulted in death due to ibuprofen overdose from this source of information.)

For completeness, the sponsor submitted the summaries of 10 case reports of ibuprofen overdose which were identified during their search of the worldwide literature (References 88-90). (Note: The parameters used by the sponsor to do the literature search are described in the preceding section, Section II.) Seven out of the 10 cases were intentional overdoses (References 97, 99, 100, 102-04, and 106) taken by adults, while the remaining 3 articles (References 98, 101, and 105) were accidental overdoses by children age 2 years and under. Despite the development of central nervous and renal toxicities, and major electrolyte disturbances that in some cases required mechanical support of respiration and temporary hemodialysis, all of the individuals described in these articles survived without permanent medical problems.

Medical Reviewer's Comments: *Although the review of the overdose data did not reveal any new information regarding drug toxicity due to diphenhydramine and ibuprofen, the effects of an overdose from either drug are well documented and known. Most overdose cases with these drugs do well following medical intervention and the administration of supportive medical care, and rarely result in permanent sequelae from the experience. The number of fatalities associated with acetaminophen overdoses as shown in Sponsor's Table 12 is probably secondary to the drug's associated hepatotoxicity. From the limited information submitted by the sponsor, it is*

impossible for this medical reviewer to draw any conclusions regarding the possibility of accidental overdoses in adults due to misinterpretation of the current dosing instructions present on the labels of OTC diphenhydramine and ibuprofen containing products.

V. Postmarketing surveillance review of serious adverse event case reports for non-injectable formulations of both single ingredients (i.e., diphenhydramine and ibuprofen) of the proposed combination product and adverse events due to co-administration of both ingredients.

Since diphenhydramine is marketed under the monograph system, the sponsor was unable to estimate how many doses of this drug have been distributed in the United States. They did estimate that approximately 3 billion doses ibuprofen have been distributed in this country since its introduction to the OTC market in 1984. In support of the safety profile of this proposed combination product, the sponsor submitted the results from a postmarketing surveillance review of adverse event case reports for both single ingredients diphenhydramine and ibuprofen as well as co-administration of both ingredients that was generated from the following sources:

1. Whitehall-Robins Product Safety Surveillance Department's database for the period of August 1982 through October 1996 for diphenhydramine and from February 1,1999 to February 28, 2001 for ibuprofen.
2. FDA's Spontaneous Reporting System (SRS) for the period of January 1, 1968 through October 31, 1997 for diphenhydramine.
3. FDA's Adverse Event Reporting System (AERS) for the period of November 1, 1997 through September 30, 2000 for diphenhydramine and from May 22, 1999 through September 30, 2000 for ibuprofen.
4. Whitehall-Robins Product Safety Surveillance Department's database for case reports of adverse events attributed to co-administration of both ingredients (time period undefined).

The sponsor submitted a narrative summary of the case reports identified from the above sources but did not provide copies of the case report forms in this submission. The postmarketing reports for each ingredient will be discussed separately followed by the case reports attributed to co-administration.

V.A.1. Diphenhydramine Postmarketing Adverse Event Reports collected by Whitehall-Robins Product Safety Surveillance Department for the period of August 1982 through October 1996.

The sponsor marketed a 25 mg diphenhydramine sleep-aid product (Sleep-Eze 3) from August 1982 to October 1996 during which they collected 3 non-serious adverse event reports. No further information was provided by the sponsor regarding these 3 case reports since they were classified as non-serious in nature.

V.A.2. Diphenhydramine Postmarketing Adverse Event Reports collected by the FDA's SRS database for the period of January 1, 1968 through October 31,1997.

A total of 898 reports of adverse events due to the use of non-injectable formulations of diphenhydramine in patients aged 12 and over were identified on query of the SRS database. Of the 898 reports, 254 were classified as serious in nature and involved the following COSTART Body System classes: body as a whole, nervous system, cardiovascular system and respiratory system. On 71 serious case reports or 8% of all reported cases attributed to diphenhydramine, death was the reported outcome and involved the following COSTART Body System classes: body as a whole, cardiovascular system, and nervous system. Although the sponsor did not provide tabular summaries of the above data, they concluded that no new safety issues were identified based on their review of reports identified by this search.

V.A.3. Diphenhydramine Postmarketing Adverse Event Reports collected by the FDA's AERS database for the period of November 1, 1997 through September 30, 2000.

A total of 333 reports of adverse events due to the use of non-injectable formulations of diphenhydramine in patients aged 12 and over were identified on query of the AERS database. Of the 333 reports, 137 were classified as serious in nature and involved the following MedDRA System organ classes: nervous system, psychiatric disorders, investigations, and injury and poisoning. On 41 serious case reports attributed to diphenhydramine, death was the reported outcome and involved the following MedDRA System organ classes: injury and poisoning, investigations, and psychiatric disorders. Although the sponsor did not provide tabular summaries of the above data, they concluded that no new safety issues were identified based on their review of reports identified by this search.

V.B.1. Ibuprofen Postmarketing Adverse Event Reports collected by Whitehall-Robins Product Safety Surveillance Department for the period of February 1, 1999 through February 28, 2001.

A total of 648 reports of adverse events due to the use of non-injectable formulations of ibuprofen in patients aged 12 and over were identified on query of the Whitehall-Robins' internal product safety database. Of the 648 reports, 156 were classified as serious in nature and involved the following MedDRA System organ classes: general and administration site disorders, gastrointestinal disorders, skin and subcutaneous tissue disorders, and nervous system disorders. There were 9 serious case reports attributed to ibuprofen that resulted in the death of the individuals. In 7 out of these 9 death reports, the subjects' death was due to gastrointestinal bleeding from ulcers and perforation. Table 13, shown below is a tabular listing of these 10 reported cases of death attributed to the ingestion of OTC doses of ibuprofen.

Table 13 – Tabular Listing of Deaths Associated with the Use of OTC Doses of Ibuprofen Reported for the Period of February 1, 1999 through February 28, 2001 collected by Whitehall-Robins Product Safety Surveillance Department.

Manufacturer's Control Number (Country)	Age/ Sex	Drug	Outcome	History
8-99036-106A	89yo/F	Advil Extra-Strength	Death	Developed abdominal distension with dilated cecum on x-ray S/P 10 days of ingesting 1,200 mg/day ibuprofen. Concomitant meds: Augmentin, albuterol, Atrovent ranitidine, Co-Proxamol, dihydrocodeine, calcichew, senna, acetaminophen and bendrofluazide. PMH significant for LRI, osteoporosis and COPD. Pt. died before exploratory laparotomy. Autopsy revealed colitis.
8-99120-101A	79yo/F	Ibuprofen	Death	Admitted for treatment of anemia (Hb 6.7 g/dl) associated with generalized weakness after taking 1,200 mg/day of ibuprofen for nearly 2 years. Concomitant meds: aspirin. PMH significant for gastritis. Pt. developed melena and hematemesis and died suddenly while hospitalized. Autopsy revealed 10 cm peptic ulcer.
8-99144-136A	54yo/F	Ibuprofen	Death	Pt. died S/P developing acute renal failure and anuria after ingesting ibuprofen 800 mg/day for 2 days for analgesic relief while undergoing treatment for cellulitis and an abscess. Concomitant meds: Flagyl, ciprofloxacin, probenecid, gentamycin, acetaminophen, cimetidine, spironolactone, and furosemide. No PMH provided.
8-99201-008A	58yo/M	Ibuprofen	Death	Died following the development of a perforated duodenal ulcer and peritonitis after presenting for treatment for an acute abdomen and acute renal failure. No PMH provided. Autopsy revealed a perforated duodenal ulcer.
HQ0478814JAN2000	79yo/F	Ibuprofen	Death	Died S/P massive gastric hemorrhage following the ingestion of ibuprofen 600 mg/day. Concomitant meds: aspirin, and cimetidine. PMH significant for arthritis, hiatal hernia, dyspepsia, and a CVA. Autopsy revealed gastrointestinal hemorrhage due to gastric ulcer.
HQ1327502MAR2000	85yo/F	Ibuprofen	Death	Pt. S/P acetaminophen overdose died due to perforated duodenal ulcer. Pt. had been taking unspecified amount of ibuprofen with aspirin for an unspecified period of time that was stopped approximately 3 months prior to the OD. Concomitant meds: ranitidine. PMH significant for chronic pain and an unspecified medical disorder.
HQ1342205)CT1999 (Japan) (Duplicated report number: HQ7510219JUN2000)	37yo/M	IBU A 75 mg	Death	Pt. was found dead following an overdose of 675 mg of ibuprofen. PMH significant for hip pain and previous skull injury. Autopsy revealed positive blood levels of ibuprofen without any fatal trauma or pre-existing diseases. Cause of death was thought to be due to ibuprofen poisoning made worse by heat stroke and mental confusion.
HQ8508513JUL2000	87yo/F	Advil	Death	Pt. died following treatment for a gastrointestinal hemorrhage with a duodenal ulcer S/P ingestion of Advil 1,200 mg/day with acetaminophen for treatment of back pain. Concomitant meds: Co-Amilofruse, aspirin, and Moduretic. PMH significant for osteoarthritis, hypertension, CAHD, S/P hip replacement, CVA, and DVT. Autopsy revealed a chronic duodenal ulcer with massive amounts of blood in both the small and large intestines.
HQ4992101MAY2000	78yo/M	Ibuprofen	Death	Pt. died S/P severe gastrointestinal hemorrhage and melena after taking 1,200 mg ibuprofen a day for the treatment of osteoarthritis. Concomitant meds; citralopam, calcium carbonate, salmeterol, terbutaline, prednisone, amitriptyline, furosemide, and dihydrocodeine/acetaminophen. PMH significant for depression, and a vagotomy with pyloroplasty.

Although the sponsor did not provide tabular summaries or numbers associated with each body system category for the serious cases that did not result in death, they concluded that no new safety issues were identified based on their review of reports identified by this search.

V.B.3. Ibuprofen Postmarketing Adverse Event Reports collected by the FDA's AERS database for the period of May 22, 1999 through September 30, 2000.

A total of 765 reports of adverse events due to the use of non-injectable formulations of ibuprofen in patients aged 12 and over were identified on query of the Whitehall-Robins' internal product safety database. Of the 765 reports, 380 were classified as serious in nature and involved the following MedDRA System organ classes: gastrointestinal disorders, investigations, general and administration site disorders, and nervous system disorders. On 49 serious case reports attributed to ibuprofen, death was the reported outcome due to the following MedDRA System organ classes: gastrointestinal disorders (31% of the cases), injury and poisoning (8%), investigations, and general disorders and administration site conditions. (Note: The sponsor did not provide the incidence rates for the remaining categories.) Although the sponsor did not provide tabular summaries or the numbers of cases associated with each body system category, they concluded that no new safety issues were identified based on their review of reports identified by this search.

V.4. Co-administered Postmarketing Adverse Event Reports collected by Whitehall-Robins Product Safety Surveillance Department (time period unspecified).

The sponsor identified a total of 49 cases of adverse events attributed to the co-administration of both ingredients in the proposed combination product. A tabular listing of these 49 cases is shown in Sponsor's Table 15 which can be found in Appendix III at the end of this review. Fourteen (14) out of the 49 cases listed are confounded by the concomitant use of other medications and thus should be discounted from further review. According to the sponsor, another 7 cases that were associated with a series of varicella infections during 1993-95 that resulted in necrotising fasciitis, should not be counted as part of the safety data in support of this combination product. The sponsor concludes that the remaining 28 cases do not identify any potential safety signal that could result in an adverse event associated with the co-administration of diphenhydramine and ibuprofen.

Medical Reviewer's Comments: *Based on the postmarketing data reviewed above, this medical officer concurs with the sponsor that no safety signal or new safety problem associated with the use of diphenhydramine or ibuprofen alone or in combination was identified. The number of adverse case reports generated from the sponsor's internal safety monitoring system that were associated with co-administration of these drugs was too small to draw any inferences regarding the possibility of drug-drug interactions between the two ingredients of this combination sleep-aid/analgesic product. A consultative review of the 97 cases (55 in adults and 42 in children) in the FDA's AERS database by Dr. Claudia Karwoski, safety evaluator in the Division of Drug Risk Evaluation (HFD-430) dated April 4, 2002, that was requested by this reviewing division also did not identify any potential adverse event case reports suggestive of an increase in risk for drug-drug interactions between diphenhydramine and ibuprofen.*

VI. Medical Reviewer's Conclusions and Final Recommendations : Review of the safety data generated from the 4 biopharmaceutical studies and the global safety database submitted by the sponsor in support of this combination sleep-aid/analgesic product's safety profile did not reveal any new or unexpected adverse events or potential drug-drug interactions for this combination drug product. Although analysis of the drug abuse overdose data also did not identify the existence of major risk for abuse/misuse of this combination product, the potential for such problems could rise due to increased accessibility once it is introduced to the OTC market. Based on the information reviewed, the current consumer safety warnings for both diphenhydramine and ibuprofen are appropriate and do not need to be changed or updated for this combination sleep-aid/analgesic product.

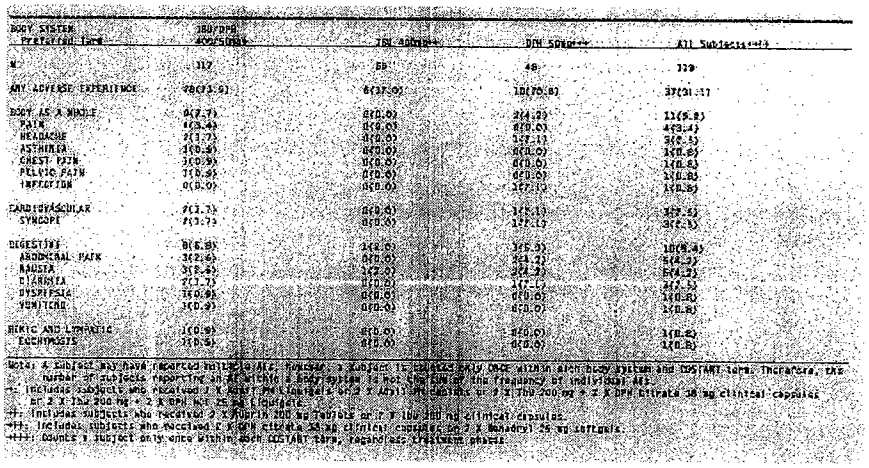
Rosemarie Neuner, MD, MPH
Medical Reviewer, HFD-560

Linda M. Katz, MD, MPH
Deputy Director, HFD-560

CC: NDA 21-393 and 21-394 Files
HFD-560 Dir/Ganley
HFD-560 Dep Dir/Katz
HFD-560 Team Leader/Chang
HFD-120 MO/Andreason
HFD-550 MO/Lim
HFD-560 MO/Neuner
HFD-560 PM/Frazier
HFD-550 PM/Dean

Appendix I

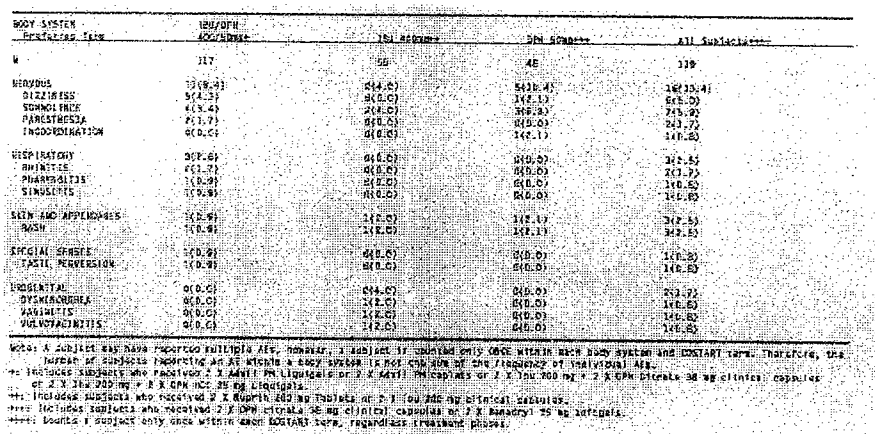
Sponsor's Table 14 – Number and Percentage of Subjects with Adverse Experiences Reported by Body System for the Pooled Population Enrolled in the 4 Pharmacokinetic Studies (WM-716, AE-97-02, AE-97-09, and AE-00-10).



BODY SYSTEM Preferred Term	180/DPH #Occ/Subj+	IBU 400mg++	DPH 50mg+++	All Subjects+++
N	117	68	48	119
ANY ADVERSE EXPERIENCE	78(73.9)	6(37.0)	10(70.8)	37(31.1)
BODY AS A WHOLE	8(7.7)	0(0.0)	2(4.2)	11(9.8)
PAIN	4(3.4)	0(0.0)	0(0.0)	4(3.4)
HEADACHE	2(1.7)	0(0.0)	1(2.1)	3(2.5)
ASTHENIA	1(0.9)	0(0.0)	0(0.0)	1(0.8)
CHEST PAIN	1(0.9)	0(0.0)	0(0.0)	1(0.8)
PELVIC PAIN	1(0.9)	0(0.0)	0(0.0)	1(0.8)
INFECTION	0(0.0)	0(0.0)	1(2.1)	1(0.8)
CARDIOVASCULAR	2(1.7)	0(0.0)	1(2.1)	3(2.5)
SYNCOPE	2(1.7)	0(0.0)	1(2.1)	3(2.5)
DIGESTIVE	8(6.8)	1(1.5)	1(2.1)	10(8.4)
ABDOMINAL PAIN	3(2.6)	0(0.0)	1(2.1)	4(3.4)
NAUSEA	3(2.6)	1(1.5)	1(2.1)	5(4.2)
DIARRHEA	2(1.7)	1(1.5)	0(0.0)	3(2.5)
DYSPEPSIA	1(0.9)	0(0.0)	0(0.0)	1(0.8)
VOMITING	1(0.9)	0(0.0)	0(0.0)	1(0.8)
HEMIC AND LYMPHATIC	1(0.9)	0(0.0)	0(0.0)	1(0.8)
ECCHYMOSIS	1(0.9)	0(0.0)	0(0.0)	1(0.8)

Note: A subject may have reported multiple AEs. However, a subject is counted only once within each body system and COSTART term. Therefore, the number of subjects reporting an AE within a body system is not the sum of the frequency of individual AEs.
+: Includes subjects who received 2 X Advil PM Liquigels or 2 X Advil PM Caplets or 2 X IBU 200 mg + 2 X DPH citrate 38 mg clinical capsules or 2 X IBU 200 mg + 2 X DPH HCl 25 mg Liquigels.
++: Includes subjects who received 2 X Motrin 200 mg Tablets or 2 X IBU 200 mg clinical capsules.
+++: Includes subjects who received 2 X DPH citrate 38 mg clinical capsules or 2 X Benadryl 25 mg softgels.
++++: Counts a subject only once within each COSTART term, regardless treatment phase.

Sponsor's Table 14 (Continued) – Number and Percentage of Subjects with Adverse Experiences Reported by Body System for the Pooled Population Enrolled in the 4 Pharmacokinetic Studies (WM-716, AE-97-02, AE-97-09, and AE-00-10).



BODY SYSTEM Preferred Term	180/DPH #Occ/Subj+	IBU 400mg++	DPH 50mg+++	All Subjects++++
N	117	68	48	119
NERVOUS	10(8.5)	0(0.0)	5(10.4)	15(12.6)
DIZZINESS	5(4.3)	0(0.0)	1(2.1)	6(5.0)
SOMNOLENCE	4(3.4)	0(0.0)	3(6.3)	7(5.9)
PARESTHESIA	2(1.7)	0(0.0)	0(0.0)	2(1.7)
INCOORDINATION	0(0.0)	0(0.0)	1(2.1)	1(0.8)
RESPIRATORY	3(2.6)	0(0.0)	0(0.0)	3(2.5)
RHINITIS	2(1.7)	0(0.0)	0(0.0)	2(1.7)
PHARYNGITIS	1(0.9)	0(0.0)	0(0.0)	1(0.8)
SINUSITIS	1(0.9)	0(0.0)	0(0.0)	1(0.8)
SKIN AND APPENDAGES	1(0.9)	1(1.5)	1(2.1)	3(2.5)
RASH	1(0.9)	1(1.5)	1(2.1)	3(2.5)
SPECIAL SENSES	1(0.9)	0(0.0)	0(0.0)	1(0.8)
TASTE PERVERSION	1(0.9)	0(0.0)	0(0.0)	1(0.8)
UROGENITAL	0(0.0)	0(0.0)	0(0.0)	2(1.7)
DYSMENORRHEA	0(0.0)	1(1.5)	0(0.0)	1(0.8)
VAGINITIS	0(0.0)	1(1.5)	0(0.0)	1(0.8)
VULVOVAGINITIS	0(0.0)	1(1.5)	0(0.0)	1(0.8)

Note: A subject may have reported multiple AEs. However, a subject is counted only once within each body system and COSTART term. Therefore, the number of subjects reporting an AE within a body system is not the sum of the frequency of individual AEs.
+: Includes subjects who received 2 X Advil PM Liquigels or 2 X Advil PM Caplets or 2 X IBU 200 mg + 2 X DPH citrate 38 mg clinical capsules or 2 X IBU 200 mg + 2 X DPH HCl 25 mg Liquigels.
++: Includes subjects who received 2 X Motrin 200 mg Tablets or 2 X IBU 200 mg clinical capsules.
+++: Includes subjects who received 2 X DPH citrate 38 mg clinical capsules or 2 X Benadryl 25 mg softgels.
++++: Counts a subject only once within each COSTART term, regardless treatment phase.

Appendix II

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Appendix III

Sponsor's Table 15 – Whitehall-Robins Product Safety Surveillance Department Case Reports of Diphenhydramine as Concomitant or Treatment Medication When Ibuprofen Reported as Suspect Drug (Time Period Unspecified).

Manufacturer Control Number	Age	Gender	Suspect Medication(s)	Concomitant or Treatment Medications	Reported Events (as MedDRA Terms)	Reported Outcome(s)	Assessment Category
8-94354-003G	33 Yrs	Female	Duyano	Depo-Medrol	Hypersensitivity NOS	Hospitalized	Confounding by other Rx products
			Ibuhufen	Unspecified steroids	Oedema NOS	Recovered	
			Prozac	Tagamet	Dermatitis bullous		
				Benadryl			
8-95031-006A	9 Yrs	Male	Children's Advil	Nafcillin	Necrotising fasciitis NOS	Hospitalized	Necrotizing Fasciitis case series
			Acetaminophen	Clindamycin	Infection NOS	Recovered	
			Acetaminophen w/ codeine				
			Benadryl				
			Cephalexin				
			Erythromycin Ethylsuccinate				
			Caladryl				
			Colloidal Oatmeal				
			Aveeno				
8-95031-007A	4 Yrs	Male	Children's Advil	Nafcillin	Necrotising fasciitis NOS	Hospitalized	Necrotizing Fasciitis case series
			Benadryl	Ceftriaxone	Renal impairment NOS	Recovered	
			Bacitracin Creme	Gentamycin	Sepsis NOS		
				Clindamycin	Infection NOS		
				Vancomycin	Coagulation disorder NOS		
				Bacitracin			
				Keflex			
				Keflex			
				Rifampin			

Sponsor's Table 15 (Continued)

Manufacturer Control Number	Age	Gender	Suspect Medication(s)	Concomitant or Treatment Medications	Reported Events (as MedDRA Terms)	Reported Outcome(s)	Assessment Category
				SilvAline cream			
				Acyclovir			
				Acetaminophen			
8-95031-008A	3 Yrs	Male	Children's Advil	Penicillin	Necrotizing fasciitis NOS	Hospitalized	Necrotizing Fasciitis case series
			Acetaminophen	Clindamycin	Infection NOS	Recovered	
			Benadryl	IDS			
			Caladryl	Timentin			
			Duricef				
			Ointment				
8-95032-007A	4 Yrs	Male	Children's Advil	Vancomycin	Necrotizing fasciitis NOS	Hospitalized	Necrotizing Fasciitis case series
			Calamine	IDS (?)	Infection NOS	Recovered	
			Diphenhydramine	Clindamycin			
				Penicillin			
8-95032-011A	14 Mths	Male	Children's Advil	Nafcillin	Septic arthritis NOS	Hospitalized	Necrotizing Fasciitis case series
			Calamine	Penicillin	Infection NOS	Recovered	
			Diphenhydramine	Amoxicillin			
				Keflex			
				Acetaminophen			
8-95060-001A	13 Mths	Female	Children's Advil	Unspecified pressors	Necrotizing fasciitis NOS	Hospitalized	Necrotizing Fasciitis case series
			Benadryl	Fluids	Infection NOS	Recovered	
			Pediapenfen	Timentin			
				Ceftriaxone			
				Keflex			
8-95073-005A	12 Mths	Female	Children's Advil	Cefotaxime	Infection NOS	Hospitalized	Necrotizing Fasciitis case series
			Benadryl	Oxacillin		Recovered	

Sponsor's Table 15 (Continued)

Manufacturer Control Number	Age	Gender	Suspect Medication(s)	Concomitant or Treatment Medications	Reported Events (as MedDRA Terms)	Reported Outcome(s)	Assessment Category
8-96165-003C	18 Yrs	Female	Fluoxetine		Overdose NOS	Recovered	Confounding by other Rx products
			Diphenhydramine				
			Ibuprofen				
			Tylenol				
			Levonorgestrel				
			Tylenol #3				
			Ibuprofen				
8-96366-015P	40 Yrs	Female	Depro	Epinephrine (SC)	Anaphylactic shock	Life Threatening	Confounding by other Rx products
			Ibuprofen	Benadryl			
				Kenalog			
8-97126-001U	53 Yrs	Male	Advil	Benadryl (IV)	Hypersensitivity NOS	Recovered	Related
8-97347-001N	40 Yrs	Female	Desnet		Hepatic failure	Hospitalized	Confounding by other Rx products
			Ibuprofen		Flatulence	Recovered	
			Ultram		Diarrhea NOS	Life Threatening	
			Flexeril		Nausea	Disability	
			Ibuprofen		Cardiac murmur NOS		
			Zyrtec		Depression NEC		
					Arthralgia		
					Memory impairment		
					Dyspnea NOS		
					Anxiety NEC		
					Fatigue		
					Vomiting NOS		
8-98208-004G	62 Yrs	Female	Advil	Prednisone	Anaphylactic reaction	Life Threatening	Confounding by other Rx products

Sponsor's Table 15 (Continued)

Manufacturer Control Number	Age	Gender	Suspect Medication(s)	Concomitant or Treatment Medications	Reported Events (as MedDRA Terms)	Reported Outcome(s)	Assessment Category
			Tetracycline	Benadryl		Hospitalized	
			Unspecified "Bug Spray"			Recovered	
8-98211-004P	56 Yrs	Female	Advil	Naproxen	Gastric ulcer	Hospitalized	Related
				Capasiven	Gastritis NOS		
				Lansoprazide	Bronchitis NOS		
				Alumina / Magnesia / Simethicone	Hernia NOS		
				Psyllium	Anemia NOS		
				Pepcid	Polyp NOS		
				Tylenol			
				Zithromax			
				Reglan			
				Ferrous sulfate			
				Allegra			
				Benadryl			
8-99201-023X	59 Yrs	Male	Recombinant human interleukin 12		Aortic	Recovered	Confounding by other Rx products
			Compazine				
			Diphenhydramine				
			Bubifen				
			Percocet				
			Ibuprofen				
HQ0209224AUG2000	4 Yrs	Male	Children's Advil	Diphenhydramine	Urticaria NOS	Recovered	Related
			Ibuprofen				
HQ0409029AUG2000	49 Yrs	Female	Advil Liquigels	Diphenhydramine	Face edema	Recovered	Related

Sponsor's Table 15 (Continued)

Manufacturer Control Number	Age	Gender	Suspect Medication(s)	Concomitant or Treatment Medications	Reported Events (as MedDRA Terms)	Reported Outcome(s)	Assessment Category
HQ0618708MAY2001	14 Mths	Male	Infant Advil Concentrated Drops		Rash erythematous	Recovered	Related
			Maalox				
			Benadryl				
HQ894215MAY2001	30 Yrs	Female	Minocycline	Epinephrine	Serum sickness	Hospitalized	Confounding by other Rx products
			Ibuprofen	Hydroxyzine	Angioneurotic edema	Recovered	
				Soln-emulsif			
				Diphenhydramine			
HQ1212624FEB2000	74 Yrs	Male	Advil		Prostatic disorder NOS		Related
			Benadryl		Urinary retention		
					Hematuria present		
HQ1216524FEB2000	62 Yrs	Female	Advil		Abdominal pain NOS		Confounding by other Rx products
			Celecoxib		Asthenia		
			Evista		Flatulence		
			Lactase		Exacerbation		
			Diphenydramine Hydrochloride		Pruritus NOS		
HQ1216524FEB2000, Cont'd.			Triamcinolone acetonide		Dermatitis NOS		
			Zyrtec				
			Vitamins				
			NoDzAEx				
			Motrin				
HQ1240325FEB2000	58 Yrs	Female	Advil	Benadryl	Hypersensitivity NOS		Related
HQ1409307MAR2000	19 Yrs	Female	Advil	Benadryl	Angioneurotic edema		Related
					Urticaria NOS		
HQ1446508MAR2000	13 Yrs	Female	Advil	Benadryl	Face edema	Recovered	Related

Sponsor's Table 15 (Continued)

Manufacturer Control Number	Age	Gender	Suspect Medication(s)	Concomitant or Treatment Medications	Reported Events (as MedDRA Terms)	Reported Outcome(s)	Assessment Category
HQ1495310MAR2000	6 Yrs	Female	Children's Advil	Benadryl	Face edema	Recovered	Related
HQ1495910MAR2000	8 Yrs	Female	Children's Advil	Benadryl	Dyspnea NOS		Related
					Dermatitis NOS		
					Pyrexia		
					Hypersensitivity NOS		
HQ1539213MAR2000	4 Yrs	Male	Children's Advil	Benadryl	Urticaria NOS	Recovered	Related
HQ1554614MAR2000	7 Yrs	Female	Children's Advil	Benadryl	Edema NOS	Recovered	Related
					Pruritus NOS		
					Arthralgia		
					Pain NOS		
					Dermatitis NOS		
HQ1555914MAR2000	9 Yrs	Male	Children's Advil	Benadryl	Tachycardia NOS		Related
				Tagamet	Dyspnea NOS		
					Face edema		
					Hypersensitivity NOS		
					Tremor NEC		
HQ1581115MAR2000	14 Yrs	Male	Advil	Inhaled albuterol	Anaphylactic reaction		Confounding by other Rx products
			Flovent	Epinephrine (SC)	Chest pain		
			Zafirlukast	Methylprednisolone (IV)	Laryngospasm		
			Albuterol	Loratidine	Dyspnea NOS		
			Cromolyn Sodium	Diphenhydramine	Cough		
			Ipratropium		Rhinitis		
HQ1598415MAR2000	73 Yrs	Female	Advil	Diphenhydramine	Dermatitis NOS		Related
				Methylprednisolone	Edema NOS		
HQ2061304APR2000	28 Yrs	Female	Advil Liquigels	Diphenhydramine	Pruritus NOS	Recovered	Related

Sponsor's Table 15 (Continued)

Manufacturer Control Number	Age	Gender	Suspect Medication(s)	Concomitant or Treatment Medications	Reported Events (as MedDRA Terms)	Reported Outcome(s)	Assessment Category
				Prednisone	Urticaria NOS		
					Nausea		
HQ3062104APR2000	56 Yrs	Female	Advil Liquigels	Diphenhydramine	Hypersensitivity NOS		Confounding by other Rx products
			Multivitamins	Steroids	Dermatitis NOS		
			Vitamin C		Pruritus NOS		
			Calcium		Dermatitis exfoliative NOS		
			Magnesium				
			Vitamin D3				
			Lysine				
			Acetylsalicylic acid enteric				
			Pramphase				
HQ2063704APR2000	22 Yrs	Female	Advil Liquigels	Benadryl	Hypersensitivity NOS		Related
HQ2093405APR2000	53 Yrs	Female	Advil Liquigels	Benadryl	Hypersensitivity NOS	Recovered	Related
					Face edema		
HQ2094505APR2000	42 Yrs	Female	Advil Liquigels	Epinephrine	Hypersensitivity NOS		Related
				Benadryl	Nausea		
				Compazine	Dry Skin		
HQ2127806APR2000	33 Yrs	Female	Advil Liquigels	Diphenhydramine	Dermatitis NOS	Recovered	Related
					Pruritus		
HQ2244407APR2000	17 Yrs	Male	Advil		Prothrombin time shortened		Related
			Diphenhydramine		Confusion		
					Vomiting NOS		
					Sedation		
					Non-accidental overdose		

Sponsor's Table 15 (Continued)

Manufacturer Control Number	Age	Gender	Suspect Medication(s)	Concomitant or Treatment Medications	Reported Events (as MedDRA Terms)	Reported Outcome(s)	Assessment Category
HQ3431209NOV2000	23 Mths	Male	Children's Advil	Benadryl	Urticaria NOS	Recovered	Related
					Face edema		
					Eyelid edema		
HQ3898931JUL2001	68 Yrs	Female	Advil		Temperature response decreased		Confounding by other Rx products
			Benadryl				
			Hyoscyamine				
			Amaryl				
			Synthroid				
HQ4314501DEC2000	46 Yrs	Female	Advil		Rash erythematous	Recovered	Related
			Tylenol PM				
HQ4428604DEC2000	37 Yrs	Female	Advil	Diphenhydramine	Eyelid edema	Recovered	Related
HQ4092127APR2000	66 Yrs	Female	Advil	Diphenhydramine	Pruritus NOS	Recovered	Confounding by other Rx products
			Celecoxib				
			Atorvastatin				
			Acetylsalicylic Acid				
			Levothyroxine sodium				
			Synvisc				
HQ6224322MAY2000	36 Yrs	Female	Advil Liquigels		Hypersensitivity NOS	Recovered	Confounding by other Rx products
			Claritin				
			Loestrin				
			Ascorbic acid				
			Diphenhydramine				
HQ6846105FEB2001	40 Yrs	Female	Advil	Diphenhydramine	Urticaria NOS	Recovered	Related
HQ7286214JUN2000	60 Yrs	Female	Advil	Benadryl	Dysphagia	Recovered	Related

Sponsor's Table 15 (Continued)

Manufacturer Control Number	Age	Gender	Suspect Medication(s)	Concomitant or Treatment Medications	Reported Events (as MedDRA Terms)	Reported Outcome(s)	Assessment Category
					Face edema		
HQ73491147UN2000	Unk	Female	Advil Gelcaps	Benadryl	Face edema	Recovered	Related
HQ83188203UL2000	26 Yrs	Female	Advil Liqui-gels		Overdose NOS		Related
			Diphenhydramine hydrochloride		Drug ineffective		
			Advil				
HQ8877124TUL2000	44 Yrs	Female	Children's Advil		Death NOS	Death	Conforming by other Rx products
			Fluoxetine		Retching		
			Thalidomide		Vomiting NOS		
			Diphydramine hydrochloride				
			Alprazolam				

NDA 21-393

Neuropharmacological Review

M E M O R A N D U M

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

DATE: April 8, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 21-393, for Advil PM (ibuprofen 200 mg/diphenhydramine 25 mg) as a nighttime sleep aid and analgesic

TO: File, NDA 21-393
[Note: This memo should be filed with the 10-16-01 original submission of this application.

This NDA was primarily assigned to HFD-550 for review, and HFD-120 has been asked to review the data pertinent to the claim for a benefit in insomnia for this combination product. The clinical review has been done by Paul Andreason, M.D., from the clinical group, in cooperations with Sharon Yan, Ph.D. and Kun Jin, Ph.D., from biometrics. My comments will focus exclusively on outcomes pertinent to sleep.

The labeling claim is "for relief of occasional sleeplessness when associated with [redacted] minor aches and pains; helps you get to sleep [redacted] Thus, the insomnia claim is for both improved latency and maintenance of sleep [redacted]

The combination policy [21CFR300.50(a)] requires that each component makes a contribution, i.e., the combination must beat each individual component. Furthermore, such a finding would need to be replicated to support a claim for a combination product.

While the sponsor provided the results of 6 studies (97-01; 98-01; 98-02; 98-03; 98-04; 97-08), only 3 of these studies are even relevant on face, in that they involved comparisons of the combination with at least one of the components. These were studies: 97-01; 98-01; and 98-02.

Study 97-01:

This was a single dose study involving patients who had dental surgery, for their night in the hospital. The study design was full factorial, i.e., 4 groups, as follows: IB 400/DPH 76; IB 400; DPH 76; pbo. Sleep assessments for latency involved checks by a nurse at 10, 20, 30, 40, 50, 60, 75, 90, 120, and 180 minutes, to determine if the patient was awake or asleep. Sleep latency was designated as the first time point at which the patient was determined to be asleep. Patients also recorded in a diary the next morning the following: ease in falling asleep; duration of sleep (6 categories: 0-5; 5-6; 6-7; 7-8; 8-9; and >9 hrs); and a global sleep evaluation. The primary outcomes were the nurse rated latency measure and a pain measure.

P-values for the key contrasts on sleep latency were as follows:

IB/DPH > DPH = 0.019
IB/DPH > IB = 0.675
IB/DPH > PBO = 0.068
IB > PBO = 0.033
DPH > PBO = 0.881
IB > DPH = 0.005

The results for sleep duration also showed a benefit for IB and IB/DPH, but no benefit for DPH.

Comment: There are a number of problems with this study, including the approach to sleep assessment, but none of this is particularly pertinent, since the study fails to show what is needed, i.e., that the combination beats the individual components. In fact, it is clear that all of the effect on improved sleep is coming entirely from the ibuprofen, with no benefit alone or in combination with ibuprofen coming from the diphenhydramine.

Study 98-02:

This was a single dose study involving patients who had dental surgery, for their night in the hospital. The study design was not a full factorial, i.e., it had only 3 groups, as follows: IB 400/DPH 50; IB 400; pbo. Sleep assessments for latency involved checks by an observer at specified intervals during a 3-hour observation period. The latency variable was cumulative percent of patients asleep at 60 minutes. Patients also recorded in a diary the next morning the following: ease in falling asleep; duration of sleep (6 categories: 0-5; 5-6; 6-7; 7-8; 8-9; and >9 hrs); and a global sleep evaluation. The primary outcomes for sleep were the nurse rated latency measure and sleep duration as rated by the patient.

In a revised analysis plan, the sponsor proposed to analyze the outcomes sequentially, beginning with sleep duration. Our statistical consultants agreed with this approach, however, not with the proposed statistical model (ANOVA). Since the data were categorical, Dr. Jin re-analyzed the data using a categorical Chi-square test, yielding p=0.242 for sleep duration. Given this negative p-value, it would not be appropriate to proceed further with an analysis of sleep latency.

Comment: In addition to the negative outcome for this trial, the design is fundamentally flawed since it does not provide an opportunity to examine the effect of DPH alone vs the combination. As was true of study 97-01, the data for both sleep duration and sleep latency suggest that whatever effect being observed is coming mostly from the ibuprofen:

Duration	PBO	IB/DPH	IB
<5	97.5%	21.8%	33.3%
5-6	0%	15.1%	14.6%
6-7	2.5%	10.1%	12.2%
7-8	0%	10.1%	11.4%
8-9	0%	19.3%	17.9%
9+	0%	23.5%	10.6%

Latency	PBO	IB/DPH	IB
(% asleep at 60 min)	27.5%	66.4%	75.6%

Study 98-01:

This study was similar in design to 98-02, except that the primary sleep outcome was changed to the latency measure rather than duration.

Again, as was true of study 98-02, the data for both sleep duration and sleep latency suggest that whatever effect being observed is coming mostly from the ibuprofen:

Duration	PBO	IB/DPH	IB
<5	85.0%	25.2%	31.6%
5-6	10.0%	10.9%	17.9%
6-7	0%	5.9%	8.5%
7-8	2.5%	10.1%	6.0%
8-9	2.5%	9.2%	7.7%
9+	0%	38.7%	28.2%

Latency	PBO	IB/DPH	IB
(% asleep at 60 min)	40.0%	63.9%	64.4%

Conclusions:

In summary, there is only one study in this program (97-01) that has an appropriate design (full factorial), and that study fails the combination policy, in that the combination does not beat DPH. Studies 98-02 and

studies 98-02 and

98-01 do not allow a comparison of the combination with DPH alone, and are therefore irrelevant. Nevertheless, the data available, actually from all 3 studies, suggest that whatever beneficial effect on sleep that is being observed is coming from the iburofen, and not from DPH. This, the DPH is adding nothing to the improved sleep that is occurring, likely due secondarily to pain relief. Thus, in my view this is a completely failed program with regard to any claims for an effect of the combination on sleep problems.

cc:
Orig NDA 21-393
HFD-120/Consult File
HFD-120/TLaughren/RKatz/PAndreason/KJin/SYan
HFD-550/BGould

DOC: NDA21393.01

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/s/

Thomas Laughren
4/8/02 11:04:56 AM
MEDICAL OFFICER

REVIEW AND EVALUATION OF CLINICAL DATA
Consultative Review

NDA:	21-393
Sponsor:	Whitehall Robbins Healthcare
Drug:	Advil PM-combination-Solubilized ibuprofen 400-mg and diphenhydramine 50-mg
Indication:	Nighttime sleep aid / pain reliever
Dates of Consult Request:	October 26, 2001
Materials Reviewed:	NDA submission for combination formulation dated October 16, 2001
Consult requested by:	HFD-550

Background
Whitehall Robbins submits studies supporting Advil PM as a pain reliever/nighttime sleep aid. The suggested dose for adults is two capsules that contain solubilized ibuprofen (IB) 200-mg and diphenhydramine (DPH) 25-mg [for a total dose of IB 400-mg and DPH 50-mg]. HFD-550 requests that we make an assessment of the efficacy of the combination versus the single agents at sleep enhancement.

21 CFR 300.50(a) states, "two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug." The Division of Neuropharmacological Drug Products (DNDP) currently requires two well designed adequately controlled studies that provide evidence that the fixed-combination formulation is statistically superior to the individual components- especially when it can be expected that the individual components will have a therapeutic effect on their own. This submission contains only one study with a full factorial design-study 97-01.

Studies that support claims of therapeutic benefits for sleep must provide evidence of improvement in one or more sleep parameters that may be measured subjectively (i.e. by asking patients to estimate times or sleep quality) or objectively (sleep laboratory polysomnographic measurements). Pivotal studies in this development program have used subjective caregiver assessments of whether or not a patient appeared asleep at a given time. Though this is not the usual fashion in which studies of this nature are done, it does not appear that this method would introduce potential bias in a double blind study design. On the contrary, this method appears on its face to be potentially less sensitive than the standard measures at detecting therapeutic differences in treatment outcome if they were present.

Materials reviewed –
The sponsor presents six studies in support of their proposed efficacy claims. Only three of these studies (97-01, 98-01, and 98-02) examined one or both of the individual components along with the combination. In study 98-01 the sponsor states, "the combination was no different than ibuprofen alone for the primary sleep assessment (cumulative percent of subjects asleep at 60

minutes)." This consultative review therefore focuses on studies 97-01 and 98-02 with a brief description and comment on study 98-01.

Study 97-01- Advil PM Pilot Oral Surgery Study
Objectives
The objective of the study was to evaluate the analgesic and sedative efficacy of a single dose of ibuprofen 400 mg/diphenhydramine citrate 76 mg compared to ibuprofen 400 mg alone, diphenhydramine citrate 76 mg alone, and placebo in subjects who had undergone oral surgery for the removal of impacted third molars who were inpatient overnight, and were required to go to bed at least 1 hour earlier than usual.

Subject Population
Subjects were 105 otherwise healthy men and women aged 16-45 years who had undergone surgical extraction of one or two impacted third molars, one of which was at least a partial bony mandibular impaction. If two molars were extracted, the other was the corresponding maxillary molar. Patients received only the following preoperative medication(s)/ anesthetic(s): bupivacaine with or without vasoconstrictor, nitrous oxide, and, in the event significant post-surgical pain was experienced before 6:00 PM, lidocaine or mepivacaine.

All of the 105 randomized subjects completed the study and were evaluable. There were 14 subjects in the placebo group, 29 subjects in the ibuprofen/diphenhydramine combination group, and 31 subjects each in the ibuprofen alone and diphenhydramine alone groups.

Design and Assessments
This was a double blind, placebo and active controlled single dose trial. When patients experienced pain between the hours of 7:30 and 10:30 PM they randomly received one of four treatments as follows:
1. IB 400-mg
2. DPH citrate 76-mg
3. IB 400-mg+DPH citrate 76-mg
4. Placebo .

Patients were randomized 2:2:2:1.

After receiving study medication patients were told to go to bed for the evening. Patients were left undisturbed for 90-minutes and a nurse observer looked in on the patient at 10, 20, 30, 40, 50, 60, 75, 90, 120, and 180 minutes post-dose, to determine whether or not the subject was sleeping. Patients were awakened, if asleep, at 90, 120, and 180 minutes to assess pain.

The following morning patients reported ease of falling asleep, sleep duration, a global sleep and global pain evaluation. Instead of reporting actual times that patients judged that they were asleep, categorical time frames were used (i.e. 0=les than 5 hours to 5=greater than 9-hours).

The primary efficacy variables were nurse observed sleep latency and SPRID3 for pain. The first observation time point in which the nurse observer recorded that a subject was asleep was considered the sleep latency for that subject. If a subject took rescue medication prior to being

observed as asleep, or if a subject was awake at all the observation time points, his or her sleep latency was considered censored at 180 minutes (the last observation time point).

Efficacy Results for Sleep

IB but not IB/DPH was significantly better than placebo but both IB and IB/DPH were superior to DPH with respect to nurse observed sleep latency (NOSL). The DPH and placebo groups were statistically comparable with respect to NOSL.

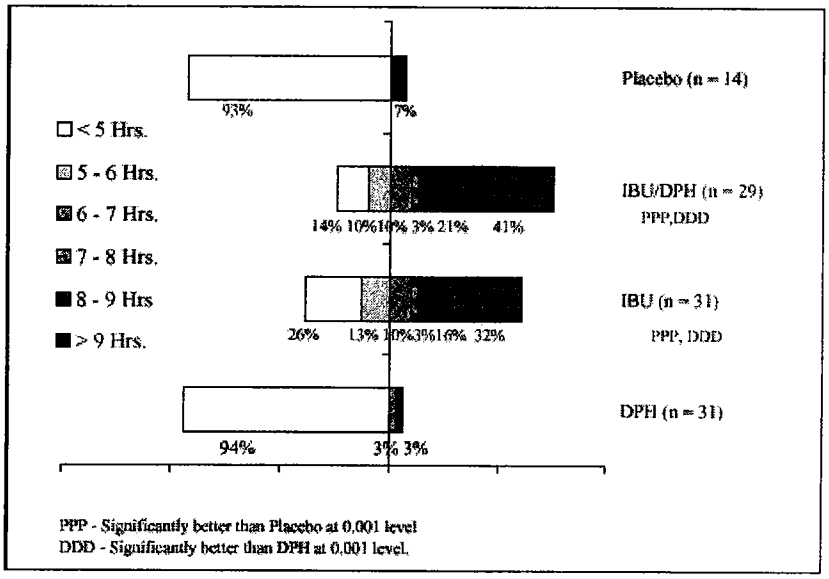
Median Time to Sleep Onset (Nurse Observed) in Study 97-01

	Placebo N=14	IBU/DPH N=29	IBU N=31	DPH N=31	p-values Trt *
Median (min) #	30.0	36.3	25.0	51.3	0.012
% with sleep onset by 180 minutes	57.1%	93.1%	93.5%	71.0%	

	IBU /DPH vs. Placebo	IBU vs. Placebo	DPH vs. Placebo	IBU/DPH vs DPH	IBU vs. DPH	IBU vs.IBU/DPH
Hazard Ratio+:	2.112	2.366	1.064	1.985	2.224	1.120
p-value	0.068	0.033	0.881	0.019	0.005	0.675

*P-values using proportional hazards model with terms for treatment, baseline PSR and gender.

The following reproduced figure (Figure 4 from NDA Section 8; Volume 88, page 72) displays the results of the sleep duration variable in study 97-01. It is striking that sleep duration in the DPH group was numerically less than placebo. This is completely unexpected.



Study 98-02 Advil® PM Oral Surgery Study II
Objectives

The ojective of the study was to evaluate the analgesic and sedative efficacy of Advil PM Liqui-Gels (ibuprofen 400 mg/diphenhydramine hydrochloride 50 mg) compared to ibuprofen liquigel (400 mg) and placebo.

Subjects
Subjects were males and females 16 to 45 years of age, underwent extraction of one to four impacted third molars, one of which had to be at least a partial bony mandibular impaction.

Design
This was a double blind placebo and IB controlled single dose inpatient study. There were three treatment arms IB 400-mg/DPH 50-mg, IB 400-mg, and placebo. There was not a DPH alone arm. Subjects had oral surgery for third molar extraction performed and were transported to an inpatient facility for overnight care. When at least moderate pain was experienced and it was between 6:00 and 8:15 PM, subjects were randomized to receive either IB 400-mg/DPH 50-mg, IB 400-mg or placebo, and were then required to go to bed for the evening. At specified intervals over a 3-hour evaluation period, an observer determined visually whether or not the subject was asleep. At 90 and 120 minutes post-dose, subjects were awakened (if necessary) and interviewed to assess their pain severity and pain relief. The following morning (or at the time of rescue medication, if applicable), subjects were asked to provide assessments of the ease with which they fell asleep, the duration of sleep, and global assessments of the study medication as a sleep-aid and pain-reliever.

Primary efficacy variables were set for sleep and pain. Sleep primary variables were sleep duration (as described above in study 97-01) and the cumulative percent of patients asleep at 60-minutes post dose administration by nurse observation. The primary variable for pain was the SPRID2 (time-weighted sum of pain intensity differences from baseline from hours 0 to 2).

Percentage of Patients in Each Categorical Sleep Duration Group
Study 98-02

	Placebo N=40	IBU400/DPH50 N=119	IBU400 N=123
Duration of Sleep			
<5 hours(0)	39 (97.5%)	26 (21.8%)	41 (33.3%)
5 to 6 hours(1)	0 (0%)	18 (15.1%)	18 (14.6%)
6+ to 7 hours(2)	1 (2.5%)	12 (10.1%)	15 (12.2%)
7+ to 8 hours(3)	0 (0%)	12 (10.1%)	14 (11.4%)
8+ to 9 hours(4)	0 (0%)	23 (19.3%)	22 (17.9%)
>9 hours(5)	0 (0%)	28 (23.5%)	13 (10.6%)
Mean	0.05	2.61	1.98
SD	0.32	1.92	1.81
Median	0.00	3.00	2.00
Range	(0, 2)	(0, 5)	(0, 5)

The sponsor amended the analysis plan during the study based on the results of study 98-01. The sponsor stated in the amendment that they would analyze the primary sleep variables sequentially with an alpha of p=0.05 for each analysis. If sleep duration was positive then the study would be considered positive at an alpha level of p=0.05. Dr. Sharon Yan and Dr. Kun Jin of the Division of Biometrics were consulted. They stated that the alpha in the analysis of study 98-02 was preserved correctly by the sequential analysis plan. The sponsor did not have to adjust alpha for multiple

comparisons if the analysis was done sequentially; however, Dr. Jin stated that the sponsor had used the incorrect statistical test. Since the sponsor elected to collect categorical data instead of continuous data, then a categorical Chi-square statistical test should have been employed. Dr. Jin analyzed the data from study 98-02 with a Chi-square test and found that there was no treatment effect on sleep duration (p=0.242).

Sleep Onset and Primary Pain Measures in Study 98-02

	Placebo N=40	IBU400/DPH50 N=119	IBU400 N=123
Cumulative % Asleep at 60 min Number (%)	11 (27.5%)	79 (66.4%)	93 (75.6%)
SPRID2+			
Mean	0.26	7.03	7.81
Std	2.07	3.47	2.87
Median	0.00	7.00	8.00
Range			

Statistical Comparisons of Primary Efficacy Variables in Study 98-02

	IBU400/DPH50 vs. Placebo	IBU400/DPH50 vs. IBU400	IBU400 vs. Placebo
Duration of Sleep			
ANOVA (a)	< 0.001F	0.005F	< 0.001F
CMH (b)	< 0.001F	0.009F	< 0.001F
Chi-square (d)		**0.2424**	
Cumulative % Asleep at 60 min(c)	< 0.001F	0.112s	< 0.001F
SPRID2 (a)	< 0.001F	0.050S	< 0.001F

a: p-values from ANOVA model with treatment, baseline PSR, and gender terms.
b: p-values from the Cochran-Mantel-Haenszel test, controlling for baseline PSR and gender, using modified ridit scores.
c: p-values from the Cochran-Mantel-Haenszel test, controlling for baseline PSR and gender.
The pairwise comparisons were tested sequentially in the order displayed (see section VII.D.4 of report).
d: performed by FDA-Division of Biometrics-Dr. Kun Jin
F: First treatment significantly better at 0.05 level.
S: IB significantly better than IB/DPH at 0.05 level.
s: IB treatment numerically better than IB/DPH.

Study 98-01 was similar in many ways to 98-02 with the exception of the sponsor's choice of primary efficacy variable. The patient population, randomization of 3:3:1 (IB/DPH: IB: placebo) dosage and administration, numbers of patients enrolled in the various treatment groups, schedule of events, rating instruments, and design of the trial were otherwise similar. The primary efficacy variables were

- Sleep: Cumulative percentage of subjects asleep at 60minutes post-dosing (based on nurse observed sleep latency assessments)
- Pain: SPRID2 (time-weighted sum of pain relief and pain intensity differences from baseline over 0-2 hours)

These variables were originally the same in the beginning of 98-02; however, the primary efficacy variables in 98-02 were amended based on the outcome of study 98-01.

The results of 98-01 follow in tabular form.

	Placebo N=40	IBU400/DPH50 N=122	IBU400 N=118
Cumulative % Asleep at 60 min			
Number (%)	16 (40.0%)	78 (63.9%)	76 (64.4%)
SPRID2			
MEAN	1.33	7.67	7.63
STD	3.02	4.26	4.39
MEDIAN	0.00	8.00	8.00
RANGE			

Statistical Comparisons of Primary Efficacy Variables in 98-01

	IBU400/DPH50 vs. Placebo	**IBU400/DPH50 vs. IBU400**	IBU400 Vs. Placebo
Cumulative % Asleep at 60 min	0.008	**0.915**	0.006
SPRID2	< 0.001	**0.952**	< 0.001

Percentage of Patients in Each Categorical Sleep Duration Group -Study 98-01

	Placebo N=40	IBU400/DPH50 N=122	IBU400 N=118
<5 hours(0)	34 (85.0%)	30 (25.2%)	37 (31.6%)
5 to 6 hours(1)	4 (10.0%)	13 (10.9%)	21 (17.9%)
6+ to 7 hours(2)	0 (0%)	7 (5.9%)	10 (8.5%)
7+ to 8 hours(3)	1 (2.5%)	12 (10.1%)	7 (6.0%)
8+ to 9 hours(4)	1 (2.5%)	11 (9.2%)	9 (7.7%)
>9 hours(5)	0 (0%)	46 (38.7%)	33 (28.2%)
Missing	0	3	1
MEAN	0.28	2.83	2.25
STD	0.82	2.10	2.08
MEDIAN	0.00	3.00	2.00
RANGE	(0, 4)	(0, 5)	(0, 5)

Statistical Comparisons of Sleep Duration in 98-01

p-values	IBU400/DPH50 vs. Placebo	**IBU400/DPH50 vs. IBU400**	IBU400 vs. Placebo
ANOVA	< 0.001	**0.022**	< 0.001
CMH	< 0.001	**0.042**	< 0.001

Conclusion

In this reviewer's opinion, there are no prospective, well-designed, adequately controlled studies in this submission that stand on there own as convincing that the IB/DPH fixed combination is superior to its component parts in the treatment of nighttime sleeplessness associated with pain.

Study 97-01 failed with respect to NOSL. IB/DPH was superior to DPH alone in this study with regard to sleep duration but not to IB alone; however, DPH alone in this study was numerically inferior to placebo. I suggest that the sponsor has over-interpreted the DPH alone data in study 97-01. The sponsor has taken this surprising finding and concluded that DPH alone need not further be tested against the combination product for either sleep duration or latency. If DPH alone were not expected to have a contribution to sleep efficacy by itself then it would be reasonable to drop the DPH alone arm from future studies; however, the body of evidence is that DPH alone does effect sleep parameters. This was a small pilot study. Since the approval of the IB/DPH combination hinges on the notion that it must provide a benefit over the individual parts, then this surprising finding needs to be replicated in the context of evidence that the combination IB/DPH is superior to IB alone with respect to sleep. On the contrary, IB/DPH was not superior to IB alone on sleep parameters in this study. This study might as easily lead one to conclude that DPH either alone or in combination adds nothing to the treatment of sleeplessness associated with pain after oral surgery.

The complete lack of any measurable effect of DPH alone on sleep in study 97-01 is unexpected and is not convincing in the face of a large clinical body of evidence to warrant excluding a DPH alone arm in subsequent pivotal studies. The sponsor does not present justification for leaving out the DPH arm in subsection V-SELECTION OF ACTIVE TREATMENTS (NDA 21-393 section 8, Volume 90 page 28). Even though IB alone had significant effects on both sleep duration and sleep latency in study 97-01, the sponsor states in this section that IB alone was included as an active control for analgesia.

In study 98-02, the IB/DPH combination fails to show superiority on all variables if they are analyzed via Chi-square. The IB/DPH combination is statistically superior with regard to sleep duration by the sponsor's analysis but IB alone is numerically superior to IB/DPH on the cumulative number of patients asleep at 60-minutes. IB alone is significantly superior to IB/DPH with respect to pain relief in this study ($p=0.05$). There was an assumption on the part of the sponsor that IB/DPH need not necessarily be superior to IB alone with respect to pain relief; however, one can not ignore that IB alone was superior to IB/DPH with respect to pain relief. This could imply that DPH somehow decreases the effectiveness of IB alone in this setting; however, study 98-01 does not provide confirmatory data to support the notion of a potentially consistent counter-therapeutic drug interaction.

In summary, this development program presents only one study (study 98-02) that the sponsor defines as pivotal (DNDP would require two positive pivotal studies). The sponsor declared sleep duration as a new primary efficacy variable in study 98-02 and they argue via ANOVA that IB/DPH showed superiority over IB alone with respect to this variable. By Chi-square test of the categorical sleep duration data, sleep duration for IB/DPH was not significantly superior to IB alone ($p=0.242$). Irrespective of the appropriateness of the sponsor's chosen statistical test, other primary variables were either significantly or numerically inferior when the IB/DPH was tested against IB alone. IB alone was significantly superior to the IB/DPH combination with respect to pain relief ($p=0.05$) and numerically superior with respect to sleep onset. Since the fixed

combination must provide a benefit over the individual components, the IB/DPH combination does not pass the combination policy test based on study 98-02 data even if one did accept the sponsor's original analysis using ANOVA for the categorical data.

Paul J. Andreason, MD
Medical Officer, DNDP HFD-120

Cc:
T Laughren
R Katz
K Jin
S Yan

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

/s/

Paul Andreason
3/28/02 03:05:17 PM
MEDICAL OFFICER

Thomas Laughren
4/8/02 11:14:00 AM
MEDICAL OFFICER
I agree that this application is problematic; see my memo to file for detailed comments.--TPL

Russell Katz
4/24/02 10:23:30 AM
MEDICAL OFFICER

NDA 21-393

Postmarketing Safety Review

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

DATE: April 4, 2002

FROM: Claudia B. Karwoski, Pharm.D., Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety (ODS)

TO: Charles Ganley, M.D., Director
Division of Over-the-Counter Drug Products, HFD-560

SUBJECT: POSTMARKETING SAFETY REVIEW (PID D020900)
Drugs: Diphenhydramine – Ibuprofen (NDAs 21-393, 21-394)
Reaction: Drug interactions

EXECUTIVE SUMMARY

This memorandum responds to a consult dated February 22, 2002 from Dr. Linda Katz, M.D., of HFD-560 requesting information on drug interactions between diphenhydramine and ibuprofen. We searched AERS for all cases that included both ingredients where at least one was reported as a suspect medication.

Ninety-seven cases involving 42 children and 55 adults were evaluated. There are no cases in which a drug interaction between diphenhydramine and ibuprofen was suspected. There are also no cases that are suggestive that the reported reaction resulted because these two products were used concomitantly. Some of the more common reactions including adverse gastrointestinal and acute renal failure are well known reactions associated with ibuprofen. There were also cases involving central nervous system events that are well known to occur with diphenhydramine. Events involving allergic or hypersensitivity reactions could have occurred with ibuprofen, diphenhydramine, and/or other reported medications that the individuals were receiving.

They additionally requested the same information on products involving acetaminophen and diphenhydramine. Because of the large number of reports for acetaminophen products, we limited our review of acetaminophen to an overview of reports with acetaminophen, reports found which listed both acetaminophen and diphenhydramine as suspect, and reports involving products known to contain only acetaminophen and diphenhydramine such as Tylenol PM. This overview is provided in a table 2 at the end of this document.

INTRODUCTION

Advil PM Liquigel and Advil PM Caplet are the first nighttime OTC products under review which combine ibuprofen and diphenhydramine. The review division requested that we search the FDA's Adverse Event Reporting System (AERS) for all adverse event and drug interaction reports involving ibuprofen and diphenhydramine. They requested that we provide all available data on combination ibuprofen-diphenhydramine products, as well as the single ingredients themselves. Target populations include all ages, with an emphasis in elderly populations. Because of the large number of reports for the individual ingredients, we limited our review to reports that included both ingredients as well as an overview of the individual ingredients (table 1).

SELECTION OF CASES

AERS was searched on February 28,2002 for all reports that contained both diphenhydramine and ibuprofen where either ingredient was listed as a suspect drug. This search resulted in 160 reports of which 15 were identified as duplicates for a total of 145 cases. The following 48 cases were excluded for the following reasons:

- There were 29 reports from two attorneys in Louisiana that reported that consumers took one or more numerous OTC products containing PPA (at least 15) and suffered the following: stroke, atrial arrhythmias, severe elevation of blood pressure, disability, emotional distress, and physical and mental pain and suffering. Some of these might have been duplicates, however there was too little clinical information provided on the individuals that allegedly suffered the injury.
- There were 9 cases involving a suicide or suicide attempt of one or more medications including diphenhydramine and/or ibuprofen.
- Greater than three suspect drugs (excluding ibuprofen and/or diphenhydramine) - There were 7 cases that reported numerous suspect agents (from 4 to 17) and the role of diphenhydramine and ibuprofen could not be determined.
- Two cases reported a reaction to ibuprofen but diphenhydramine was not reported as a co-suspect or concomitant medication.
- One case reported accidental overdose of an ibuprofen product in a 4-year-old female. She was on concomitant diphenhydramine and suffered no adverse event or outcome.

SUMMARY OF CASES

Ninety-seven cases involving 42 children and 55 adults were evaluated. There are no cases in which a drug interaction between diphenhydramine and ibuprofen was suspected. Moreover, there are no cases suggestive that the reported reaction resulted because the two products were used concomitantly. However, the summaries below provide information on the types of events that were reported when the products were used concomitantly. Some reactions including adverse gastrointestinal events and acute renal failure are well known reactions associated with ibuprofen. There were also cases involving central nervous system events that are well known to occur with

diphenhydramine. Events involving allergic or hypersensitivity reactions could have occurred with ibuprofen, diphenhydramine, and/or other reported medications that the individuals were receiving. In several of these cases, use of diphenhydramine might have been used to treat these symptoms although it was not explicitly stated in the report.

Pediatric Cases

Forty-two cases involved children less than 18 years of age. The ages ranged from 1 to 15 years of age (mean 4.4 years, median 4 years). Twenty were female and 22 were male. Eight cases reported both products as suspect, of which four also listed 1-2 additional suspect medications. In thirteen cases either ibuprofen or diphenhydramine was listed as suspect with the opposite being listed as the only concomitant medication. In the remaining 21 cases ibuprofen (17) or diphenydramine (4) was reported as suspect and the individual was receiving two or more concomitant medications including either ibuprofen or diphenhdyramine. The 42 cases included one or more of the following adverse events:

Hypersensitivity or skin reactions
Face Edema-4
Anaphylaxis-1
Pruritus/rash/hives/urticaria-8
Wheezing/hyperventilation-2
Steven-Johnson Syndrome-1

CNS
Hallucinations-1
Insomnia-1
Convulsion-1
Nervousness/paradoxical excitement-2

Infectious Reactions
Infection of Varicella Lesion-3
Necrotizing faciitis/cellulitis-6
Septic arthritis-1

Miscellaneous reactions
Dehydration-1
Hemolytic anemia-1
Glossitis-2
Stomatitis/burning or itching throat-7
Injection site reaction-1
Poorly characterized respiratory disorder-1
Hyperventilation-1
Duodenal ulcer perforation-1
Vomiting-1
Thrombocytopenia-1
Mydriasis-1

There were no reported deaths in children receiving a combination of diphenhdyramine and ibuprofen. Seventeen cases reported either hospitalization or a visit to an emergency room. Ten of the 17 cases were of infectious reactions including necrotizing fasciitis or cellulitis (6), septic arthritis (1), and infection of a varicella lesion (3). In all 10 cases, the children were receiving ibuprofen and diphenhydramine for symptoms associated with varicella. Three physicians reported the 10 cases in 1995 and all three physicians worked for county health departments. One physician was co-author of a case-control study that investigated ibuprofen use and other risk factors for necrotizing faciitis in the setting of primary varicella. The authors concluded that ibuprofen use was associated with necrotizing faciitis in the setting of primary varicella.[1] We did not conduct a thorough review of this and other related studies[2-3] (which may or may not have found an association) because it was beyond the scope of this review.

There were seven remaining cases in children that reported hospitalization. There is no indication in these cases that the event occurred as a result of the individual taking both medications simultaneously and these events could have occurred with either product or possibly from underlying illness. These cases are briefly described below:

- Two were allergic/anaphylactic reactions that were possibly related ibuprofen and/or diphenhydramine. One was described as wheezing and fast respirations following ingestion of ibuprofen. It appears as though the child may have been given diphenhydramine (and other products such as albuterol and solu medrol) to treat her allergic reaction even though these medications were reportedly ingested concomitantly with ibuprofen. There was no further information provided in this case. In the second case, a child reportedly developed an anaphylactic reaction consisting of coldness of his hands and feet, difficulty breathing, shaking, and swelling of his lips and face following ingestion of both diphenhydramine elixir and ibuprofen suspension. This case was confounded because he had an allergy to pork and other foods and his mother suspected that his breast-feeding after she had eaten pork might have contributed to this event.
- A 2-year-old female who developed Stevens-Johnson Syndrome (SJS) which was felt to be associated with either ibuprofen suspension or varicella virus. The child had received ibuprofen for fever associated with varicella infection. She was also receiving diphenhydramine and several topical products concomitantly presumably for varicella lesions. She was hospitalized with SJS (91.5% TBA involvement) but reportedly recovered.
- A 2-year-old male who developed a duodenal ulcer perforation following 12 days of ibuprofen for fever. The child was also receiving diphenhydramine for a rash and amoxicillin for an ear infection.
- A 4-year-old female experienced a convulsion following one dose of ibuprofen suspension. The child was however taking ibuprofen for fever. She was concomitantly receiving diphenhydramine for itching.
- A 1-year-old female who was taking ibuprofen suspension and diphenhydramine for an unknown reason was hospitalized for dehydration.
- A 4-year-old male was hospitalized for jaundice and anemia (possibly hemolytic) after receiving diphenhydramine and ibuprofen. His physicians noted that all

laboratory tests to explore the etiology were unrevealing and that the events were possibly due to either viral causes or to his medication (diphenhydramine or ibuprofen).

Adult Cases

Fifty-five cases involved adults 18 years of age and greater. The ages ranged from 18 to 94 years of age (mean 48.2 years, median 46 years, n=51). Twenty-six were female and 29 were male. Seven cases reported both products as suspect, of which five also listed additional suspect medications. In eight cases, either ibuprofen or diphenhydramine was listed as suspect with the opposite being listed as the only concomitant medication. In the remaining 40 cases ibuprofen (37) or diphenydramine (3) was reported as suspect and the individual was receiving two or more co-suspect or concomitant medications including either ibuprofen or diphenhdyramine. The 55 cases included one or more of the following adverse events:

Hypersensitivity or skin reactions
Allergic reaction or allergic symptoms-5
Anaphylaxis/anaphylactoid reaction/angioedema-3
Pruritus/rash/hives/urticaria-11
Steven-Johnson Syndrome-2

CNS
Dizziness/vertigo-7
Somnolence/stupor-4
Syncope-2
Headache-2
Agitation-1
Depression-1
Hallucinations-1
Insomnia-1
Loss of memory-1
Paresthesia-1

Gastrointestinal (GI)
Upper GI bleed-4
Melena/hematemesis-2
Gastritis-1
Nausea/ "queasy stomach"-2
Abdominal pain-1

Renal Events
Acute renal failure-4
Renal insufficiency/renal toxicity/elevated BUN & Scr-3

Miscellaneous reactions
Tinnitus/decreased hearing-2
Anemia & leukopenia-1
Hyperglycemia-1
Hypertension-1
Hypotension & cyanosis-1
Increased SOB & DOE, ankle edema-1
Liver & Esophageal Cancer-1
No drug effect-1
Respiratory depression-1
Thrombocytopenia-1
Urinary retention-1

There was one reported death in 1982 in an 85-year-old male who was receiving ibuprofen 600mg QID for arthritis (follow-up mentions a total of 900mg/day). He was also receiving diphenhydramine and Moni-Stat Topical cream concomitantly. He was admitted with hallucinations, CNS depression, metabolic encephalopathy, and cessation of spontaneous respirations. The case wasn't well documented but suggested the patient suffered respiratory depression from ibuprofen accumulation secondary to renal insufficiency. He remained on a ventilator for four months and eventually died of an acute myocardial infarction.

Twenty-six cases reported either hospitalization or a visit to an emergency room. There is no indication in these cases that the event occurred as a result of the individual taking both medications simultaneously and these events could have occurred with either product or in a few cases they could have been due to underlying illness. These cases are briefly described below:

- Thirteen cases were of GI and renal adverse reactions including GI bleed and acute renal failure. These events are well known to occur with ibuprofen alone and in all 13 cases ibuprofen was listed as the only suspect medication and diphenhydramine was listed among a number of concomitant medications.
- Four were allergic/anaphylactic reactions that were possibly related to ibuprofen and/or diphenhydramine. One described the reaction as "blacked out or fainted" following ibuprofen and diphenhydramine ingestion. This patient had a previous history of rash and itching with ibuprofen use. In a second case a patient developed angioedema felt to be associated with enalapril use. The patient also received diphenhydramine for the reaction and experienced chest pain. He was on concomitant ibuprofen and docusate. In the third case, an asthmatic male took ibuprofen and 15 minutes later experienced an itchy mouth and acute asthma progressing to unconsciousness. He was on concomitant diphenydramine as well as other asthma medications. In the fourth case, a consumer reported that use of ibuprofen/pseudoephedrine was associated with an anaphylactoid reaction characterized as urticaria, facial and throat swelling, and dyspnea. She was taken to the ER. She also reports that she took excessive diphenhydramine the following day and experienced sleepiness, dizziness, shakiness, and blurred vision.

- There were two patients that developed SJS possibly associated with ibuprofen, however both cases reported additional co-suspect medications which may have played a role in the adverse event (ketorolac & Bactrim-1, cefepime-1). Diphenhydramine was listed as one of many concomitant medications in both cases.
- There were two patients that developed hematologic adverse events. One reported anemia and leukopenia possibly associated with ibuprofen, albuterol, and enteric-coated aspirin. The patient was hospitalized and ibuprofen was discontinued however at the time of this report, his white and red cells remained depressed. The other case reported thrombocytopenia in association with the use of ibuprofen intermittently over 2-3 years. The patient was admitted with a platelet count of 7000 and was treated with prednisone and platelet transfusion. Both reports listed diphenhydramine (cream in the latter case) as concomitant medication.
- A 52-year-old female consumer presented to an ER following an insect bite. She was prescribed Keflex, diphenhydramine cream, and hydrocortisone cream. That evening she self-medicated with ibuprofen. Four days later the insect bite turned black and a rash spread all over her abdomen. A new rash appeared on her thigh and her neck. She returned to the ER and was prescribed doxycycline and fluocinonide cream. She later required biopsy of the rash however the results were not provided. The consumer reported that she discontinued ibuprofen and the rash was resolving. There were additional reports of rash or hives however these did not appear to require an ER visit or hospitalization.
- There was one case of somnolence following ingestion of ibuprofen, diphenhydramine, ciprofloxacin and another product (not legible). This case was old and poorly documented. It is unclear why the patient required hospitalization.
- There were three cases with miscellaneous adverse events. In all three cases, ibuprofen was listed as a suspect agent and diphenhydramine was listed as a concomitant medication. The events include:
  - Shortness of breath, dyspnea on exertion, and ankle swelling four days after starting ibuprofen. The patient had a history of COPD and lung cancer.
  - Hyperglycemia in a patient with diabetes who took a dose of ibuprofen suspension.
  - Adenocarcinoma of the esophagus and liver in a patient who took ibuprofen and Darvocet for one year.

CONCLUSIONS

The cases in AERS provide no evidence of a drug interaction between diphenhydramine and ibuprofen. There is no indication in these cases that the event occurred as a result of the individual taking both medications simultaneously and these events could have occurred with either product or possibly from underlying illness.

Claudia B. Karwoski, PharmD

REFERENCES

1. Zerr DM, Alexander ER, Duchin JS, et al. A Case-Control Study of Necrotizing Fasciitis During Primary Varicella. Pediatrics 1999;103(4):783-90.
2. Choo PW, Donahue JG, Platt R. Ibuprofen and skin and soft tissue superinfections in children with varicella. Ann Epidemiol 1997;7(7):440-5.
3. Lesko SM, O'Brien KL, Schwartz B, et al. Invasive group A streptococcal infection with nonsteroidal antiinflammatory drug use among children with primary varicella. Pediatrics 2001;107(5):1108-15.

Table 1. Overview of AERS reports for individual ingredients		
	Diphenhydramine	**Ibuprofen**
Total reports in AERS	1823	19,178
Total deaths reported in AERS	228	615
Gender	Females – 894 Males – 670 Unknown – 259	Females – 10,251 Males – 7417 Unknown – 1510
Age distribution	< 17 years old – 230 18-70 years old – 926 >70 years old – 118 unknown - 549	< 17 years old – 4474 18-70 years old – 7763 >70 years old – 1917 unknown - 5024
20 most common preferred terms	Anxiety 107 Overdose NOS 102 Non-accidental OD 101 Pain NOS 90 Sedation 90 Dermatitis NOS 84 Convulsions NOS 83 CVA 78 Dyspnoea NOS 76 Drug interaction 74 Pruritus NOS 73 Supraventricular arrhythmia NOS 71 Urticaria 71 Drug ineffective 70 Hypersensitivity 70 Hypotension NOS 68 Tachycardia NOS 67 Dizziness 64 Hallucination NOS 64 Agitation 64	Drug ineffective 1877 Dermatitis 1114 Gastrointestinal hem 904 Vomiting NOS 839 Urticaria NOS 838 Abdominal pain 813 Accidental OD 664 Stomatitis 648 Pruritus NOS 615 Dizziness 563 Nausea 543 Dyspepsia 521 Hypersensitivity 462 Melaena 453 Dyspnoea NOS 451 Haematemesis 449 Throat irritation397 Glossitis 394 Anaemia NOS 391 Pyrexia 391

Table 2. Overview of Acetaminophen Searches			
	Acetaminophen	***Diphenhydramine-acetaminophen**	****** **Diphenhydramine-acetaminophen brand name search**
Total reports in AERS	12,602	234	97
Total deaths reported in AERS	2403	58	13
Gender	Females – 7536 Males – 4148 Unknown – 918	Females – 111 Males – 97 Unknown – 26	Females – 72 Males – 23 Unknown – 2
Age distribution	< 17 years old – 1318 18-70 years old – 6553 >70 years old – 1970 unknown – 2761	< 17 years old – 14 18-70 years old – 118 >70 years old – 5 unknown - 97	< 17 years old – 5 18-70 years old – 70 >70 years old – 8 unknown - 14
20 most common preferred terms	Drug ineffective 1764 Overdose NOS 1103 Non-accidental OD 1101 Vomiting NOS 856 Nausea 628 Hepatic Failure 556 Dermatitis NOS 524 Coma 504 Completed suicide 503 Abdominal pain NOS 493 Sedation 425 Dizziness 419 Drug Level above therapeutic 409 Hepatic function abnl 402 Pyrexia 391 Pruritus NOS 377 Hypotension NOS 341 Headache NOS 336 Accidental OD 324 Dyspnoea NOS 305	Blood pressure increase 53 Pain NOS 51 CVA 50 Anxiety 49 Supraventricular arrhythmia 49 Emotional Distress 36 Overdose NOS 25 Non-accidental OD 22 Anhedonia 18 Toxicology abnormal 18 Completed suicide 16 Drug ineffective 14 Injury NOS 14 Drug interaction 13 Vomiting 13 Fear, Focus 12 Sedation 12 Coma 10 Nausea 10 Drug Level above therapeutic 9	Overdose NOS 13 Non-accidental OD 12 Insomnia 10 Fatigue 9 LFT abnormal 8 Drug Interaction 7 Dyspnoea NOS 7 Vomiting NOS 7 Coma 6 Drug Level above therapeutic 6 Hypertension 6 Hypotension 6 Sedation 5 Confusion 5 Hepatic failure 5 Nausea 5 Thrombocytopenia 5 Agitation 4 Asthenia 4 Blood Bilirubin increased 4

* Search was for reports that contain both ingredients as suspect agents, may include products with multiple ingredients.

** Search was for brand name products that contain only acetaminophen and diphenhydramine (i.e., Tylenol PM).

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/s/

Claudia Karwoski
4/4/02 11:57:28 AM
PHARMACIST

Julie Beitz
4/5/02 07:15:08 AM
DIRECTOR

Medical Officer's Review of NDA 21-393 and NDA 21-394
Original

NDA 21-393, NDA 21-394 Medical Officer's Review	**Submission Date**: October 16, 2001 **Received Date:** October 16, 2001 **Review Completed:** March 6, 2002
Proposed Trademark:	Advil PM Liqui-Gels Advil PM Caplets
Generic Name:	Ibuprofen 200 mg/diphenhydramine HCl 25 mg liquid filled capsule Ibuprofen 200 mg/diphenhydramine citrate 38 mg tablet
Chemical Name:	
Name:	ibuprofen
Chemical Name:	2-(4-isobutylphenyl)-propionic acid
Molecular Formula:	$C_{13}H_{18}O_2$
Molecular Weight:	206.27 daltons
Name:	diphenhydramine hydrochloride
Chemical Name:	2-(Diphenylmethoxy)-N,N- dimethylethylamine monocitrate
Molecular Formula:	$C_{17}H_{21}NO \cdot C_6H_8O_7$
Molecular Weight:	291.82 daltons

Sponsor:	Whitehall-Robbins Healthcare 5 Giralda Farms Madison, NJ 07940 Contact: Mary H. Davis (973) 660-5825
Pharmacologic Category:	NSAID/antihistamine
Proposed Indication:	Analgesic/nighttime sleep-aid
Dosage Form and Route of Administration:	Oral liquid filled capsule Oral capsule-shaped tablet
NDA Drug Classification:	4S
Related IND:	IND 44,767 IND 56,521 (Advil PM Liquigels) IND — (Advil PM Caplets)
Related NDA:	NDA 20-402 (Advil Liquigels) NDA 18-989 (Advil Tablets)

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Executive Summary

I. Recommendations

A. The sponsor should submit additional information to support the efficacy of ibuprofen 400mg/diphenhydramine 50mg fixed combination liquid filled capsule in relieving occasional sleeplessness when associated with → minor aches and pain.

II. Summary of Clinical Findings

A. Efficacy

Summary of Efficacy

Study Number **Study Type** **Treatment Groups**	**Sleep Latency**	**Sleep Duration**	**Pain**
AE-97-01 Pilot Study IBU 400mg/DPH 50mg IBU 400mg DPH 50mg Placebo	Hi IBU Combo > DPH IBU > Placebo IBU > DPH	Hi IBU Combo > Placebo Hi IBU Combo > DPH IBU > Placebo IBU > DPH	Hi IBU Combo > Placebo Hi IBU Combo > DPH IBU > Placebo IBU > DPH
AE-98-01 Efficacy & Safety Study IBU 400mg/DPH 50mg IBU 400mg Placebo	Hi IBU Combo > Placebo IBU > Placebo	Hi IBU Combo > Placebo Hi IBU Combo > IBU IBU > Placebo	Hi IBU Combo > Placebo IBU > Placebo
AE-98-02 Efficacy & Safety Study IBU 400mg/DPH 50mg IBU 400mg Placebo	Hi IBU Combo > Placebo IBU > Placebo	Hi IBU Combo > Placebo Hi IBU Combo > IBU IBU > Placebo	Hi IBU Combo > Placebo IBU > Placebo IBU > Hi IBU Combo
AE-98-03 Dose-Response Study IBU 400mg/DPH 50mg IBU 200mg/DPH 25mg	Hi IBU Combo >Placebo Lo IBU Combo >Placebo	Hi IBU Combo > Placebo Hi IBU Combo > Lo IBU Combo Lo IBU Combo > Placebo	Hi IBU Combo > Placebo Hi IBU Combo > Lo IBU Combo Lo IBU Combo > Placebo
AE-98-04 Headache Study IBU 400mg/DPH 50mg Placebo		Hi IBU Combo > Placebo	Hi IBU Combo > Placebo
AE-07-08 Maximum Use Safety & Efficacy Study IBU 400mg/DPH 50mg ACT 1000mg/DPH 50mg IBU 200mg/DPH 50mg Placebo	Hi IBU Combo > Placebo Hi IBU Combo > ACT Combo Lo IBU Combo > Placebo ACT Combo > Placebo	Hi IBU Combo > Placebo Hi IBU Combo > ACT Combo Lo IBU Combo > Placebo ACT Combo > Placebo	Hi IBU Combo > Placebo Hi IBU Combo > Lo IBU Combo ACT Combo >Placebo

IBU=ibuprofen DPH=diphenhydramine HCl ACT=acetaminophen
Hi IBU Combo=IBU 400mg/DPH 50mg Lo IBU Combo=IBU 200mg/DPH 25mg
ACT Combo=ACT 1000mg/DPH 50mg >=Statistically significant ($p<0.050$, not corrected for multiple comparisons)

B. Safety

The use of ibuprofen 400mg/diphenhydramine 50mg fixed combination in relieving occasional sleeplessness when associated with minor aches and pain was not associated with any new safety findings.

C. Dosing – N/A

D. Special Population –N/A

Clinical Review

I. Clinical Background

A. Sleeplessness may occasionally accompany nighttime pain. Conditions such as muscle soreness, sprains, strains, arthritis, headaches, and outpatient surgical procedures are typical painful episodes that may interfere with sleep. To varying extents, analgesics ameliorate the painful conditions; however, either residual pain or recurring pain may still be a factor causing sleeplessness.

Analgesic/sedative combination products have been sold over-the-counter (OTC) since the early 1970's. Most of the currently marketed products contain either acetaminophen or aspirin in combination with diphenhydramine.

Since ibuprofen's pharmacokinetic/pharmacodynamic profile is indicative of fast pain relief, there is reason to believe that fast pain relief would shorten latency time to falling asleep. Because OTC antihistamines, including diphenhydramine, take time to reach peak plasma concentrations, they are most effective when taken in anticipation of sleeplessness. It is reasoned that diphenhydramine in combination with ibuprofen would be beneficial by increasing sleep duration. Consequently a fixed combination of ibuprofen 200mg and diphenhydramine HCl 25mg, intended for use at bedtime was developed and has been evaluated in a clinical program.

Both ibuprofen and diphenhydramine have been marketed throughout the world as single-ingredient products. Ibuprofen is marketed worldwide as a pain reliever and is available OTC in most countries. Diphenhydraminine is marketed globally primarily as an antihistamine for symptoms of allergy, and secondarily, as a sleep aid. Its regulatory status varies (RX or OTC) depending on the country.

Ibuprofen in combination with diphenhydramine has not been marketed either domestically or outside the United States.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, and/or other Consultant Reviews

A. Chemistry - See Chemistry Review

Drug Product Components/Composition

Component	mg/liquigel	kg/batch
Gelatin Shell		
Gelatin, NF		
FD & C Blue No. 1		
D & C Red No. 33		
Fractionated Coconut Oil, EP [c]		
/Lecithin NF		
Total Shell Weight		
Fill Material		
Ibuprofen, USP	200	
Diphenhydramine HCl, USP	25.0	
Polyethylene Glycol		
Potassium Hydroxide, NF		
Purified Water, USP		
Total Fill Weight		
Total Liquigel Weight	**887**	**1189**
Liquigels per Batch		

B. Animal Pharmacology and Toxicology - See Pharmacology and Toxicology Review

C. Microbiology – N/A

D. Neuropharmacology Consult – See Neuropharmacology Review

III. Human Pharmacokinetics and Pharmacodynamics

A. See Biopharmceutics Review

IV. Description of Clinical Data Sources

The materials reviewed include NDA 21-393, Volumes 28-48.

Clinical data in support of NDA 21-394 is cross-referenced to NDA 21-393. In support of NDA 21-394, a bioequivalence study (protocol AE-00-10) which compared the pharmacokinetic profile of ibuprofen 200mg/diphenhydramine hydrochloride 25mg liquigels to ibuprofen 200 mg/diphenhydramine citrate 38mg caplet is submitted.

Included in this medical officer's review is the evaluation of six clinical trials conducted in the United States. See Table 1 for a descriptive summary of the clinical data sources.

Table 1 – Description of Clinical Data Sources

Protocol Number	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	No. Sites	No. Subjects Randomized	Status
Phase II Study								
Pilot Study Safety/Efficacy AE-97-01 US	Double-masked, randomized, placebo-controlled	Single dose	Post-oral surgery with at least moderate pain	IBU 400mg + DPH citrate 76mg IBU 400mg DPH citrate 76mg Placebo	qhs qhs qhs qhs	1	105 (2:2:2:1)	Completed
Phase III Studies								
Safety/Efficacy AE-98-01 US	Double-masked, randomized, placebo-controlled	Single dose	Post-oral surgery with at least moderate pain	IBU 400mg + DPH HCl 50mg IBU 400mg Placebo	qhs qhs qhs	1	281 (3:3:1)	Completed
Safety/Efficacy AE-98-02 US	Double-masked, randomized, placebo-controlled	Single dose	Post-oral surgery with at least moderate pain	IBU 400mg + DPH HCl 50mg IBU 400mg Placebo	qhs qhs qhs	1	283 (3:3:1)	Completed
Dose Response AE-98-03 US	Double-masked, randomized, placebo-controlled	Single dose	Post-oral surgery with at least moderate pain	IBU 400mg + DPH HCl 50mg IBU 200mg + DPH HCl 25mg Placebo	qhs qhs qhs	1	284 (3:3:1)	Completed
Safety/Efficacy AE-98-04 US	Double-masked, randomized, Placebo-controlled	Single dose	History of tension headaches of at least moderate severity	IBU 400mg + DPH HCl 50mg Placebo	qhs qhs	1	162 (1:1)	Completed
Maximum Use Safety/Efficacy AE-97-08 US	Double-masked, randomized, placebo-controlled	10 days	OTC consumers of analgesic /nighttime combination products	ACT 1000mg + DPH HCl 50 mg IBU 400mg + DPH HCl 50mg IBU 200mg + DPH HCl 25mg Placebo	qhs qhs qhs qhs		1016 (2:2:1:1)	Completed

IBU = ibuprofen DPH = diphenhydramine ACT = acetaminophen

Advil PM Liquigel (ibuprofen 200mg/dihenhydramine HCl 25mg)
Advil PM Caplet (ibuprofen 200mg/dihenydramine citrate 38mg)

V. Clinical Review Methods

The primary objective in this review was to determine the safety and efficacy of the combination ibuprofen and diphenhydramine as a pain reliever and nighttime sleep-aid. This includes the evaluation of the contribution of each component to the efficacy of the combination.

VI. Integrated Review of Efficacy

Study No. AE-97-01

Title: Advil PM Pilot Oral Surgery Study

Objectives: To determine whether the inpatient oral surgery model with phase advancement is an appropriate paradigm for evaluating the efficacy of analgesic/sleep aid combination products;

To evaluate the analgesic and sedative efficacy of a single dose of ibuprofen 400mg/diphenhydramine citrate 76mg to ibuprofen 400mg, diphenhydramine citrate 76mg, and placebo.

Study Design

This was a randomized (stratified by gender and baseline pain), inpatient, four-arm, placebo-controlled, single-dose, double-blinded, double-dummy, parallel group, single-center trial. Following oral surgery, subjects were housed at the site overnight. When subjects experienced at least moderate pain and it was between 7:30 PM and 10:30 PM (at least 1 hour earlier than their usual bedtime), they received masked study medication and were required to go to bed for the evening. The four treatment groups were 1) Ibuprofen 400mg/diphenhydramine citrate 76mg, 2) Ibuprofen 400mg, 3) Diphenhydramine citrate 76mg, and 4) Placebo.

One hundred five subjects (2:2:2:1), 16-45 years of age, who underwent surgical extraction of one or two impacted molars were enrolled. Enrolled subjects were stratified according to baseline pain and gender.

At specified intervals over a 3-hour evaluation period, a nurse observer determined visually whether or not the subject was asleep. At 90, 120, and 180 minutes post-dose, subjects were interviewed to assess their pain intensity and pain relief. The following morning (or at the time of rescue medication), subjects were asked to assess ease of falling asleep, duration of sleep, and global assessments of sleep and pain relief.

Test Drug Schedule: Subjects received a single dose of masked study medication when they experienced at least moderate pain and it was between 7:30 PM and 10:30 PM. Subjects were then required to go to bed for the evening.

Study Medications

Drug	Per Unit	Per Dose	Lot Number
Ibuprofen film-coated tablets	200 mg	400 mg	WH-0432-0069A
Diphenhydramine citrate capsule	38 mg	76 mg	WH-0552-005B
Matching placebo film-coated tablet	Inert Ingredients		WH-0436-0077A
Matching placebo capsule	Inert Ingredients		WH-0436-0053B

Study Population

Inclusion Criteria

Males and females of any race were eligible for inclusion in the study provided they met all of the following inclusion criteria:

1. 16-45 years of age;

2. were examined by the attending dentist or physician and medically cleared to participate in the study. In general, the subjects were in good health and had no contraindications to any of the study medications;

3. had undergone surgical extraction of one or two impacted third molars, one of which was at least a partial bony mandibular impaction (if two molars were extracted, the other was the corresponding maxillary molar);

4. received only the following preoperative medication(s)/anesthetic(s): bupivacaine with or without vasoconstrictor, nitrous oxide, and, in the event significant post-surgical pain was experienced before 6:00 PM, lidocaine or mepivacaine;

5. had not taken any form of medication within 3 days of admission (except oral contraceptives and prophylactic antibiotics) and agreed not to take any medication (other than that provided to them by the Investigator) throughout the study;

6. had not consumed alcoholic beverages or foods and beverages containing xanthines for 2 hours prior to surgery and agreed not to consume any of these foods or beverages throughout the study;

7. understood the rating scales (as judged by the study coordinator);

8. were able to read, comprehend, and sign the consent form. Subjects under 18 years of age had parental or guardian consent.

Exclusion Criteria

Subjects were to be excluded from participation in the study if any of the following were noted:

1. a serious medical condition (*e.g.,* poorly controlled hypertension, poorly controlled diabetes, significantly impaired cardiac, renal, or hepatic function, hyper- or hypothyroidism);

2. a chronic breathing problem such as asthma, emphysema, or chronic bronchitis;

3. a history (within 2 years of enrollment) or presence of peptic ulcer disease;

4. a history or presence of bleeding disorder(s);

5. symptomatic benign prostatic hyperplasia or urethral stricture;

6. glaucoma;

7. an acute local infection at the time of surgery that could confound the post-surgical evaluation;

8. use of a prescription or non-prescription drug with which the administration of ibuprofen or any other nonsteroidal anti-inflammatory drug is contraindicated (*e.g.,* coumarin-type anticoagulants, thiazides, furosemide, probenecid);

9. use of prescription or non-prescription drug with which the administration of diphenhydramine or any other antihistamine is contraindicated (*e.g.,* other antihistamines, tranquilizers, sedatives);

10. breast feeding or pregnant females (verified by a urine-based pregnancy test);

11. females of either child-bearing potential or post-menopausal for less than 2 years who were not using one of the following medically-approved methods of contraception: oral, transdermal, injectable, or implanted contraceptives, intrauterine device, diaphragm, condom, abstinence, or surgical sterility;

12. habitual use of analgesic drugs (*i.e.,* routine use of oral analgesics five or more times per week);

13. any history of alcoholism or substance abuse; or routine consumption of three or more alcohol containing beverages per day;

14. a known sensitivity to ibuprofen, other nonsteroidal anti-inflammatory agents, diphenhydramine or other antihistamines (Note: Gastric intolerance was not considered sensitivity);

15. history of regularly going to bed earlier than 11:00 PM;

16. a history or presence of chronic or severe sleeping problems which required an OTC or prescription hypnotic;

17. completed transmeridian travel within 1 week prior to study participation;

18. received any form of treatment for depression in the past year;

19. use of tobacco containing products or nicotine transdermal patches within 6 months of enrollment;

20. had taken an investigational drug within the past 30 days;

21. previous participation in the study;

22. a member or a relative of the study site staff or Sponsor directly involved in the study.

Efficacy Variables

Primary Efficacy Variables

- Sleep: Nurse-observed sleep latency
- Pain: Sum of pain relief plus pain intensity difference over 0-3 hours (SPRID3)

Secondary Efficacy Variables: Sleep

- Ease of falling asleep
- Duration of sleep
- Global assessment of the study medication as a sleep-aid
- Actual and cumulative proportions of subjects asleep at each observation point
- Post-surgical actigraphic assessments of sleep latency, total sleep time, and sleep efficiency

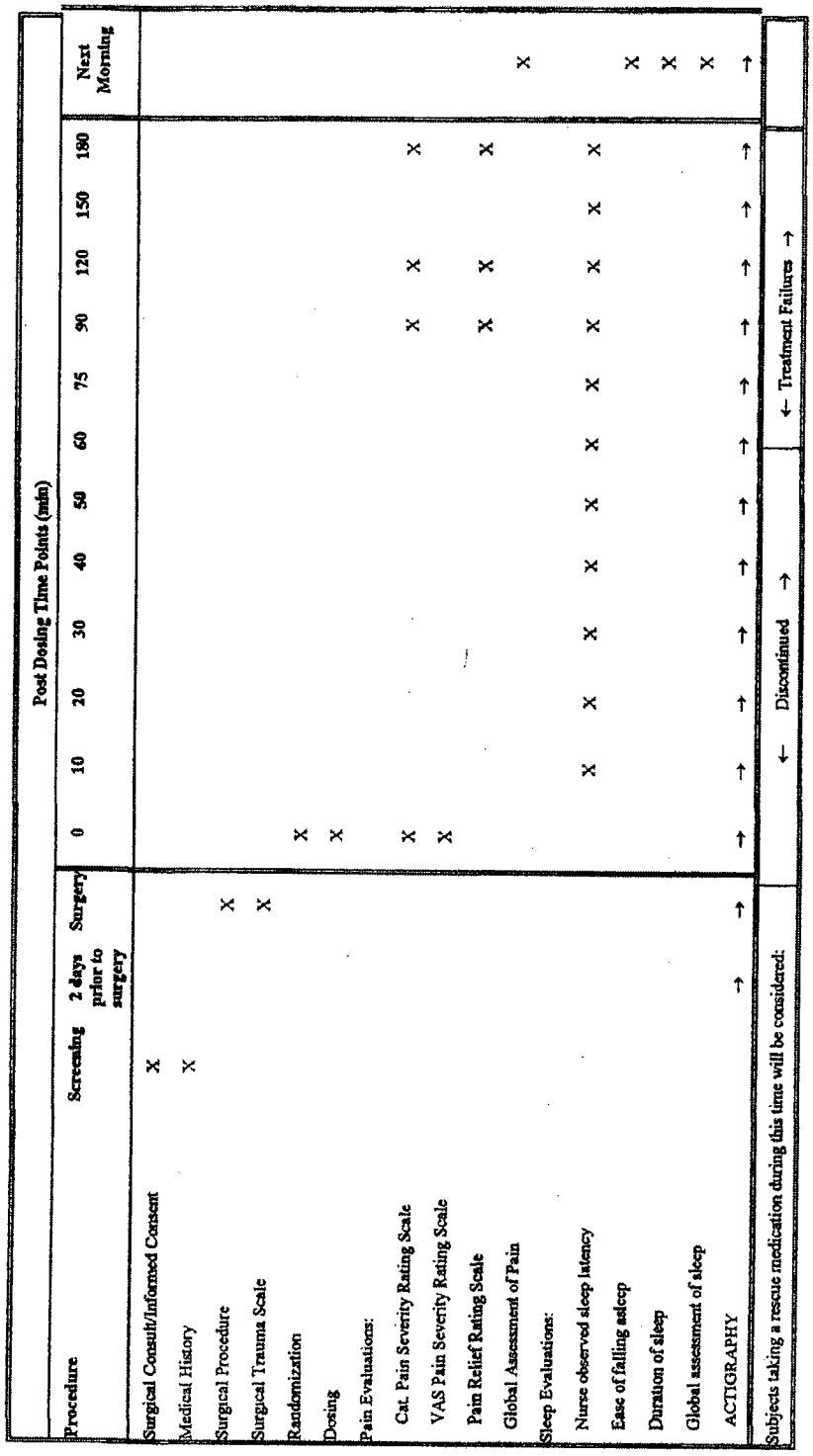
Secondary Efficacy Variables: Pain

- Pain intensity difference (PID), pain relief rating (PRR), and pain relief combined with pain intensity (PRID) scores at 90, 120, and 180 minutes
- Sum of PID and the sum of PRR scores over 0-3 hours (SPID3 and TOTPAR3, respectively)
- Global assessment of the study medication as a pain reliever
- Duration of analgesia (time to rescue medication and, although not specified in the protocol, proportion of subjects taking rescue medication by each pain assessment time point and by the wake-up time)

Safety Variables

- Adverse events

STUDY FLOW CHART



Procedure	Screening	2 days prior to surgery	Surgery	Post Dosing Time Points (min) 0	10	20	30	40	50	60	75	90	120	150	180	Next Morning
Surgical Consult/Informed Consent	X															
Medical History	X															
Surgical Procedure			X													
Surgical Trauma Scale			X													
Randomization				X												
Dosing				X												
Pain Evaluations:																
Cat. Pain Severity Rating Scale				X								X	X		X	
VAS Pain Severity Rating Scale				X												
Pain Relief Rating Scale												X	X		X	
Global Assessment of Pain																X
Sleep Evaluations:																
Nurse observed sleep latency					X	X	X	X	X	X	X	X	X	X	X	
Ease of falling asleep																X
Duration of sleep																X
Global assessment of sleep																X
ACTIGRAPHY		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Subjects taking a rescue medication during this time will be considered:					←	Discontinued	→				← Treatment Failure →					

Advil PM Liquigel (ibuprofen 200mg/dihenhydramine HCl 25mg)
Advil PM Caplet (ibuprofen 200mg/dihenydramine citrate 38mg)

Subject Disposition and Demographics

Table 2 - Subject Disposition

	Number of Subjects (%)				
	IBU + DPH	**IBU**	**DPH**	**Placebo**	**Total**
Randomized	29 (27.6)	31 (29.5)	31 (21.5)	14 (13.3)	105
Completed Study	29 (27.6)	31 (29.5)	31 (29.5)	14 (13.3)	105 (100.0)

IBU=ibuprofen 400mg DPH=diphenhydramine citrate 76mg

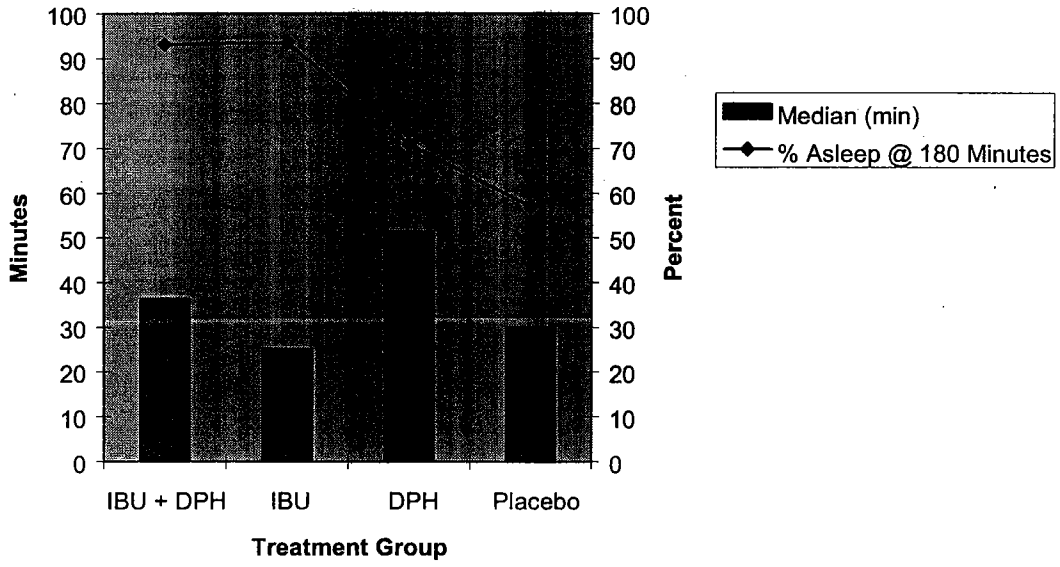
Summary of Demographic Data

	Total N=105	Placebo N=14	IBU/DPH N=29	IBU N=31	DPH N=31	Trt p-value #
Gender						
MALE	42 (40.0%)	6 (42.9%)	12 (41.4%)	12 (38.7%)	12 (38.7%)	0.991
FEMALE	63 (60.0%)	8 (57.1%)	17 (58.6%)	19 (61.3%)	19 (61.3%)	
RACE						
CAUCASIAN	78 (74.3%)	11 (78.6%)	24 (82.8%)	24 (77.4%)	19 (61.3%)	0.734
BLACK	7 (6.7%)	1 (7.1%)	0 (0%)	2 (6.5%)	4 (12.9%)	
ASIAN	4 (3.8%)	0 (0%)	1 (3.4%)	1 (3.2%)	2 (6.5%)	
HISPANIC	16 (15.2%)	2 (14.3%)	4 (13.8%)	4 (12.9%)	6 (19.4%)	
AGE (yrs.)						
MEAN	23.8	24.2	23.9	23.5	23.7	0.989
STD	7.5	9.7	7.5	7.2	6.9	
MEDIAN	22.0	21.0	21.0	22.0	21.0	
RANGE	(16, 44)	(16, 44)	(16, 42)	(16, 44)	(16, 43)	
WEIGHT (lbs.)						
MEAN	157.6	160.2	151.8	163.4	155.9	0.485
STD	36.5	39.9	35.4	31.1	41.4	
MEDIAN	145.0	142.0	141.0	160.0	140.0	
RANGE	(105, 271)	(118, 245)	(110, 271)	(120, 240)	(105, 250)	
HEIGHT (ins.)						
MEAN	67.1	67.6	66.7	67.5	66.9	0.684
STD	4.3	5.3	3.6	4.4	4.3	
MEDIAN	67.0	66.0	66.0	68.0	66.0	
RANGE	(57, 78)	(61, 78)	(57, 73)	(59, 77)	(60, 76)	

#: P-values for gender and race were computed using the Cochran-Mantel-Haenszel test, controlling for baseline PSR, and gender when appropriate. P-values for age, weight, and height were computed using ANOVA, with treatment, baseline PSR and gender effects.
*: Statistically significant at $p \leq 0.15$.

Efficacy **Intent-to-Treat Population**

Median and % of Subjects Asleep at 180 Minutes



Reviewer's Comments:

The median sleep latencies were 36 minutes for the fixed combination, 25 minutes for ibuprofen, 50 minutes for diphenhydramine citrate, and 30 minutes for placebo.

The percentage of subjects who were asleep 180 minutes after administration of masked study medication were 93.1% for the fixed combination, 93.5% for ibuprofen, 71.0% for diphenhydramine citrate, and 57.1% for placebo.

Treatment Group Comparisons – Nurse Observed Sleep Latency

	IBU + DPH vs. IBU	IBU + DPH vs. DPH	IBU + DPH vs. Placebo	IBU vs. Placebo	DPH vs. Placebo	IBU vs. DPH
p-value	0.675	0.019	0.068	0.033	0.881	0.005

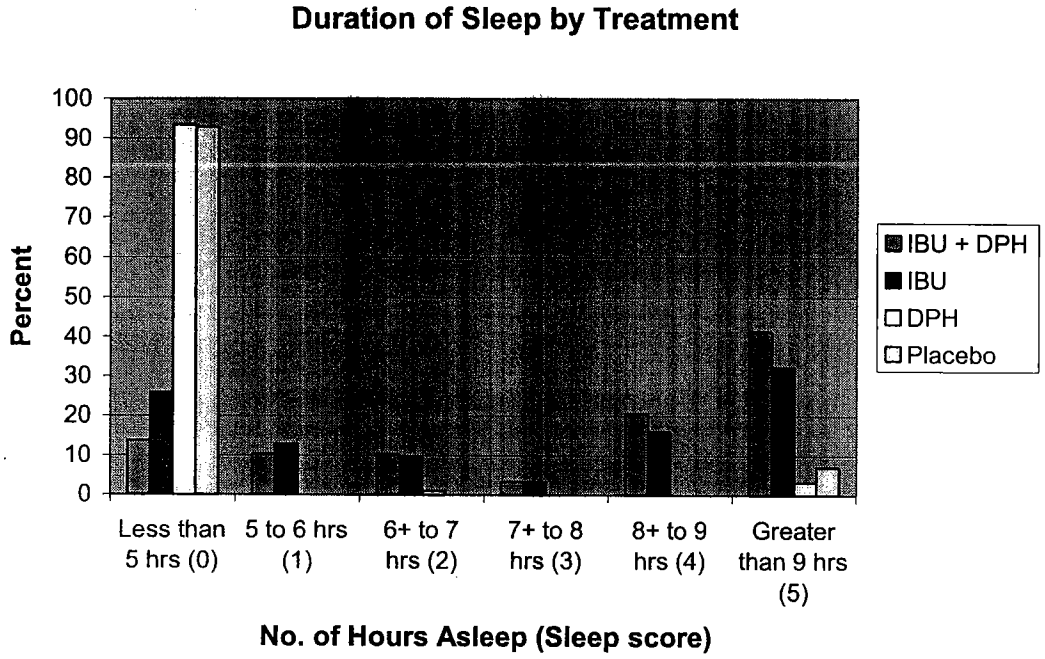
IBU=ibuprofen 400mg DPH=diphenhydramine citrate 76mg

Reviewer's Comments:

The effect on sleep latency of the fixed combination as compared to ibuprofen monotherapy (p=0.675) and placebo (p=0.068) were <u>not</u> statistically significant.

The effect on sleep latency of the fixed combination as compared to diphenhydramine citrate monotherapy (p=0.019) and the effect on sleep latency of ibuprofen (p=0.033) as compared to placebo demonstrate the effect of ibuprofen.

The effect on sleep latency of diphenhydramine citrate (p=0.881) as compared to placebo was <u>not</u> statistically significant.



Mean Sleep Score – Categorical Scale (0-5)

	IBU + DPH	IBU	DPH	Placebo
Mean Sleep Score	3.31	2.68	0.23	0.36

IBU=ibuprofen 400mg DPH=diphenhydramine 50mg

Advil PM Liquigel (ibuprofen 200mg/dihenhydramine HCl 25mg)
Advil PM Caplet (ibuprofen 200mg/dihenydramine citrate 38mg)

Treatment Group Comparisons – Duration of Sleep

	IBU + DPH vs. Placebo	IBU + DPH vs. DPH	IBU vs. IBU + DPH	IBU vs. Placebo	IBU vs. DPH	DPH vs. Placebo
*p-value	<0.001	<0.001	0.131	<0.001	<0.001	0.845

*p-values from ANOVA model with treatment, baseline PSR, and gender terms
IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Reviewer's Comments:

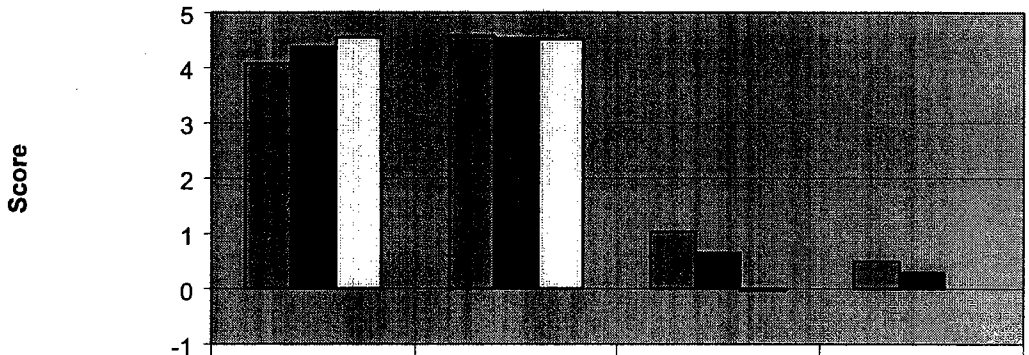
The effect on duration of sleep of the fixed combination as compared to ibuprofen monotherapy (p=0.131) was not statistically significant.

The effect on duration of sleep of the fixed combination as compared to diphenhydramine monotherapy (p<0.001) and placebo (p<0.001) were statistically significant.

The effect on sleep duration of ibuprofen monotherapy as compared to diphenhydramine monotherapy (p<0.001) and placebo (p<0.001) were statistically significant.

The effect on duration of sleep of diphenhydramine monotherapy as compared to placebo (p=0.845) was not statistically significant.

Mean Summary Pain Scores (SPRID) Over Time



	IBU + DPH	IBU	DPH	Placebo
90 Minutes	4.07	4.58	1.03	0.5
120 Minutes	4.38	4.53	0.65	0.29
180 Minutes	4.55	4.52	-0.03	0

Treatment

Advil PM Liquigel (ibuprofen 200mg/dihenhydramine HCl 25mg)
Advil PM Caplet (ibuprofen 200mg/dihenydramine citrate 38mg)

Reviewer's Comments:

The mean summary pain scores (sum of pain relief and pain intensity difference) for the fixed combination and ibuprofen monotherapy were comparable at all time points measured.

The mean summary pain scores for diphenhydramine citrate and placebo were comparable and were approximately 25% or less as compared to the scores for the fixed combination and ibuprofen at all time points measured.

Treatment Group Comparisons – Summary Pain Scores

p-value @	IBU vs. IBU + DPH	IBU + DPH vs. DPH	IBU + DPH vs. Placebo	IBU vs. Placebo	DPH vs. Placebo	IBU vs. DPH
90 minutes	0.301	< 0.001	< 0.001	< 0.001	0.418	< 0.001
120 minutes	0.740	< 0.001	< 0.001	< 0.001	0.592	< 0.001
180 minutes	0.989	< 0.001	< 0.001	< 0.001	0.928	< 0.001

IBU=ibuprofen 400mg DPH=diphenhydramine citrate 76mg

Reviewer's Comments:

The pain relief effect of the fixed combination as compared to ibuprofen alone was <u>not</u> statistically significant at all time points measured.

The pain relief effect of the fixed combination as compared to DPH alone and placebo <u>were</u> statistically significant at all time points measured

The pain relief effect of ibuprofen as compared to placebo <u>was</u> statistically significant at all time points measured.

The pain relief effect of DPH as compared to placebo was <u>not</u> statistically significant at all time points measured.

Safety

Adverse Events

All of the 105 randomized subjects received study medication and were included in the safety analysis. One serious adverse event was reported during the study and it occurred in the diphenhydramine treatment group. The event resolved with treatment and the subject completed the study. There were no deaths during the study.

Serious Adverse Events

Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C from Study
40021	Diphenhydramine HCl	Cellulitis	Resolved w/Tx	No

The most frequent adverse events in subjects treated with the fixed combination were headaches (2 patients).

Number (%) of Subjects with Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	IBU + DPH N=29	IBU N=31	DPH N=31	Placebo N=14
	N (%)	N (%)	N (%)	N (%)
All events	4 (13.8)	4 (12.9)	3 (9.7)	1 (7.1)
Body as a Whole				
Headache	2 (6.9)			
Cellulitis			1 (3.2)	
Digestive				
Vomitting	1 (3.4)	1 (3.2)	1 (3.2)	1 (7.1)
Nausea	1 (3.4)	2 (6.5)		
Diarrhea		1 (3.2)		
Nervous				
Dizziness			1 (3.2)	

IBU=ibuprofen 400mg DPH=diphenhydramine citrate 76mg

Reviewer's Summary of Efficacy and Safety

The effect on sleep latency and pain relief of the fixed combination was numerically superior to diphenhydramine monotherapy demonstrating an effect of ibuprofen. No significant difference between the combination and ibuprofen was observed.

Adverse experiences for the fixed combination were similar to those of the individual monotherapies.

Study No. AE-98-01

Title: Advil PM Oral Surgery Study I

Objectives: To evaluate the analgesic and sedative efficacy of Advil PM Liqui-Gels (ibuprofen 400mg/diphenhydramine hydrochloride 50mg) compared to ibuprofen liquigels (400mg) and placebo.

Study Design

This was a randomized (stratified by baseline pain and gender), inpatient, placebo-controlled, three-arm, single-dose, double-blinded, parallel group, single-center trial. Following oral surgery, subjects were housed and observed at a clinic site overnight. When subjects experienced at least moderate pain and it was between approximately 6:30 PM and 8:00 PM (at least 3 hours earlier than their usual bedtime), they received masked study medication and were required to go to bed for the evening. The three treatment groups were 1) Ibuprofen 400mg/diphenhydramine HCl 50mg, 2) Ibuprofen 400mg, and 3) Placebo.

Two hundred eighty-one subjects (3:3:1), 16-45 years of age, who underwent extraction of one or two molars were enrolled. Enrolled subjects were stratified according to baseline pain and gender.

At specified intervals over a 3-hour period, a nurse observer determined visually whether or not the subject was asleep. At 90 and 120 minutes post-dose, subjects were interviewed to assess their pain severity and pain relief. The following morning (or at the time of rescue medication), subjects were asked to assess ease of falling asleep, duration of sleep, and global assessment of the medication as a sleep-aid and pain reliever.

Test Drug Schedule: Subjects received a single dose of masked study medication when they experienced at least moderate pain and it was approximately between 6:30 PM and 8:00 PM. Subjects were then required to go to bed for the evening.

Study Medications

Drug	Per Unit	Per Dose	Lot Number
Ibuprofen/Diphenhydramine hydrochloride liquigel (Advil PM Liqui-Gel)	200 mg/25 mg	400 mg/50 mg	WH-0723-0005
Ibuprofen liquigel (Advil Liqui-Gel)	200 mg	400 mg	WH-0693-0003
Placebo	Inert Ingredients		WH-0689-0005

Study Population

Inclusion Criteria

Males and females of any race were eligible for inclusion in the study provided they met all of the following inclusion criteria:

1. they were 16 to 45 years of age;

2. they were examined by the attending dentist or physician and medically cleared to participate in the study. In general, the subjects were in good health and had no contraindications to any of the study medications;

3. they were outpatients who had undergone surgical extraction of one or two impacted third molars, one of which was at least a partial bony mandibular impaction (if two molars were extracted, the other was the corresponding maxillary molar);

4. they received only one of the following two preoperative medication(s)/anesthestic(s) regimens: i) long-acting local anesthetic (bupivacaine) with or without vasoconstrictor, nitrous oxide, and, in the event significant postsurgical pain was experienced before 4 PM, lidocaine or mepivacaine; or ii) short-acting local anesthetic(lidocaine or mepivacaine) with or without vasoconstrictor and nitrous oxide;

5. they had not taken any form of medication within 3 days of admission (except oral contraceptives and prophylactic antibiotics) and agreed not to take any medication (other than that provided to them) throughout the study;

6. they had not consumed alcoholic beverages, or food and beverages containing xanthines for 2 hours prior to surgery and agreed not to consume any of these foods or beverages throughout the study;

7. they understood the rating scales (as judged by the study coordinator);

8. they were able to read, comprehend, and sign the consent form; and

9. if they were under 18 years of age, they must have had parental or guardian consent.

Exclusion Criteria

Subjects were excluded from participating in the study if any of the following were noted:

1. a serious medical condition (*e.g.,* poorly controlled hypertension, poorly controlled diabetes, significantly impaired cardiac, renal, or hepatic function, hyper- or hypothyroidism);

2. a chronic breathing problem such as asthma, emphysema, or chronic bronchitis;

3. a presence or history (within 2 years of enrollment) of peptic ulcer disease;

4. a presence or history of bleeding disorder(s);

5. symptomatic benign prostatic hyperplasia or urethal stricture;

6. glaucoma;

7. an acute local infection at the time of surgery that could confound the post-surgical evaluation;

8. use of a prescription or non-prescription drug with which the administration of ibuprofen or any other NSAID was contraindicated (*e.g.,* coumarin-type anticoagulants, thiazides, furosemide, probenecid);

9. use of a prescription or non-prescription drug with which the administration of diphenhydramine or any other antihistamines, tranquilizers, sedatives);

10. use of an antihistamines prior to study entry within the time periods listed:

- non- and low-sedating oral antihistamines (*e.g.,* Claritin, Allegra, Zyrtec, or Semprex): 72 hours;
- Hismanal (astemizole) (if regular use is > 3 days): 14 days;
- Hismanal (if regular use is ≤ 3 days): 72 hours;
- all other oral antihistamines: 48 hours;
- nasal and ocular antihistamines (*e.g.,* Astelin, Livostin, levocabastine): 72 hours;
- intramuscular administration of any antihistamine: 72 hours;

11. breast feeding or pregnant females, as verified by a urine-based pregnancy test;

12. women of child-bearing potential or who were post-menopausal for less than 2 years who were not using one of the following medically-approved methods of contraception: oral, injectable, transdermal, or implanted contraceptives, IUD, diaphragm, condom, abstinence, or surgical sterility;

13. habituation to analgesic drugs (*i.e.,* routine use of oral analgesics five or more times per week);

14. a history of alcoholism or substance abuse or routine consumption of three or more alcohol containing beverages per day;

15. a known sensitivity to ibuprofen, other NSAIDs, diphenhydramine, or other antihistamines (Note: gastric intolerance is not considered sensitivity);

16. a history of regularly going to bed earlier than 11 PM;

17. a history or presence of chronic or severe sleep problems which does not respond to OTC medication and requires a prescription hypnotic or sedative;

18. had traveled across time zones within one week prior to study participation;

19. received any form of treatment for depression in the past 6 months;

20. had taken any form of psychotropic agent in the past 6 months;

21. were using nicotine transdermal patches, spray, or gum at the time of screening;

22. had taken an investigational drug within the past 30 days;

23. previous participation in the study;

24. a member or a relative of the study site staff or Sponsor directly involved in the study.

Efficacy Variables

Primary Efficacy Variables

- Sleep: Cumulative percentage of subjects asleep at 60 minutes post-dosing (based on nurse observed sleep latency assessments)

- Pain: Time-weighted sum of pain relief and pain intensity differences from baseline over 0-2 hours (SPRID2)

Secondary Efficacy Variables: Sleep

- Duration of sleep;

- Sleep latency (based on the nurse observer);

- Cumulative and actual percentage of subjects asleep at each observed time point (other than the 60-minute time point for the cumulative percentage of subjects asleep);

- Ease of falling asleep;

- Global evaluation of study medication as a sleep-aid.

Secondary Efficacy Variables: Pain

- Pain intensity difference (PID), pain relief, and pain intensity difference combined with pain relief (PRID) scores at 90 and 120 minutes;
- Summary efficacy measures: Time-weighted sum of pain intensity difference scores (SPID) and pain relief scores (TOTPAR) over 0-2 hours;
- Global evaluation of study medication as a pain reliever.

Safety Variables

- Adverse events

STUDY FLOW CHART

Procedure	Screening	Surgery	Post Dosing Timepoints (min)													
			0	10	20	30	40	50	60	75	90	120	150	180	Next Morning
Surgical Consult/Informed Consent	X														
Medical History	X														
Surgical Procedure (between 1-2:30pm or 3-4pm)		X													
Surgical Trauma Scale		X													
Randomization			X												
Dosing			X												
Pain Evaluations:															
Cat. Pain Severity Rating Scale[a]			X[c]								X	X			
VAS Pain Severity Rating Scale			X[c]												
Pain Relief Rating Scale[a]											X	X			
Global Assessment of Pain[b]															X
Sleep Evaluations:															
Nurse observed sleep latency				X	X	X	X	X	X	X	X	X	X	X	
Ease of falling asleep[b]															X
Duration of sleep[b]															X
Global assessment of sleep[b]															X
Subjects taking a rescue medication during this time will be considered:			← Discontinued →										← Treatment Failure →		

[a] If rescue occurs prior to 120 minutes post-dose, pain severity and pain relief assessments will be completed within ± 1 minute of the time rescue medication is taken.
[b] If rescue occurs prior to waking the next morning, these assessments will be completed within ± 1 minute of the time rescue medication is taken.
[c] To be completed within 5 minutes prior to the administration of study medication.

Protocol Version: September 8, 1998

Subject Disposition and Demographics

Subject Disposition

	Number of Subjects (%)			
	IBU + DPH	IBU	Placebo	Total
Randomized	122 (43.4)	119 (42.3)	40 (14.2)	281
Discontinued from Study	1 (0.8)	1 (0.8)	0 (0)	2 (0.7)
Completed Study	121 (99.2)	118 (99.2)	40 (100)	279 (99.3)

IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Summary of Reasons for Premature Discontinuation from Study

Reason for Discontinuation	Number (%) of Subjects		
	IBU + DPH N=122	IBU N=119	Placebo N=40
Adverse events	1 (0.8)	1 (0.8)	0 (0)

IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

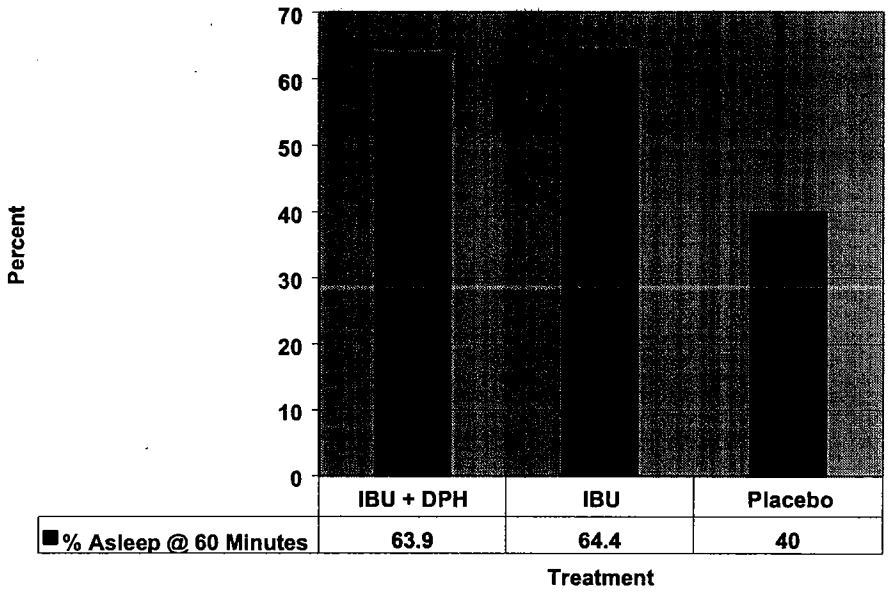
Demographic Data
Intent-to-Treat Subjects

		Total N=280	Placebo N=40	IBU400/DPH50 N=122	IBU400 N=118	p-value#
GENDER						
	MALE	122 (43.6%)	17 (42.5%)	54 (44.3%)	51 (43.2%)	0.977
	FEMALE	158 (56.4%)	23 (57.5%)	68 (55.7%)	67 (56.8%)	
RACE						
	CAUCASIAN	201 (71.8%)	32 (80.0%)	91 (74.6%)	78 (66.1%)	0.414
	BLACK	12 (4.3%)	2 (5.0%)	5 (4.1%)	5 (4.2%)	
	ASIAN	10 (3.6%)	0 (0%)	6 (4.9%)	4 (3.4%)	
	HISPANIC	54 (19.3%)	5 (12.5%)	19 (15.6%)	30 (25.4%)	
	OTHER	3 (1.1%)	1 (2.5%)	1 (0.8%)	1 (0.8%)	
AGE (yrs.)						
	MEAN	21.4	21.8	21.5	21.1	0.696
	STD	4.6	4.9	4.7	4.5	
	MEDIAN	20.0	21.0	20.5	20.0	
	RANGE	(16, 39)	(16, 34)	(16, 39)	(16, 36)	
WEIGHT (lbs.)						
	MEAN	154.5	159.2	156.1	151.2	0.221
	STD	32.7	30.6	36.1	29.4	
	MEDIAN	150.0	157.5	150.0	147.0	
	RANGE	(90, 310)	(113, 242)	(90, 310)	(100, 263)	
HEIGHT (ins.)						
	MEAN	67.7	68.4	67.8	67.3	0.051b
	STD	3.8	3.5	3.9	3.8	
	MEDIAN	67.0	68.0	68.0	67.0	
	RANGE	(60, 77)	(60, 76)	(61, 77)	(60, 77)	

#: P-values for gender and race from the Cochran-Mantel-Haenszel test, controlling for baseline pain severity rating(PSR) and gender when appropriate
P-values for age, weight, and height from ANOVA model with treatment, baseline PSR, and gender terms.
*: Statistically significant at $p \leq 0.05$.
b: Marginally significant ($0.05 < p \leq 0.10$).

Efficacy **Intent-to-Treat Population**

Cumulative % of Subjects Asleep at 60 Minutes



Reviewer's Comments:

The cumulative percentage of subjects asleep at 60 minutes after administration of masked study medication were 63.9% for the fixed combination, 64.4% for ibuprofen monotherapy, and 40.0% for placebo.

Treatment Group Comparisons – Nurse Observed Sleep Latency

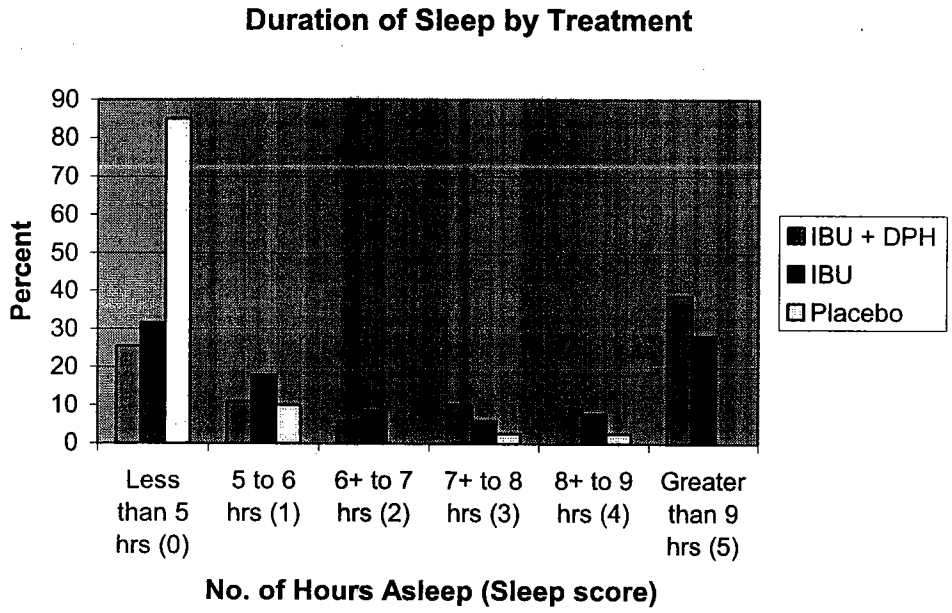
	IBU + DPH vs. IBU	IBU + DPH vs. Placebo	IBU vs. Placebo
p-value	0.915	0.008	0.006

IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Reviewer's Comments:

The effect on sleep latency of the fixed combination as compared to ibuprofen monotherapy (p=0.915) was not statistically significant.

The effect on sleep latency of the fixed combination as compared to placebo (p=0.008) was statistically significant.



Mean Sleep Score – Categorical Scale (0-5)

	IBU + DPH	IBU	Placebo
Mean Sleep Score	2.83	2.25	0.28

IBU=ibuprofen 400mg DPH=diphenhydramine 50mg

Treatment Group Comparisons – Duration of Sleep

	IBU + DPH vs. Placebo	IBU + DPH vs. IBU	IBU vs. Placebo
*p-value	<0.001	0.022	<0.001

*p-values from ANOVA model with treatment, baseline PSR, and gender terms
IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

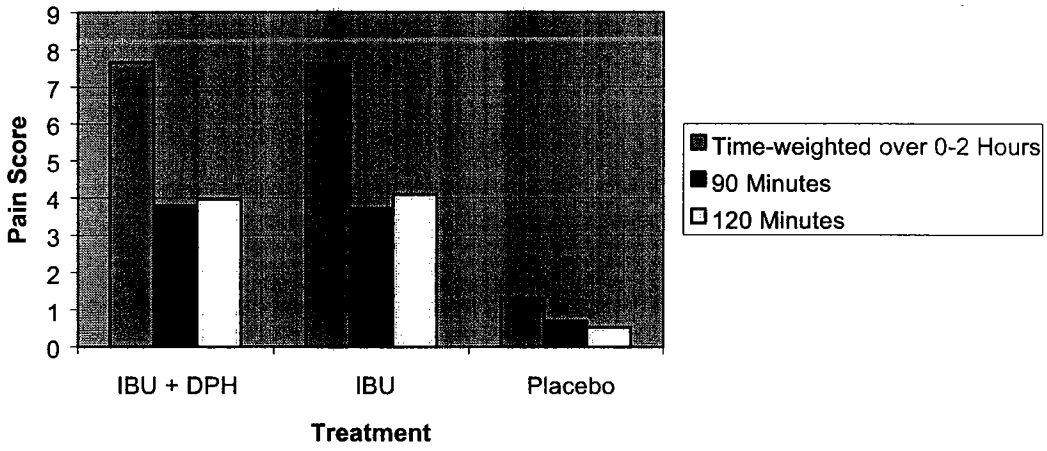
Advil PM Liquigel (ibuprofen 200mg/dihenhydramine HCl 25mg)
Advil PM Caplet (ibuprofen 200mg/dihenydramine citrate 38mg)

Reviewer's Comments:

The effect on duration of sleep of the fixed combination as compared to ibuprofen monotherapy (p=0.022) and placebo (p<0.001) were statistically significant if not corrected for multiple comparisons.

The effect on duration of sleep of ibuprofen monotherapy as compared to placebo (p<0.001) was statistically significant.

Mean Summary Pain Scores (SPRID) Over Time (0-2 Hours)



Reviewer's Comments:

The mean summary pain scores (sum of pain relief and pain intensity difference) for the fixed combination and ibuprofen monotherapy were comparable at all time points measured.

The mean summary pain scores for placebo was consistently lowered than the fixed combination and ibuprofen monotherapy at all time points measured.

Treatment Group Comparisons – Summary Pain Scores

p-value @	IBU + DPH vs. IBU	IBU + DPH vs. Placebo	IBU vs. Placebo
Time-weighted 0-2 hours	0.952	<0.001	<0.001
90 minutes	0.807	<0.001	<0.001
120 minutes	0.632	<0.001	<0.001

IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Advil PM Liquigel (ibuprofen 200mg/dihenhydramine HCl 25mg)
Advil PM Caplet (ibuprofen 200mg/dihenydramine citrate 38mg)

Reviewer's Comments:

The pain relief effect of the fixed combination as compared to ibuprofen monotherapy was not statistically significant at all time points measured.

The pain relief effect of the fixed combination as compared to placebo was statistically significant at all time points measured.

Safety

Adverse Events

Two hundred eighty-one randomized subjects received study medication and were included in the safety analysis. No serious adverse events or deaths occurred during the study. Two subjects, one from the ibuprofen/diphenhydramine HCl treatment group and the other from the ibuprofen treatment group, discontinued from the study due to an adverse event.

Subjects Discontinued Due to Adverse Events

Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C from Study
30196	Ibuprofen/Diphenhydramine HCl	Anxiety	Resolved w/o Tx	Yes
40175	Ibuprofen	Vomiting	Resolved w Tx	Yes

The most frequent adverse events in subjects treated with the fixed combination were nausea (4.1%).

Number (%) of Subjects with Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	IBU + DPH N=122	IBU N=119	Placebo N=40
	N (%)	N (%)	N (%)
All Events	13 (10.7)	10 (8.4)	6 (15.0)
Body as a Whole			
Headache			4 (10.0)
Digestive			
Nausea	5 (4.1)	4 (3.4)	
Vomiting		3 (2.5)	
Abdominal pain			1 (2.5)
Nervous			
Dizziness	4 (3.3)		1 (2.5)

IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Reviewer's Summary of Efficacy and Safety

The effect on sleep latency of the fixed combination was comparable to ibuprofen monotherapy.

Adverse experiences for the fixed combination were similar to ibuprofen monotherapy.

Study No. AE-98-02

Title: Advil PM oral Surgery Study II

Objectives: To evaluate the analgesic and sedative efficacy of Advil PM Liqui-Gels (ibuprofen 40mg/diphenhydramine hydrochloride 50mg) compared to ibuprofen liquigel (400mg) and placebo

Study Design

Except for the primary and secondary efficacy variables, the study design of this trial was identical to that of Study No. AE-98-01.

The protocol was amended, prior to the breaking of the blind, to make duration of sleep a co-primary efficacy variable for sleep.

Efficacy Variables

Primary Efficacy Variables

- Sleep: Duration of sleep and the cumulative percentage of subjects asleep at 60 minutes post-dosing (based on observed sleep latency assessments);
- Pain: Time-weighted sum of pain relief and pain intensity differences from baseline over 0-2 hours (SPRID2).

Secondary Efficacy Variables: Sleep

- Sleep latency (based on the observer);
- Cumulative and actual percentage of subjects asleep at each observed time point (other than the 60-minute time point for the cumulative percentage of subjects asleep);
- Ease of falling asleep
- Global evaluation of study medication as a sleep-aid

Secondary Efficacy Variables: Pain

- Pain intensity difference (PID), pain relief, and pain intensity difference combined with pain relief (PRID) scores at 90 and 120 minutes;
- Summary efficacy measures: Time-weighted sum of pain intensity difference scores (SPID) and pain relief scores (TOTPAR) over 0-2 hours;

- Global evaluation of study medication as a pain reliever.

Efficacy Analysis

Protection for Multiple Comparisons

In order to protect the Type I error at 0.05 level, the comparisons will be performed in the following sequential order. Each step must be significant for the following steps to be eligible for significance. However, in order to present the full clinical picture, all pairwise comparisons will be presented.

1. IBU/DPH 400/50mg vs. placebo: In order to be eligible for being declared significant, both primary sleep parameters and the primary pain parameter should be significant at the 0.05 level.
2. IBU/DPH 400/50mg vs. IBU 400mg: Duration of sleep will be tested first followed by cumulative percentage of subjects asleep at 60 minutes, each at the 0.05 level. The cumulative percentage of subjects asleep at 60 minutes will be eligible for being declared significant only if the duration of sleep is significant. If duration of sleep is significant, the combination will be considered more effective than ibuprofen alone for sleep.
3. IBU 400mg vs. placebo: In order to be eligible for being declared significant, the primary pain parameter should be significant at the 0.05 level.

Reviewer's Comments:

The description for the Protection for Multiple Comparisons is not consistent with the co-primary endpoints listed in the efficacy endpoint section. Additionally, Section 1 and Section 2 above are not consistent.

Safety Variables

- Adverse events

STUDY FLOW CHART

			Post Dosing Timepoints (min)												
Procedure	Screening	Surgery	0	10	20	30	40	50	60	75	90	120	150	180	Next Morning
Surgical Consult/Informed Consent	X														
Medical History	X														
Surgical Procedure (between 1-2:30pm or 3-4pm)		X													
Surgical Trauma Scale		X													
Randomization			X												
Dosing			X												
Pain Evaluations:															
Cat. Pain Severity Rating Scale[a]			X[c]								X	X			
VAS Pain Severity Rating Scale			X[c]												
Pain Relief Rating Scale[a]											X	X			
Global Assessment of Pain[b]															X
Sleep Evaluations:															
Nurse observed sleep latency				X	X	X	X	X	X	X	X	X	X	X	
Ease of falling asleep[b]															X
Duration of sleep[b]															X
Global assessment of sleep[b]															X
Subjects taking a rescue medication during this time will be considered:				← Discontinued →						← Treatment Failures →					

[a]If rescue occurs prior to 120 minutes post-dose, pain severity and pain relief assessments will be completed within ± 1 minute of the time rescue medication is taken.
[b]If rescue occurs prior to waking the next morning, these assessments will be completed within ± 1 minute of the time rescue medication is taken.
[c]To be completed within 5 minutes prior to the administration of study medication.

Subject Disposition and Demographics

Subject Disposition

	Number of Subjects (%)			
	IBU + DPH	IBU	Placebo	Total
Randomized	120 (42.4)	123 (43.5)	40 (14.1)	283 (100.0)
Discontinued from Study	1 (0.8)	0 (0.0)	1 (2.5)	2 (0.7)
Completed Study	119 (99.2)	123 (100.0)	39 (97.5)	281 (99.3)

IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Summary of Reasons for Premature Discontinuation from Study

Reason for Discontinuation	Number (%) of Subjects		
	IBU + DPH N=120	IBU N=123	Placebo N=40
Adverse events	0 (0)	0 (0)	1 (2.5)
Patient decision	1 (0.8)	0 (0)	0 (0)
Total	1 (0.8)	0 (0)	1 (2.5)

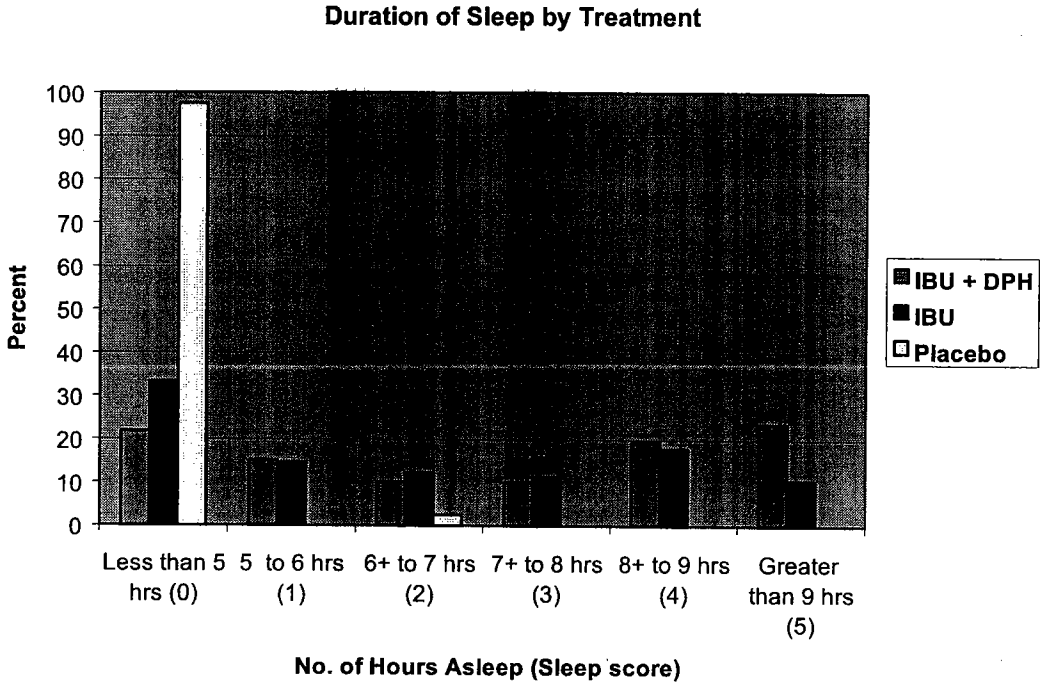
IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Demographic Data
Intent-to-Treat Subjects

		Total N=282	Placebo N=40	IBU400/DPH50 N=119	IBU400 N=123	p-value#
GENDER						
	MALE	137 (48.6%)	20 (50.0%)	58 (48.7%)	59 (48.0%)	0.974
	FEMALE	145 (51.4%)	20 (50.0%)	61 (51.3%)	64 (52.0%)	
RACE						
	CAUCASIAN	269 (95.4%)	37 (92.5%)	114 (95.8%)	118 (95.9%)	0.185
	BLACK	2 (0.7%)	1 (2.5%)	0 (0%)	1 (0.8%)	
	ASIAN	2 (0.7%)	0 (0%)	2 (1.7%)	0 (0%)	
	HISPANIC	8 (2.8%)	1 (2.5%)	3 (2.5%)	4 (3.3%)	
	OTHER	1 (0.4%)	1 (2.5%)	0 (0%)	0 (0%)	
AGE (yrs.)						
	MEAN	20.0	20.0	19.7	20.2	0.734
	STD	4.3	5.0	4.1	4.3	
	MEDIAN	19.0	18.0	19.0	19.0	
	RANGE	(15, 40)	(15, 39)	(16, 40)	(16, 39)	
WEIGHT (lbs.)						
	MEAN	150.3	152.1	148.8	151.2	0.742
	STD	32.9	42.7	30.3	32.0	
	MEDIAN	145.0	142.5	145.0	150.0	
	RANGE	(90, 310)	(105, 310)	(90, 250)	(99, 295)	
HEIGHT (ins.)						
	MEAN	68.1	67.8	68.3	68.1	0.563
	STD	3.8	3.9	3.7	3.9	
	MEDIAN	68.0	67.5	69.0	68.0	
	RANGE	(59, 78)	(59, 74)	(60, 78)	(59, 78)	

#: P-values for gender and race from the Cochran-Mantel-Haenszel test, controlling for baseline pain severity rating(PSR) and gender when appropriate.
P-values for age, weight, and height from ANOVA model with treatment, baseline PSR, and gender terms.
*: Statistically significant at $p \leq 0.05$.
b: Marginally significant ($0.05 < p \leq 0.10$).

Efficacy **Intent-to-Treat Population**



Mean Sleep Score – Categorical Scale (0-5)

	IBU + DPH	IBU	Placebo
Mean Sleep Score	2.61	1.98	0.05

IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Treatment Group Comparisons – Duration of Sleep

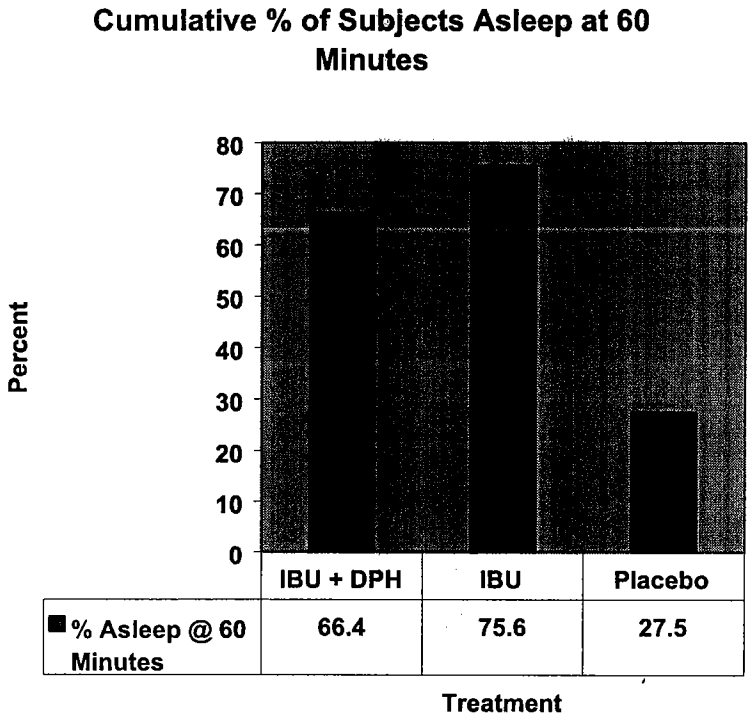
	IBU + DPH vs. IBU	IBU + DPH vs. Placebo	IBU vs. Placebo
*p-value	0.005	<0.001	<0.001

*p-values from ANOVA model with treatment, baseline PSR, and gender terms
IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Advil PM Liquigel (ibuprofen 200mg/dihenhydramine HCl 25mg)
Advil PM Caplet (ibuprofen 200mg/dihenydramine citrate 38mg)

Reviewer's Comments:

The effect on duration of sleep of the fixed combination as compared to ibuprofen monotherapy (p=0.005) and placebo (<0.001) were statistically significant.



Reviewer's Comments:

The cumulative percentage of subjects asleep at 60 minutes after administration of masked study medication were 64.4% for the fixed combination, 75.6% for ibuprofen monotherapy, and 27.5% for placebo.

Treatment Group Comparisons – Nurse Observed Sleep Latency

	IBU + DPH vs. IBU	IBU + DPH vs. Placebo	IBU vs. Placebo
p-value	0.112	<0.001	<0.001

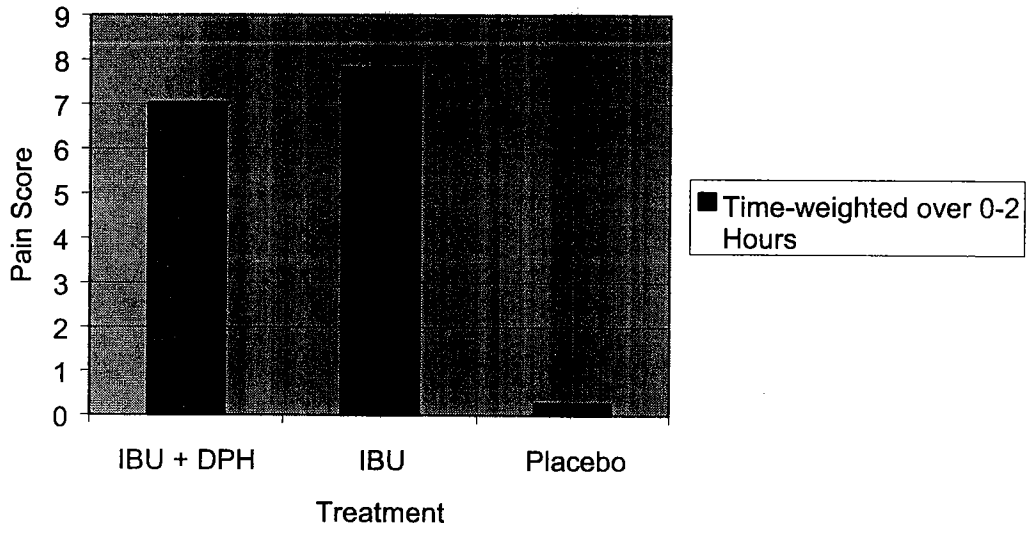
IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Reviewer's Comments:

The effect on sleep latency of the fixed combination as compared to ibuprofen monotherapy (p=0.112) was not statistically significant and was statistically significant as compared to placebo (<0.001).

The effect on sleep latency of ibuprofen monotherapy as compared to placebo (p<0.001) was statistically significant.

Mean Summary Pain Scores (SPRID) Over time (0-2 Hours)



Treatment Group Comparisons – Summary Pain Scores

	IBU + DPH vs. IBU	IBU + DPH vs. Placebo	IBU vs. Placebo
p-value	0.050	<0.001	<0.001

IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Reviewer's Comments:

The pain relief effect of the fixed combination as compared to ibuprofen monotherapy (p=0.050) was statistically significant in favor of ibuprofen monotherapy.

Ibuprofen with or without diphenhydramine was statistically significantly better than placebo.

Safety

Adverse Events

All two hundred eighty-three randomized subjects received study medication and were included in the safety analysis. No serious adverse events or deaths occurred during the study. One subject in the placebo treatment group discontinued from the study due to an adverse event.

The most frequent adverse events in subjects treated with the fixed combination were headaches (7.5%).

Number (%) of Subjects with Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	IBU + DPH N=120	IBU N=123	Placebo N=40
	N (%)	N (%)	N (%)
All Events	18 (15.0)	12 (9.8)	11 (27.5)
Body as a Whole			
Headache	9 (7.5)	5 (4.1)	2 (5.0)
Digestive			
Nausea	5 (4.2)	5 (4.1)	5 (12.5)
Vomiting			2 (5.0)
Nervous			
Agitation			1 (2.5)
Skin and Appendages			
Sweating			1 (2.5)

IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Reviewer's Summary of Efficacy and Safety

The effect on sleep duration of the fixed combination was statistically superior to ibuprofen monotherapy.

The effect on sleep latency of the fixed combination of the fixed combination was comparable to ibuprofen monotherapy.

The effect of ibuprofen on pain was superior to the combination product.

Adverse experiences for the fixed combination were similar to ibuprofen monotherapy.

Study No. AE-98-03

Title: Advil PM Oral Surgery Dose-Response Study

Objectives: To evaluate the analgesic and sedative efficacy of a single dose of one Advil PM Liqui-Gel (ibuprofen 200mg/diphenhydramine hydrochloride 25mg) and two Advil PM Liqui-Gels (ibuprofen 400mg/diphenhydramine hydrochloride 50mg) compared to each other and to placebo.

Study Design

This was a randomized (stratified by gender and baseline pain severity), inpatient, three-arm, placebo-controlled, single-dose, double-blinded, parallel group, single-center, dose-response trial. Following oral surgery, subjects were housed at the site overnight. When subjects experienced at least moderate pain and it was between approximately 6:00 PM and 8:15 PM (at least 3 hours earlier than their usual bedtime), they received masked study medication and were required to go to bed for the evening. The three treatment groups were 1) Ibuprofen 200mg/diphenhydramine 25mg, 2) Ibuprofen 400mg/ diphenhydramine 50mg, and 3) Placebo.

Two hundred eighty-four subjects (3:3:1), 16-45 years of age, who underwent extraction of one or two impacted molars were enrolled. Enrolled subjects were stratified according to gender and baseline pain severity.

At specified over a 3-hour evaluation period, an observer determined visually whether or not the subject was asleep. At 90 and 120 minutes post-dose, subjects were awakened and interviewed to assess their pain intensity and pain relief. The following morning, subjects were asked to provide assessments of the ease with which they fell asleep, the duration of sleep, and global assessments of the study medication as a sleep-aid and as a pain reliever.

Test Drug Schedule: Subjects received a single dose of masked study medication when they experienced at least moderate pain and it was approximately between 6:00 PM and 8:15 AM. Subjects were then required to go to bed for the evening.

Study Medication

Drug	Per Unit	Per Dose	Lot Number
Ibuprofen/Diphenhydramine hydrochloride liquigel (Advil PM Liqui-Gel)	200 mg/25 mg	400 mg/50 mg 200 mg/25 mg	WH-0723-0005A
Matching placebo liquigels	Inert Ingredients		WH-0689-0005A

Advil PM Liquigel (ibuprofen 200mg/dihenhydramine HCl 25mg)
Advil PM Caplet (ibuprofen 200mg/dihenydramine citrate 38mg)

Study Population

Inclusion Criteria

Males and females of any race were eligible for inclusion in the study provided they met all of the following inclusion criteria:

1. 16 to 45 years of age;

2. were examined by the attending dentist or physician and medically cleared to participate in the study. In general, the subjects were in good health and had no contraindications to any of the study medications;

3. had undergone surgical extraction of one or two impacted third molars, one of which was at least a partial bony mandibular impaction (if two molars were extracted, the other was the corresponding maxillary molar);

4. received only bupivacaine with or without vasoconstrictor, nitrous oxide, and, in the event significant post-surgical pain was experienced, lidocaine or mepivacaine as the preoperative or rescue medication/anesthetic(s). (The original protocol included a time limit of 4:00 PM for the use of a rescue anesthetic. Protocol Amendment I allowed timing of the use of short-acting rescue anesthetic to be solely at the discretion of the Investigator to ensure subject dosing within the specified time window);

5. had not taken any form of medication within 3 days of admission (except oral contraceptives and prophylactic antibiotics) and agreed not to take any medication (other than that provided to them by the Investigator) throughout the study;

6. had not consumed alcoholic beverages or foods and beverages containing xanthines for 2 hours prior to surgery and agreed not to consume any of these foods or beverages throughout the study;

7. understood the rating scales (as judged by the study coordinator);

8. were able to read, comprehend, and sign the consent form. Subjects under 18 years of age had parental or guardian consent.

Exclusion Criteria

Subjects were excluded from participating in then study if any of the following were noted:

1. a serious medical condition (e.g., poorly controlled hypertension, poorly controlled diabetes, significantly impaired cardiac, renal, or hepatic function, hyper- or hypothyroidism);

2. a chronic breathing problem such as asthma, emphysema, or chronic bronchitis;

3. a history (within 2 years of enrollment) or presence of peptic ulcer disease;

4. a history or presence of bleeding disorder(s);

5. symptomatic benign prostatic hyperplasia or urethral stricture;

6. glaucoma

7. an acute local infection at the time of surgery that could confound the post-surgical evaluation;

8. use of a prescription or nonprescription drug with which the administration of ibuprofen or any other nonsteroidal anti-inflammatory drug is contraindicated (*e.g.*, coumarin-type anticoagulants, thiazides, furosemide, probenecid);

9. use of a prescription or nonprescription drug with which the administration of diphenhydramine or any other antihistamine is contraindicated (*e.g.*, other antihistamines, tranquilizers, sedatives);

10. use of an antihistamine prior to study entry within the time periods listed: non- and low-sedating oral antihistamines (*e.g.*, Claritin, Allegra, Zyrtec, Semprex): 72 hours ; Hismanal (astemizole) (if regular use is >3 days): 14 days; Hismanal (if regular use is ≤3days): 72 hours; all other oral antihistamines: 48 hours; nasal and ocular antihistamines (*e.g.*, Astelin, Livostin, levocabastine): 72; intramuscular administration of any antihistamine: 72 hours;

11. breast feeding or pregnant females (verified by a urine-based pregnancy test);

12. females of either child-bearing potential or post-menopausal for less than 2 years who were not using one of the following medically approved methods of contraception: oral, transdermal, injectable, or implanted contraceptives, intrauterine device, diaphragm, condom, abstinence, or surgical sterility;

13. habitual use of analgesic drugs (*i.e.*, routine use of oral analgesics five or more times per week);

14. any history of alcoholism or substance abuse; or routine consumption of three or more alcohol-containing beverages per day;

15. a known sensitivity to ibuprofen, other nonsteroidal anti-inflammatory agents, diphenhydramine or other antihistamines (Note: Gastric intolerance was not considered sensitivity);

16. a history of regularly going to bed earlier than 11:00 PM;

17. a history or presence of chronic or severe sleeping problems which required an OTC or prescription hypnotic or sedative;

18. completed travel across time zones within 1 week prior to study participation;

19. received any form of treatment for depression in the past 6 months;

20. use of any form of psychotropic agent in the past 6 months;

21. use of nicotine transdermal patches, spray, or gum within 6 months of enrollment;

22. had taken an investigational drug within the past 30 days;

23. previous participation in the study;

24. a member or a relative of the study site staff or Sponsor directly involved in the study.

Efficacy Variables

Primary Efficacy Variables

- Sleep: Cumulative percentage of subjects asleep at 60 minutes post-dosing (based on observed sleep latency assessments);

- Pain: Time-weighted sum of pain relief and pain intensity differences from baseline over 0-2 hours (SPRID2).

Secondary Efficacy Variables: Sleep

- Duration of sleep;

- Sleep latency (based on the observer);

- Cumulative and actual percentage of subjects asleep at each observed time point (other than the 60-minute time point for the cumulative percentage of subjects asleep);

- Ease of falling asleep;

- Global assessment of the study medication as a sleep-aid;

Secondary Efficacy Variable: Pain

- Pain intensity difference (PID), pain relief rating(PRR), and pain intensity difference combined with pain relief (PRID) scores at 90 and 120 minutes;

- Summary efficacy measures: time-weighted sum of pain intensity differences scores (SPID) and pain relief scores (TOTPAR)over 0-2 hours;

- Global assessment of the study medication as a pain reliever.

Safety Variables

- Adverse events

STUDY FLOW CHART

	Post Dosing Timepoints (min)														
Procedure	**Screening**	**Surgery**	**0**	**10**	**20**	**30**	**40**	**50**	**60**	**75**	**90**	**120**	**150**	**180**	**Next Morning**
Surgical Consult/Informed Consent	X														
Medical History	X														
Surgical Procedure (between 1-2:30pm)		X													
Surgical Trauma Scale		X													
Randomization			X												
Dosing			X												
Pain Evaluations:															
Cat. Pain Severity Rating Scale[a]			X[c]								X	X			
VAS Pain Severity Rating Scale			X[c]											*	
Pain Relief Rating Scale[a]											X	X			
Global Assessment of Pain[b]															X
Sleep Evaluations:															
Nurse observed sleep latency				X	X	X	X	X	X	X	X	X	X	X	
Ease of falling asleep[b]															X
Duration of sleep[b]															X
Global assessment of sleep[b]															X
Subjects taking a rescue medication during this time will be considered:				← Discontinued →						← Treatment Failures →					

[a]If rescue occurs prior to 120 minutes post-dose, pain severity and pain relief assessments will be completed within ± 1 minute of the time rescue medication is taken.
[b]If rescue occurs prior to waking the next morning, these assessments will be completed within ± 1 minute of the time rescue medication is taken.
[c]To be completed within 5 minutes prior to the administration of study medication.

Subject Disposition and Demographics

Subject Disposition

	Number of Subjects (%)			
	IBU200/DPH25	IBU400/DPH50	Placebo	Total
Randomized	120 (42.3)	123 (43.3)	41 (14.4)	284
Discontinued from Study	0 (0)	3 (2.5)	0 (0)	3 (1.1)
Completed Study	120 (100.0)	120 (97.6)	41 (100.0)	281 (98.9)

IBU=ibuprofen DPH=diphenhydramine HCl

Summary of Reasons for Premature Discontinuation from Study

Reason for Discontinuation	Number (%) of Subjects		
	IBU200/DPH25 N=120	IBU400/DPH50 N=123	Placebo N=41
Adverse events	0 (0)	2 (1.6)	0 (0)
Patient decision	0 (0)	1 (0.8)	0 (0)
Total	0 (0)	3 (2.4)	0 (0)

IBU=ibuprofen DPH=diphenhydramine HCl

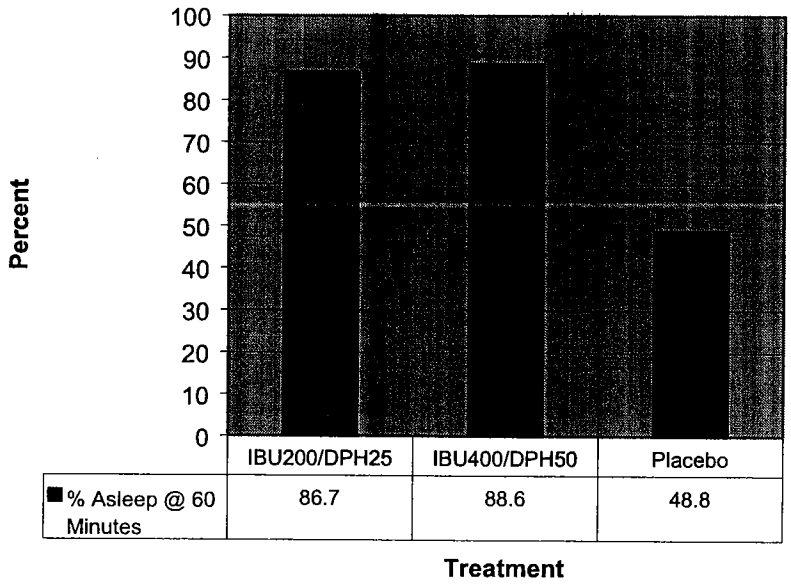
Demographic Data
Intent-to-Treat Subjects

		Total N=284	Placebo N=41	IBU200/DPH25 N=120	IBU400/DPH50 N=123	p-value#
GENDER						
	MALE	145 (51.1%)	21 (51.2%)	61 (50.8%)	63 (51.2%)	0.998
	FEMALE	139 (48.9%)	20 (48.8%)	59 (49.2%)	60 (48.8%)	
RACE						
	CAUCASIAN	160 (56.3%)	26 (63.4%)	69 (57.5%)	65 (52.8%)	0.608
	BLACK	102 (35.9%)	13 (31.7%)	41 (34.2%)	48 (39.0%)	
	ASIAN	11 (3.9%)	2 (4.9%)	5 (4.2%)	4 (3.3%)	
	HISPANIC	6 (2.1%)	0 (0%)	4 (3.3%)	2 (1.6%)	
	OTHER	5 (1.8%)	0 (0%)	1 (0.8%)	4 (3.3%)	
AGE (yrs.)						
	MEAN	24.1	23.0	23.9	24.5	0.292
	STD	5.4	4.8	5.4	5.6	
	MEDIAN	23.0	22.0	23.0	24.0	
	RANGE	(16, 45)	(16, 37)	(17, 45)	(16, 41)	
WEIGHT (lbs.)						
	MEAN	168.1	166.5	166.9	169.9	0.816
	STD	42.8	45.8	43.1	41.7	
	MEDIAN	160.0	161.0	159.5	160.0	
	RANGE	(90, 343)	(100, 281)	(98, 343)	(90, 308)	
HEIGHT (ins.)						
	MEAN	67.3	67.4	67.2	67.4	0.880
	STD	4.1	4.5	4.0	4.1	
	MEDIAN	67.0	67.0	67.0	68.0	
	RANGE	(58, 79)	(59, 76)	(59, 79)	(58, 78)	

#: p-values for gender and race from the Cochran-Mantel-Haenszel test, controlling for baseline pain severity rating(PSR) and gender when appropriate.
p-values for age, weight, and height from ANOVA model with treatment, baseline PSR, and gender terms.
*: Statistically significant at $p \leq 0.05$.
b: Marginally significant ($0.05 < p \leq 0.10$).

Efficacy **Intent-to-Treat Population**

Cumulative % of Subjects Asleep at 60 Minutes



Reviewer's Comments:

The cumulative percentage of subjects asleep at 60 minutes after administration of masked study medication were 86.7% for the ibuprofen 200mg/diphenhydramine HCl 25mg fixed combination, 88.6% for the ibuprofen 400mg/diphenhydramine HCl 50mg fixed combination, and 48.8% for placebo.

Treatment Group Comparisons – Observed Sleep Latency

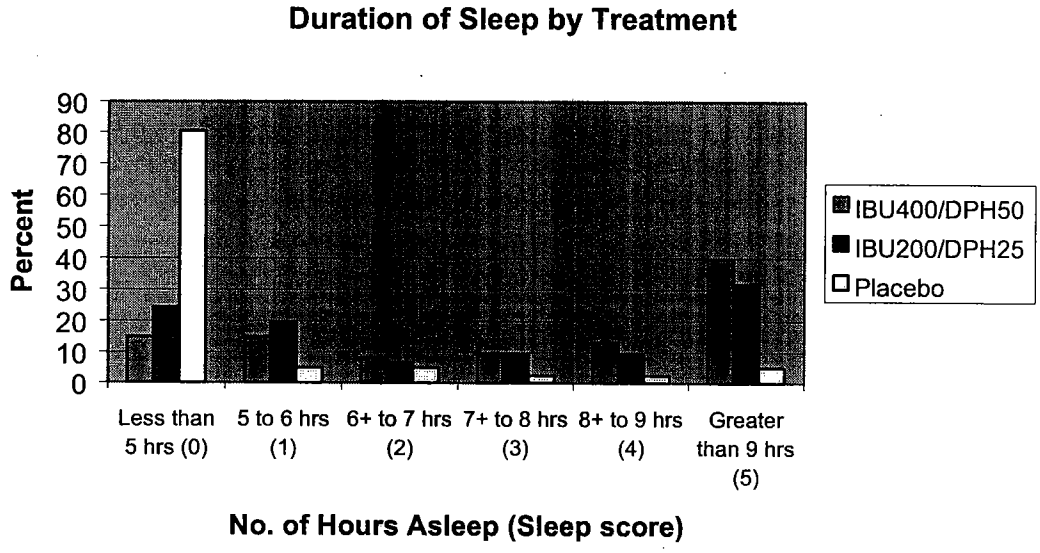
	IBU400/DPH50 vs. IBU200/DPH25	IBU200/DPH25 vs. Placebo	IBU400/DPH50 vs. Placebo
p-value	0.636	<0.001	<0.001

IBU=ibuprofen DPH=diphenhydramine HCl

Reviewer's Comments:

The effect on sleep latency of the ibuprofen 400mg/diphenhydramine HCl 50mg fixed combination as compared to the ibuprofen 200mg/diphenhydramine HCl 25mg fixed combination was <u>not</u> statistically significant (p=0.636).

The effect on sleep latency of both fixed combination products as compared to placebo <u>was</u> statistically significant (p<0.001).



Mean Sleep Score – Categorical Scale (0-5)

	IBU400/DPH50	IBU200/DPH25	Placebo
Mean Sleep Score	3.10	2.55	0.56

IBU=ibuprofen DPH=diphenhydramine

Treatment Group Comparisons – Duration of Sleep

	IBU400/DPH50 vs. IBU200/DPH25	IBI400/DPH50 vs. Placebo	IBU200/DPH25 vs. Placebo
*p-value	0.025	<0.001	<0.001

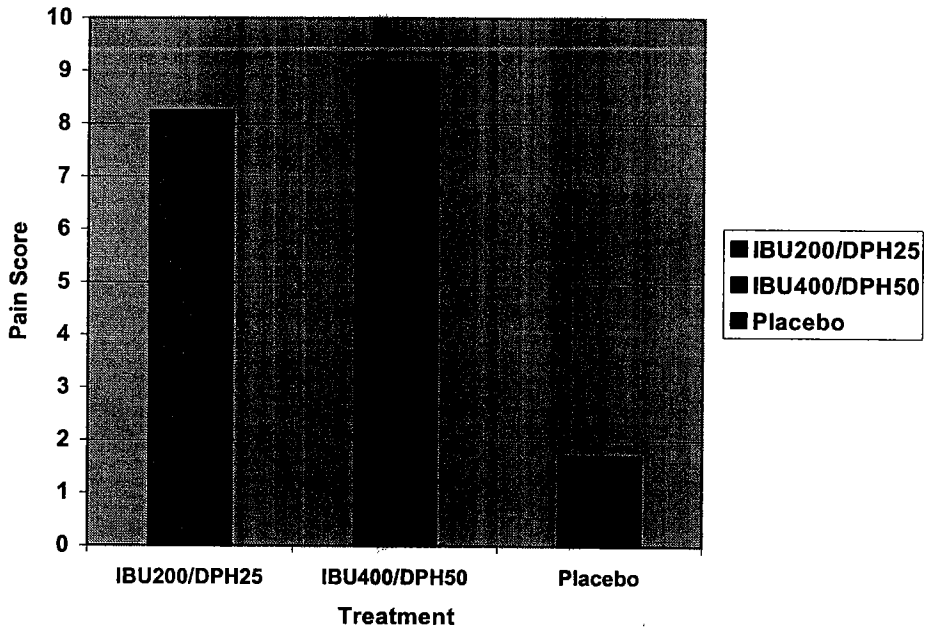
*p-values from ANOVA model with treatment, baseline PSR, and gender terms
IBU=ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Advil PM Liquigel (ibuprofen 200mg/dihenhydramine HCl 25mg)
Advil PM Caplet (ibuprofen 200mg/dihenydramine citrate 38mg)

Reviewer's Comments:

The effect on duration of sleep of the ibuprofen 400mg/diphenhydramine 50mg fixed combination as compared to the ibuprofen 200mg/diphenhydramine 25mg fixed combination ($p=0.025$) and placebo ($p<0.001$) were statistically significant.
The effect on duration of sleep of the ibuprofen 200mg/diphenhydramine 25mg fixed combination as compared to placebo ($p<0.001$) was statistically significant.

Mean Summary Pain Scores (SPRID) Over Time (0-2 Hours)



Treatment Group Comparisons - Summary Pain Scores

	IBU400/DPH50 vs. IBU200/DPH25	IBU200/DPH25 vs. Placebo	IBU400/DPH50 vs. Placebo
p-value	0.042	<0.001	<0.001

IBU=ibuprofen DPH=diphenhydramine HCl

Reviewer's Comments:

The pain relief effect of the ibuprofen 400mg/diphenhydramine HCl 50mg fixed combination as compared to the ibuprofen 200mg/diphenhydramine HCl 25mg fixed combination (p=0.042) was marginally significant. (Probably not if corrected for multiple comparisons)

The pain relief effect of both fixed combination products as compared to placebo (p<0.001) was statistically significant.

Safety

Adverse Events

All 284 randomized subjects received masked study medications and were included in the safety analysis. One serious adverse event occurred during the study (ibuprofen 200mg/ diphenhydramine HCl 25mg treatment group). Two subjects, both in the ibuprofen 400mg/diphenhydramine HCl 50mg treatment group discontinued from the study doe to an adverse event.

Serious Adverse Events

Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C from Study
20055	IBU200mg/DPH 25mg	Cellulitis	Resolved w Tx	No

IBU=ibuprofen DPH=diphenhydramine HCl

Subjects Discontinued Due to Adverse Events

Patient Number	Treatment	Coded Adverse Event	D/C from Study
10078	IBU 400mg/DPH 50mg	Gum hemorrhage	Yes
30070	IBU 400mg/DPH 50mg	Vomiting	Yes

IBU=ibuprofen DPH=diphenhydramine HCl

The most frequent adverse events in subjects treated with the ibuprofen 400mg/diphenhydramine 50mg were headaches (7.3%).

Number (%) of Subjects with Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	IBU 400/DPH 50 N=123	IBU 200/DPH 25 N=120	Placebo N=41
	N (%)	N (%)	N (%)
All Events	32 (26.0)	44 (36.7)	11 (26.8)
Body as a Whole			
Headache	9 (7.3)	16 (13.3)	2 (4.9)
Infection			1 (2.4)
Digestive			
Nausea	5 (4.1)	6 (5.0)	3 (7.3)
Vomiting	6 (4.9)	3 (2.5)	1 (2.4)
Abdominal pain	2 (1.6)		
Nervous			
Paresthesia		4 (3.3)	2 (4.9)
Dizziness		2 (1.7)	
Respiratory			
Pharyngitis	3 (2.4)	7 (5.8)	3 (2.4)

IBU=ibuprofen DPH=diphenhydramine HCl

Reviewer's Summary of Efficacy and Safety

The effect on sleep latency of the ibuprofen 400mg/diphenhydramine 50mg fixed combination was comparable to the effect seen with ibuprofen 200mg/diphenhydramine 25mg fixed combination.

The pain relief effect of the ibuprofen 400mg/diphenhydramine 50mg fixed combination was marginally superior to the effect seen with ibuprofen 200mg/diphenhydramine 25mg fixed combination.

Less adverse events occurred in subjects treated with the ibuprofen 400mg/ diphenhydramine 50mg fixed combination as compared to subjects treated with the ibuprofen 200mg/diphenhydramine 25 mg fixed combination.

Study No. AE-98-04

Title: Advil PM Inpatient Headache Study

Objectives: To compare the analgesic and sedative effects of a single dose of Advil PM Liqui-Gels (ibuprofen 400mg/diphenhydramine hydrochloride 50mg) to placebo in subjects who experienced nighttime chronic or episodic tension-type headaches and accompanying sleeplessness.

Study Design

This was a randomized (stratified by gender and baseline pain severity), inpatient, two-arm, placebo-controlled, single-dose, double-blinded, parallel group, single-center trial. The two treatment groups were 1) Ibuprofen 400mg/diphenhydramine 50mg and 2) Placebo. Subjects reported to the study site when experiencing a tension-type headache between approximately 6:30 PM and 8:00 PM. Once at the site, subjects rated their headache intensity. Subjects rating their nighttime tension-type headache as at least moderately severe in intensity were housed, observed overnight, and required to take study medication and go to bed approximately 3 hours earlier than usual (*i.e.,* no later than 8:30 PM).

One hundred sixty-two subjects (1:1), at least 12 years of age, who had a documented history of episodic or chronic tension-type headache and who were experiencing a tension-type headache of at least moderate severity between approximately 6:30 PM and 8:00 PM were enrolled. Enrolled subjects were stratified according to baseline pain and gender.

At specified intervals over a 3 hour period (*i.e.,* 10, 20, 30, 40, 50, 60, 75, 90, 120, 150, and 180 minutes), an observer determined whether the subject was asleep. Immediately after the 60- to 90-minute time point sleep assessments, subjects were interviewed to assess their pain intensity and pain relief. The following morning (or at the time rescue medication was administered), subjects were asked to provide specific assessments of their sleep and global evaluations of sleep and pain relief.

Test Drug Schedule: Subjects received a single dose of masked study medication when they experienced a tension-type headache of at least moderate severity and it was approximately between 6:30 PM and 8:00 PM). Subjects were required to immediately go to bed for the evening, no later than 8:30 PM.

Study Medication

Drug	Per Unit	Per Dose	Lot Number
Advil PM Liqui-Gel	Ibuprofen 200mg/diphenhydramine hydrochloride 25 mg	Ibuprofen 400mg/diphenhydramine hydrochloride 50 mg	WH-0723-0005A
Matching placebo liquigel	Inert Ingredients		WH-0689-0005A

Study Population

Inclusion Criteria

Males and females of any race were eligible for inclusion in the study provided they met all of the following inclusion criteria:

1. were at least 12 years of age;

2. had a diagnosis of episodic or chronic tension-type headache as defines by the International Headache Society

- Episodic Tension-Type Headache: at least 10 previous episodes occurring less than 4 episodes/week (<180 days/year and <15 days/month) that may be associated with anorexia but no nausea or vomiting; either photophobia or phonophobia may be present but not both;

- Chronic Tension-Type Headache: average headache frequency ≥15 days/month (≥180 days/year), episodes may be associated with only one of the following: nausea, photophobia, or phonophobia, with no association with vomiting;

3. headache is characterized as including at least two of the following pain characteristics: pressing/tightening (non-pulsating) quality, intensity that may inhibit but does not prohibit activities, bilateral location, no aggravation by walking stairs or similar routine activities;

4. headache is unrelated to a physical disorder per history or upon physical and/or neurological examination;

5. a history of satisfactory headache relief with OTC doses of OTC analgesics;

6. headache typically lasts more than 3 hours if left untreated with an OTC analgesic;

7. a history of experiencing at least 1 headache per month occurring in the evening for the past 6 months which prevented him/her from sleeping;

8. medically cleared to participate following examination by the study physician;

9. willing to adhere to the study conditions;

10. reliable, cooperative, and capable of comprehending the study requirements;

11. were able to read, comprehend, and sign the consent form;

12. a history of tension-type headache occurring before age 50.

Exclusion Criteria

Subjects were exclude from participation in the study if any of the following were noted:

1. a history of a serious medical condition which is not adequately controlled (*e.g.*, hypertension, diabetes), significantly impaired cardiac, renal, or hepatic function, or hyper- or hypothyroidism as determined by appropriate history and clinical evaluation by the examining physician;

2. a chronic breathing problem such as asthma, emphysema, or chronic bronchitis;

3. currently has or has a history of (within 2 years of enrollment) peptic ulcer disease;

4. currently has or has a history of a bleeding disorder(s);

5. a history of significant, symptomatic prostatic hyperplasia as determined by the examining physician;

6. glaucoma;

7. use of a prescription or nonprescription drug with which ibuprofen or any nonsteroidal anti-inflammatory drug is contraindicated (*e.g.*, coumarin-type anticoagulants, thiazides, furosemide, probenecid);

8. use of a prescription or nonprescription drug with which diphenhydramine or any other antihistamine administration is contraindicated (*e.g.*, other antihistamines, tranquilizers, sedatives);

9. use of a prescription or nonprescription drug or dietary supplement which causes sedation as a common side effect;

10. use of a prescription or nonprescription drug or dietary supplement to suppress appetite;

11. a history of sensitivity (*e.g.,* asthma, swelling, shock, or hives) to diphenhydramine, any other antihistamines, ibuprofen, or any other nonsteroidal anti-inflammatory agent;

12. any history of alcoholism, substance abuse, or routinely consumes ≥3 alcohol-containing beverages per day;

13. a nursing mother or pregnant (verified by a positive urine-based pregnancy test);

14. a women of child-bearing potential or post-menopausal for less than 2 years and is not using one of the following medically approved methods of contraception: oral, transdermal, injectable, or implanted contraceptives, intrauterine device, diaphragm, condom, abstinence, or surgical sterility;

15. a history of recurrent (*i.e.,* on average, more than one episode per month over the past 6 months) migraine headache (*i.e.,* classic or common migraine headache, associated with nausea, vomiting, unilateral onset, or visual prodromata) as confirmed by medical history;

16. a history of a chronic or severe sleep problem which does not respond to OTC medication and requires a prescription hypnotic or sedative;

17. has received any form of treatment for depression in the past 6 months;

18. has taken any form of psychotropic drug in the past 6 months;

19. is currently using nicotine transdermal patches, nicotine gum, or nicotine spray;

20. has traveled across time zones within one week prior to study participation;

21. routinely goes to bed earlier than 11:00 PM;

22. has taken an investigational drug within the past 30 days;

23. has previously been entered into this study

24. is a study site or Sponsor employee or relative of an employee who is directly involved in the study.

Efficacy Variables

Primary Efficacy Variables

- Sleep: Cumulative percentage of subjects asleep at 60 minutes;

- Pain: Time-weighted sum of relief scores combined with pain intensity difference scores over 0-90 minutes (SPRID90).

Secondary Efficacy Variables: Sleep

- Duration of sleep;
- Sleep latency (based on the observer);
- Cumulative and actual percentage of subjects asleep at each observation time point (other than the 60 minute time point for the cumulative percentage of subjects asleep);
- Ease of falling asleep;
- Global evaluation of study medication as a sleep-aid.

Secondary Efficacy Variables: Pain

- Pain intensity difference (PID), pain relief, and pain intensity difference combined with pain relief (PRID) scores at 60 and 90 minutes;
- Summary efficacy measures: time-weighted sum of pain intensity difference scores (SPID) and pain relief scores (TOTPAR) over 0-90 minutes;
- Global evaluation of study medication as a pain reliever.

Safety Variables

- Adverse events

STUDY FLOW CHART

PROCEDURE	VISIT 1 - SCREENING	VISIT 2 - EVENING OF HEADACHE EVALUATION	POST-DOSING TIMEPOINTS (10, 20, 30, 40, 50, 75, 120, 150, 180 min.)	POST-DOSING TIMEPOINTS (60 and 90 min.)	NEXT MORNING
Informed Consent	X				
Medical History	X				
Headache Questionnaire	X				
Physical Examination	X				
Urine Pregnancy Test	X				
Inclusion/Exclusion Checklist	X				
Baseline Evaluations:					
Eligibility Review		X			
Urine Pregnancy Test		X			
Categorical Pain Rating Scale[a]		X			
Visual Analog Pain Rating Scale[a]		X			
Randomization		X			
Dosing		X			
Post-Dosing Evaluations					
Sleep Latency			X	X	
Categorical Pain Relief Rating[b]				X*	
Categorical Pain Rating Scale[b]				X*	
Next Morning Assessments					
Ease of Falling Asleep[c]					X
Duration of Sleep[c]					X
Global Sleep Evaluation[c]					X
Global Pain Evaluation[c]					X
Adverse Experiences		AT ANY TIME DURING THE STUDY			

If the subject does not experience an evaluable headache within 2 months (8-9 weeks) of visit 1, the subject will be discontinued from the study.

[a] To be completed within 5 minutes prior to administration of study medication.
[b] If rescue occurs prior to 120 minutes post-dose, pain severity and relief will be assessed within ±1min of the time rescue medication is taken.
[c] If rescue occurs prior to waking the next morning, these assessments will be completed within ±1min of the time rescue medication is taken.
* Pain assessments to be completed immediately after the 60- and 90-minute sleep assessments.

Subject Disposition and Demographics

Subject Disposition

	Number of Subjects (%)		
	IBU400/DPH50	Placebo	Total
Randomized	81 (50.0)	81 (50.0)	162
Discontinued from Study	0 (0)	0 (0)	0 (0)
Completed Study	81 (100.0)	81 (100.0)	162 (100.0)

IBU=ibuprofen DPH=diphenhydramine HCl

Summary of Demographic Data
Intent-to-Treat Subjects

	Total N=162	Placebo N=81	IBU400/DPH50 N=81	p-value#
GENDER				
MALE	52 (32.1%)	25 (30.9%)	27 (33.3%)	0.760
FEMALE	110 (67.9%)	56 (69.1%)	54 (66.7%)	
RACE				
CAUCASIAN	156 (96.3%)	78 (96.3%)	78 (96.3%)	0.418
BLACK	5 (3.1%)	2 (2.5%)	3 (3.7%)	
ASIAN	1 (0.6%)	1 (1.2%)	0 (0%)	
AGE (yrs.)				
MEAN	39.5	39.7	39.4	0.849
STD	12.9	13.1	12.8	
MEDIAN	41.0	41.0	41.0	
RANGE	(18, 68)	(18, 64)	(18, 68)	
WEIGHT (lbs.)				
MEAN	161.9	162.4	161.4	0.675
STD	34.4	33.6	35.4	
MEDIAN	160.5	162.0	155.0	
RANGE	(97, 248)	(97, 248)	(99, 238)	
HEIGHT (ins.)				
MEAN	65.9	65.6	66.1	0.331
STD	3.6	3.6	3.6	
MEDIAN	66.0	65.0	66.0	
RANGE	(59, 77)	(59, 75)	(61, 77)	

#: p-values for gender and race from the Cochran-Mantel-Haenszel test, controlling for baseline pain severity rating(PSR) and gender when appropriate.
p-values for age, weight, and height from ANOVA model with treatment, baseline PSR, and gender terms.
*: Statistically significant at $p \leq 0.05$.
b: Marginally significant ($0.05 < p \leq 0.10$).

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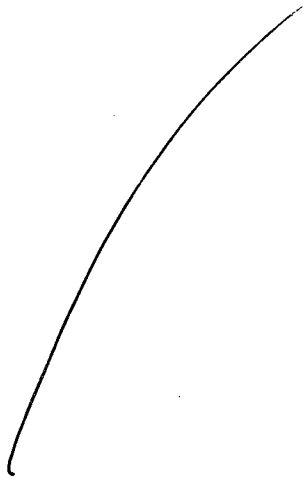
✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling



Safety

Adverse Events

All 182 randomized subjects received masked study medication and were included in the safety analysis. No serious adverse events or deaths occurred during the study. No subject discontinued from the study prematurely due to an adverse event.

The most frequent adverse events in subjects treated with the fixed combination were dry mouth (22.2%).

Number (%) of Subjects with Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	IBU + DPH N=81	Placebo N=81
	N (%)	N (%)
All Events	20 (24.7)	13 (16.0)
Digestive		
Dry Mouth	18 (22.2)	9 (11.1)
Nervous		
Hyperkinesia		1 (1.2)
Insomnia		1 (1.2)
Nervousness		1 (1.2)
Respiratory		
Rhinitis	2 (2.5)	1 (1.2)

IBU=Ibuprofen 400mg DPH=diphenhydramine HCl 50mg

Reviewer's Summary of Efficacy and Safety

Treatment with the fixed combination was associated with more adverse experiences as compared to placebo.

Study No. AE-97-08

Title: Advil PM Maximum Use Safety and Efficacy Study

Objectives: To evaluate and compare the safety of one Advil PM Liqui-Gel (ibuprofen 200mg/diphenhydramine HCl 25mg), two Advil PM Liqui-Gel (ibuprofen 400mg/diphenhydramine 50mg), two Tylenol PM caplets (acetaminophen 1000mg/diphenhydramine 50mg), and placebo when administered for 10 consecutive evenings in a population representative of OTC consumers of analgesic/ nighttime combination products. In addition, the relative efficacy of the four treatments (post-first medication dose) was evaluated.

Study Design

This was a randomized (stratified by age and gender), outpatient, four-arm, placebo-controlled, double-blinded, parallel group, multi-center study. Subjects with a history of experiencing occasional sleeplessness associated with headaches or minor aches and pains were recruited via an advertisement. The advertisement targeted current users of OTC analgesic/sleep-aid combination products and/or individuals who experienced nighttime pain associated with sleeplessness. Subjects who met all the study criteria were enrolled and randomized to one of four treatment groups. The treatment groups were 1) Ibuprofen 400mg/diphenhydramine 50mg, 2) Acetaminophen 1000mg/diphenhydramine 50mg, 3) Ibuprofen 200mg/diphenhydramine 25mg, and 4) Placebo.

One thousand sixteen subjects (2:2:1:1), at least 12 years of age were enrolled. Enrolled subjects were stratified according to gender and baseline pain severity.

Subjects were instructed to begin masked study medication on the first evening that they experienced sleeplessness associated with a headache or minor aches and pains. Subjects were permitted to take rescue medication of their choice. However, they were instructed not to take more than 800 mg of ibuprofen, 300 mg of acetaminophen, or 50 mg of diphenhydramine daily as rescue mediation. Prior to taking the first dose, subjects recorded the following information in a diary: whether they were taking study medication to treat pain, the painful condition that they were treating, their baseline pain severity, whether they had taken the study medication to help them sleep, the date, time, and number of liquigels or caplets taken, and their bedtime. The following morning, subjects recorded what time they arose and completed the sleep and pain efficacy assessments.

Subjects continued taking study medications, regardless of whether they were experiencing symptoms of pain and sleeplessness, for the next nine consecutive evenings (immediately before bedtime). Prior to taking each of the remaining nine doses of study medications, subjects recorded the following information in their diary: the date, time, and number of liquigels or caplets taken, whether they had experienced symptoms of nighttime pain and/or sleeplessness (and the painful condition), and their bedtime. On the morning following each dose of study medication, they recorded what time they arose

for the day. Also, subjects recorded any adverse events occurring during the 10-day study period, as well as the use of any other concomitant medications, including rescue medication, taken during the study period.

Test Drug Schedule: Subjects received a single dose of masked study medication on the first evening that they experienced sleeplessness associated with a headache or minor aches and pains. They continued taking study medication for the next nine consecutive evenings (before bedtime), regardless of whether they were experiencing symptoms of pain and sleeplessness.

Study Medication

Drug	Per Unit	Per Dose	Lot Number
Two Advil PM Liqui-Gels	Ibuprofen 200mg/ Diphenhydramine HCl 25mg	Ibuprofen 400mg/ Diphenhydramine HCl 50mg	WH-0723-0007-002
One Advil PM Liqui-Gel	Ibuprofen 200mg/ Diphenhydramine HCl 25mg	Ibuprofen 200mg/ Diphenhydramine HCl 25mg	WH-0723-0007-002
Matching liquigel placebo	Inert Ingredients		WH-0689-0005-001
Tylenol PM caplet	Acetaminophen 500mg/ Diphenhydramine HCl 25mg	Acetaminophen 1000mg/ Diphenhydramine HCl 50mg	WH-0001-0015-004
Matching caplet placebo	Inert Ingredients		WH-0436-0107-002

Study Population

Inclusion Criteria

Subjects were eligible for inclusion in the study provided they met all of the following criteria:

1. were male or female, 12 years of age or older;

2. had a history of experiencing sleeplessness accompanied by headaches or minor aches and pains at least two times but not continually for more than 14 days per month in at least 2 of the 3 months preceding study entry;

3. were able to read, comprehend, and sign the informed consent form (parental consent and minor assent was required for minors).

Exclusion Criteria

Subjects were excluded from participating in the study if any of the following were noted:

Medical Exclusion Criteria:

The following medically related exclusion criteria were based on the proposed label for the product:

1. allergy to acetaminophen, aspirin, ibuprofen, other nonsteroidal anti-inflammatory drugs (NSAIDS);

2. females known to be pregnant or breast-feeding;

3. the presence of any medical condition that precluded the subject from safely participating in the study (based on the proposed labeled warnings for Advil PM or in the investigator's medical judgement);

4. a history of a chronic or severe sleep problem that did not respond to OTC medication and required a prescription hypnotic or sedative; this included subjects using dietary supplements (*i.e.,* melatonin, kava kava, and valerian) 5 to 7 times per week to either treat or prevent sleeplessness);

5. current chronic NSAID therapy (defined as taking a daily [5 to 7 days per week] regimen of prescription doses of prescription or OTC NSAIDs).

Administrative Exclusion Criteria:

1. participation in an investigational study within 30 days preceding screening;

2. prior participation in this trial; or

3. employee or relative of an employee of the study site or Sponsor (directly involved with the study).

Efficacy Variables

- Next morning (or at the time of rescue medication) evaluations following the first night of dosing:
    - Sleep duration (categorical scale and number of hours slept)
    - Sleep latency

- Sleep quality
- Pain relief

- The proportion of subjects who are treatment failures.

Sleep duration (number of hours slept) and pain relief will be considered the primary sleep and pain parameters, respectively.

Safety Variables

- Incidence of any adverse event
- Any adverse event within each body system
- Each adverse event
- Proportion of subjects who discontinued due to an adverse event

The overall incidence rates for all subjects within the nervous system and digestive system will be considered primary.

Subject Disposition and Demographics

Subject Disposition

	Number of Subjects (%)				
	ACT 1000mg/ DPH 50mg	IBU 1000mg/ DPH 50mg	IBU 200mg/ DPH 25mg	Placebo	Total
Screened					1308
Randomized	340 (33.5)	338 (33.3)	164 (16.1)	174 (17.1)	1016 (77.7)
Discontinued from Study	28 (8.2)	24 (7.1)	10 (1.1)	12 (6.9)	74 (7.3)
Included in Safety Evaluations	326 (95.9)	324 (95.9)	158 (96.3)	167 (96.0)	974 (95.9)
Included in Intent-to- treat Analysis	326 (95.9)	326 (95.6)	158 (96.3)	166 95.4)	973 (95.8)
Included in Evaluable Subjects Analysis	320 (94.1)	320 (92.6)	153 (93.3)	156 (89.7)	942 (92.7)

IBU=ibuprofen DPH=diphenhydramine HCl

Summary of Reasons for Discontinuation from Study

Reason for Discontinuation	Number of Subjects (%)			
	ACT 1000mg/ DPH 50 mg N=340	IBU 400mg/ DPH 50mg N=338	IBU 200mg/ DPH 25mg N=164	Placebo N=174
Adverse events	11 (3.2)	5 (1.5)	2 (1.2)	2 (1.1)
Protocol violations	3 (0.9)	3 (0.9)	1 (0.6)	2 (1.1)
Voluntary withdrawal	2 (0.6)	2 (0.6)	2 (1.2)	2 (1.1)
Did not dose within 30 days of screening	10 (2.9)	7 (2.1)	3 (1.8)	6 (3.4)
Lost to follow-up	2 (0.6)	5 (1.5)	1 (0.6)	0 (0)
Administrative/ other	0 (0)	2 (0.6)	1 (0.6)	0 (0)

IBU=ibuprofen DPH=diphenhydramine HCl

Demographic Data
Safety Population#

		Total N=974	Placebo N=167	1 Advil PM LG N=158	2 Advil PM LG N=323	2 Tyl PM Caps N=326	p-value+
Gender							
	MALE	290 (29.8%)	54 (32.3%)	49 (31.0%)	86 (26.6%)	101 (31.0%)	0.450
	FEMALE	684 (70.2%)	113 (67.7%)	109 (69.0%)	237 (73.4%)	225 (69.0%)	
Race							
	CAUCASIAN	746 (76.6%)	129 (77.2%)	122 (77.2%)	246 (76.2%)	249 (76.4%)	0.148
	BLACK	120 (12.3%)	19 (11.4%)	16 (10.1%)	45 (13.9%)	40 (12.3%)	
	ASIAN	3 (0.3%)	1 (0.6%)	1 (0.6%)	0 (0%)	1 (0.3%)	
	HISPANIC	94 (9.7%)	13 (7.8%)	15 (9.5%)	30 (9.3%)	36 (11.0%)	
	OTHER	11 (1.1%)	5 (3.0%)	4 (2.5%)	2 (0.6%)	0 (0%)	
Age (yrs.)							
	Less than 45 Years	304 (31.2%)	54 (32.3%)	48 (30.4%)	101 (31.3%)	101 (31.0%)	
	Males @	92 (30.3%)	18 (33.3%)	15 (31.3%)	29 (28.7%)	30 (29.7%)	
	Females @	212 (69.7%)	36 (66.7%)	33 (68.8%)	72 (71.3%)	71 (70.3%)	
	45-64 Years	403 (41.4%)	66 (39.5%)	66 (41.8%)	134 (41.5%)	137 (42.0%)	
	Males @	108 (26.8%)	18 (27.3%)	18 (27.3%)	33 (24.6%)	39 (28.5%)	
	Females @	295 (73.2%)	48 (72.7%)	48 (72.7%)	101 (75.4%)	98 (71.5%)	
	65 Years or Older	267 (27.4%)	47 (28.1%)	44 (27.8%)	88 (27.2%)	88 (27.0%)	
	Males @	90 (33.7%)	18 (38.3%)	16 (36.4%)	24 (27.3%)	32 (36.4%)	
	Females @	177 (66.3%)	29 (61.7%)	28 (63.6%)	64 (72.7%)	56 (63.6%)	
	MEAN	51.2	51.6	51.8	50.5	51.3	0.814
	STD	16.8	16.8	16.1	17.3	16.7	
	MEDIAN	52.0	51.0	52.0	51.0	53.0	
	RANGE	(12, 87)	(13, 86)	(14, 79)	(12, 85)	(12, 87)	

#: Includes all subjects who took at least one dose of study medication.
+: p-values for gender, race, alcohol use and education from the Cochran-Mantel-Haenszel test, controlling for site, gender, and age group, as appropriate.
p-values for age, weight, and height from ANOVA model with terms for treatment and site, gender and age group, as appropriate.
*: Statistically significant at $p \leq 0.05$.
m: Marginally significant ($0.05 < p \leq 0.10$).
@: As a percentage of subjects within the age group.
^: As a percentage of alcohol users.

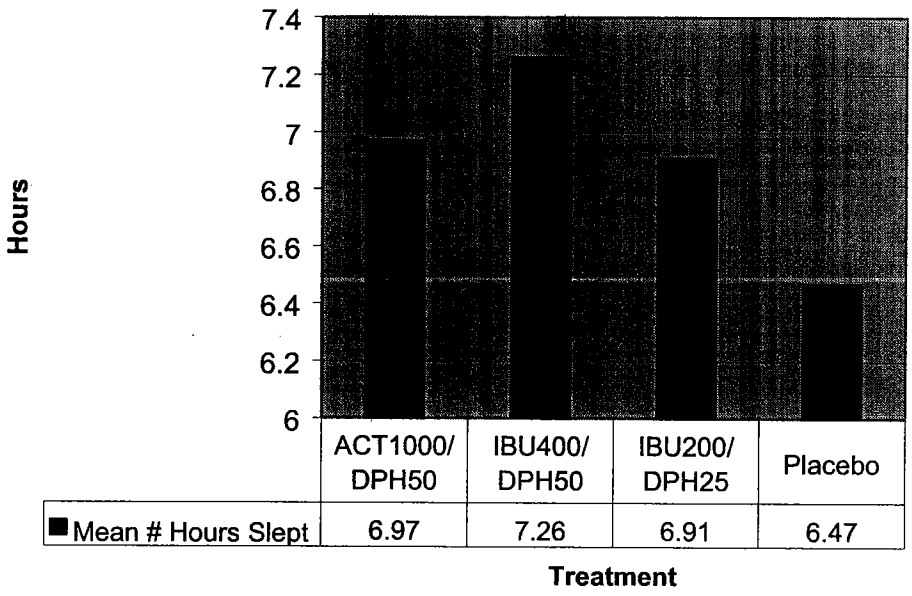
Demographic Data
Safety Population#

	Total N=974	Placebo N=167	1 Advil PM LG N=158	2 Advil PM LG N=323	2 Tyl PM Caps N=326	p-value+
Weight (lbs.)						
MEAN	175.8	180.5	174.3	174.9	175.1	0.390
STD	44.9	48.6	40.7	46.4	43.5	
MEDIAN	169.0	172.0	167.5	165.0	170.0	
RANGE	(78, 370)	(97, 350)	(111, 320)	(78, 350)	(94, 370)	
Height (ins.)						
MEAN	66.0	66.2	66.0	66.0	66.0	0.785
STD	3.8	4.3	3.6	3.9	3.7	
MEDIAN	66.0	66.0	65.0	65.0	66.0	
RANGE	(54, 76)	(54, 76)	(59, 76)	(54, 75)	(54, 75)	
Alcohol Use						
No	370 (38.0%)	66 (39.5%)	55 (34.8%)	124 (38.4%)	125 (38.3%)	0.815
Yes	604 (62.0%)	101 (60.5%)	103 (65.2%)	199 (61.6%)	201 (61.7%)	
No. Drinks/Day						
0-2 ^	601 (99.5%)	99 (98.0%)	103 (100.0%)	199 (100.0%)	200 (99.5%)	
3-4 ^	3 (0.5%)	2 (2.0%)	0 (0%)	0 (0%)	1 (0.5%)	
Highest Level of Education Completed						
7th to 8th Grade	17 (1.7%)	2 (1.2%)	3 (1.9%)	5 (1.5%)	7 (2.1%)	0.574
Some High School	56 (5.7%)	4 (2.4%)	6 (3.8%)	23 (7.1%)	23 (7.1%)	
High School Graduate	217 (22.3%)	39 (23.4%)	31 (19.6%)	74 (22.9%)	73 (22.4%)	
Some College	372 (38.2%)	68 (40.7%)	70 (44.3%)	117 (36.2%)	117 (35.9%)	
College Graduate	217 (22.3%)	37 (22.2%)	30 (19.0%)	79 (24.5%)	71 (21.8%)	
Some Graduate School	39 (4.0%)	7 (4.2%)	7 (4.4%)	8 (2.5%)	17 (5.2%)	
Masters or PhD Degree	56 (5.7%)	10 (6.0%)	11 (7.0%)	17 (5.3%)	18 (5.5%)	

#: Includes all subjects who took at least one dose of study medication.
+: p-values for gender, race, alcohol use and education from the Cochran-Mantel-Haenszel test, controlling for site, gender, and age group, as appropriate.
p-values for age, weight, and height from ANOVA model with terms for treatment and site, gender and age group, as appropriate.
*: Statistically significant at $p \leq 0.05$.
m: Marginally significant ($0.05 < p \leq 0.10$).
@: As a percentage of subjects within the age group.
^: As a percentage of alcohol users.

Efficacy **Intent-to-Treat Population**

Duration of Sleep (mean # of hours slept)



Reviewer's Comments:

The mean number of hours slept were 6.97 for the acetaminophen 1000mg/ diphenhydramine 50mg fixed combination, 7.26 for the ibuprofen 400mg/ diphenhydramine 50mg fixed combination, 6.91 for the ibuprofen 400mg/ diphenhydramine 25mg fixed combination, and 6.47 placebo.

Treatment Group Comparisons – Duration of Sleep

	IBU400/ DPH50 vs. ACT1000/ DPH50	IBU400/ DPH50 vs. IBU200/ DPH25	IBU400/ DPH50 vs. Placebo	IBU200/ DPH25 vs. Placebo	ACT1000/ DPH50 vs. Placebo	IBU200/ DPH25 vs. ACT1000/ DPH50
p-value	0.045	0.051	<0.001	0.030	0.004	0.738

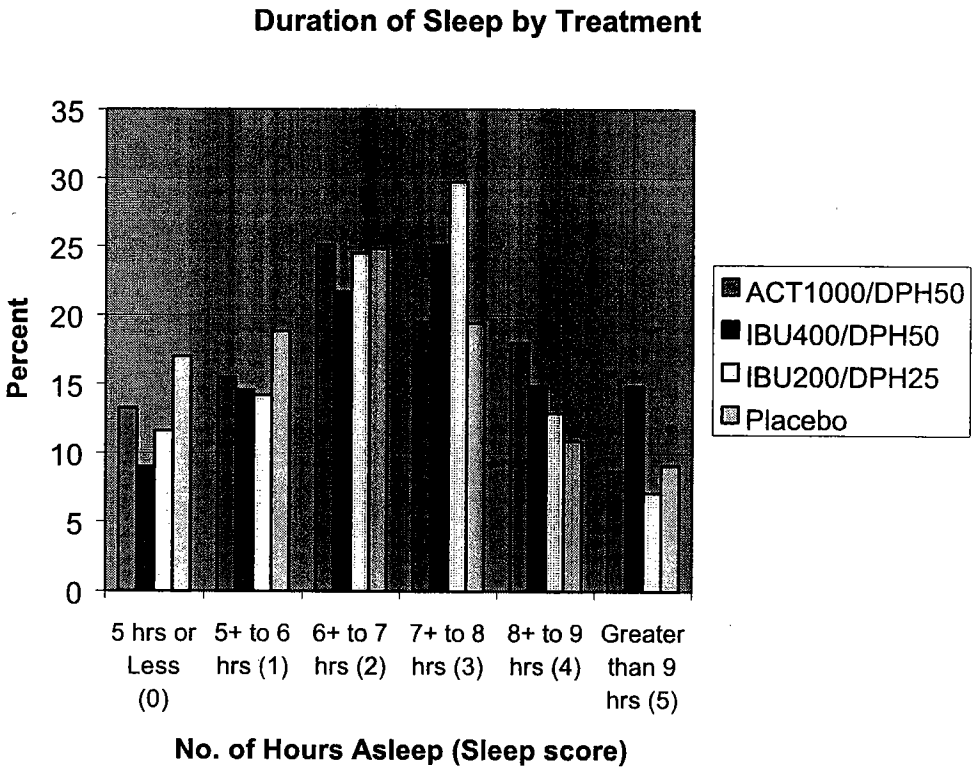
IBU=ibuprofen DPH=diphenhydramine HCl

Reviewer's Comments:

The effect on sleep duration of the ibuprofen 400 mg/diphenhydramine 50 mg fixed combination as compared to acetaminophen 1000 mg/diphenhydramine 50 mg fixed combination (p=0.045) and placebo (<0.001) were statistically significant and not statistically significant as compared to the ibuprofen 200 mg/diphenhydramine 25 mg fixed combination. (Uncorrected for multiple comparisons)

The effect on sleep duration of the ibuprofen 200mg/diphenhydramine 25 mg fixed combination (p=0.030) as compared to placebo was statistically significant but was not statistically significant as compared to the acetaminophen 100 mg/diphenhydramine 50 mg fixed combination (p=0.738). (Uncorrected for multiple comparisons)

The effect on sleep duration of the acetaminophen 1000mg/diphenhydramine 50 mg fixed combination (p= 0.004) as compared to placebo was statistically significant.



Mean Sleep Score – Categorical Scale (0-5)

	ACT1000/ DPH50	IBU400/ DPH50	IBU200/ DPH25	Placebo
Mean Sleep Score	2.39	2.67	2.39	2.16

IBU=ibuprofen DPH=diphenhydramine HCl

Treatment Group Comparisons – Duration of Sleep

	IBU400/ DPH50 vs. ACT1000/ DPH50	IBU400/ DPH50 vs. IBU200/ DPH25	IBU400/ DPH50 vs. Placebo	IBU200/ DPH25 vs. Placebo	ACT1000/ DPH50 vs. Placebo	IBU200/ DPH25 vs. ACT1000/ DPH50
P-value	0.018	0.060	<0.001	0.121	0.074	0.979

IBU=ibuprofen DPH=diphenhydramine HCl

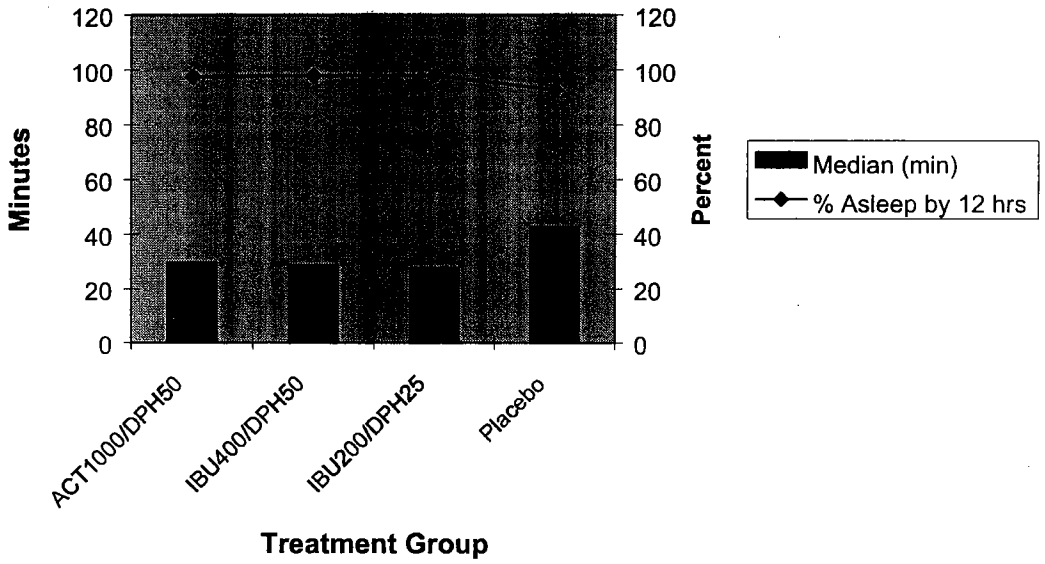
Reviewer's Comments:

The effect on duration of sleep (categorical scale) of the ibuprofen 400mg/ diphenhydramine 50mg fixed combination as compared to acetaminophen 1000mg diphenhydramine HCl 50mg (p=0.018) and placebo (<0.001) were statistically significant and was not statistically significant as compared to ibuprofen 200mg/diphenhydramine HCl 50mg.

The effect on duration of sleep (categorical scale) of ibuprofen 200mg/diphenhydramine HCl 25mg as compared to placebo (p=0.121) and acetaminophen 1000mg/ diphenhydramine HCl 50mg (p=0.979) were not statistically significant.

The effect on duration of sleep (categorical scale) of acetaminophen 1000mg/ diphenhydramine HCl 50mg as compared to placebo (p=0.074) was not statistically significant.

Median and % of Subjects Asleep by 12 Hours



Reviewer's Comments:

The median sleep latencies were approximately 30 minutes for acetaminophen 1000mg/diphenhydramine 50mg, 28 minutes for ibuprofen 400mg/diphenhydramine 50mg, 27 minutes for ibuprofen 200mg/diphenhydramine 25mg, and 43 minutes for placebo.

The percentage of subjects asleep by 12 hours after administration of masked study medication were approximately 98% for acetaminophen 100mg/diphenhydramine 50mg, ibuprofen 400mg/diphenhydramine 50mg, and ibuprofen 200mg/diphenhydramine 25mg, and 93% for placebo.

Treatment Group Comparisons – Sleep Latency

	IBU400/ DPH50 vs. ACT1000/ DPH50	IBU400/ DPH50 vs. IBU200/ DPH25	IBU400/ DPH50 vs. Placebo	IBU200/ DPH25 vs. Placebo	ACT1000/ DPH50 vs. Placebo	IBU200/ DPH25 vs. ACT1000/ DPH50
p-value	0.015	0.414	<0.001	<0.001	0.008	0.250

IBU=ibuprofen DPH=diphenhydramine HCl

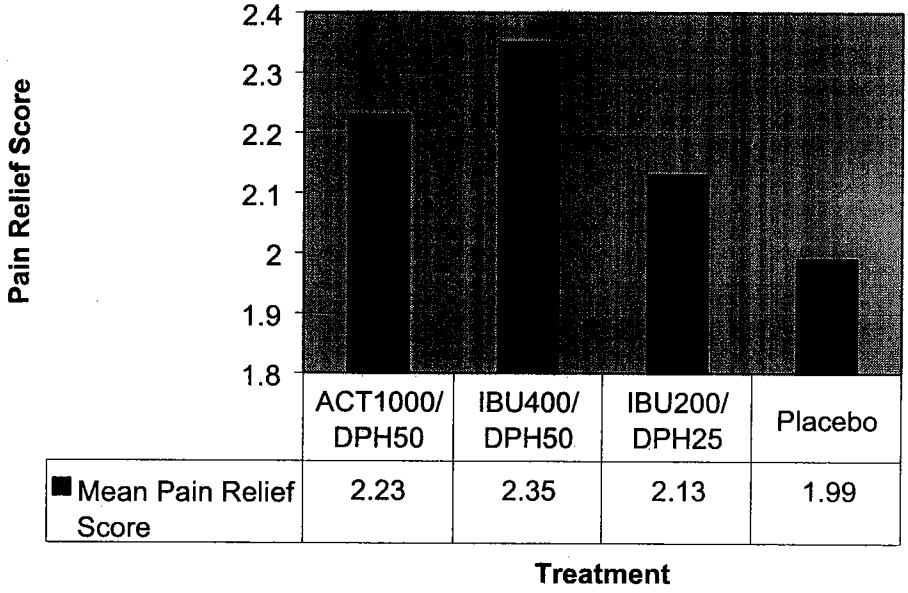
Reviewer's Comments:

The effect on sleep latency of the ibuprofen 400mg/diphenhydramine 50 mg fixed combination as compared to acetaminophen 1000mg/diphenhydramine 50mg (p=0.015) and placebo (<0.001) were statistically significant and was not statistically significant as compared to ibuprofen 200mg/diphenhydramine 25mg (p=0.414). (Uncorrected for multiple comparisons)

The effect on sleep latency of ibuprofen 200mg/diphenhydramine 25mg as compared to placebo (<0.001) was statistically significant and was not statistically significant as compared to acetaminophen 1000mg/diphenhydramine 50mg (p=0.250).

The effect on sleep latency of acetaminophen 1000mg/diphenhydramine 50mg as compared to placebo (p=0.008) was statistically significant.

Mean Pain Relief Rating (categorical scale)



Reviewer's Comments:

The mean pain relief scores (0=None, 1=A little, 2=Some, 3=A lot, 4=Complete) were 2.23 for the acetaminophen 1000mg/diphenhydramine 50mg fixed combination, 2.35 for the ibuprofen 400mg/diphenhydramine 50mg fixed combination, 2.13 for the ibuprofen 200mg/diphenhydramine 25mg fixed combination, and 1.99 for placebo.

Treatment Group Comparisons – Pain Relief Rating

	IBU400/ DPH50 vs. ACT1000/ DPH50	IBU400/ DPH50 vs. IBU200/ DPH25	IBU400/ DPH50 vs. Placebo	IBU200/ DPH25 vs. Placebo	ACT1000/ DPH50 vs. Placebo	IBU200/ DPH25 vs. ACT1000/ DPH50
p-value	0.144	0.040	<0.001	0.277	0.031	0.380

IBU=ibuprofen DPH=diphenhydramine HCl

Reviewer's Comments:

The pain relief effect of the ibuprofen 400mg/diphenhydramine 50mg fixed combination as compared to acetaminophen 1000mg/diphenhydramine 50mg fixed combination (p=0.144) was not statistically significant and was statistically significant as compared to the ibuprofen 200mg/diphenhydramine 25 mg fixed combination (p=0.040) and placebo (p<0.001). (Uncorrected for multiple comparisons)

The pain relief effect of the ibuprofen 200mg/diphenhydramine 25mg fixed combination as compared to the acetaminophen 1000mg/diphenhydramine 50mg (p=0.380) and placebo (p=0.277) were not statistically significant.

The pain relief effect of the acetaminophen 1000mg/diphenhydramine 50mg fixed combination as compared to placebo (p=0.031) was statistically significant. (Uncorrected for multiple comparisons)

Safety

Adverse Events

Nine hundred seventy-four of the 1016 randomized subjects received at least one dose of masked study medication and were included in the safety analysis. One serious adverse event occurred during the study. No deaths occurred during the study. Twenty subjects (2.0%), two (1.2%) in the placebo treatment group, two (1.3%) in the Ibuprofen 200mg/diphenhydramine 25mg treatment group, five (1.5%) in the ibuprofen 400mg/ diphenhydramine treatment group, and eleven (3.4%) in the acetaminophen 1000mg/diphenhydramine treatment group discontinued prematurely from the study due to an adverse event.

Serious Adverse Events

Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C from Study
60151	ACT1000/DPH50	Atrial fibrillation	Resolved w/Tx	No

IBU=ibuprofen DPH=diphenhydramine HCl

Subjects Discontinued Due to Adverse Events

Parient Number	Treatment	Coded Adverse Event	Outcome of Event
30005	ACT 1000mg/DPH 50mg	Agitation	Resolved wo/Tx
		Agitation	Resolved w/Tx
40040	ACT 1000mg/DPH 50mg	Pruritis	Resolved w/Tx
		Dyspepsia	Resolved w/Tx
40196	ACT 1000mg/DPH 50mg	Vomiting	Resolved wo/Tx
40121	ACT 1000mg/DPH 50mg	Back pain	Resolved w/Tx
		Pain	Resolved w/Tx
		Somnolence	Resolved w/Tx
		Urinary tract infection	Resolved w/Tx
40206	ACT 1000mg/DPH 50mg	Headache	Resolved w/Tx
		Dyspnea	Resolved w/Tx
		Rhinitis	Resolved w/Tx
		Headache	Resolved w/Tx
40381	ACT 1000mg/DPH 50mg	Palpitation	Resolved wo/Tx
		Pain	Resolved w/Tx
50104	ACT 1000mg/DPH 50mg	Somnolence	Resolved wo/Tx
		Vertigo	Resolved wo/Tx
60015	ACT 1000mg/DPH 50mg	Flu syndrome	Resolved w/Tx
60059	ACT 1000mg/DPH 50mg	Somnolence	Resolved wo/Tx
60151	ACT 1000mg/DPH 50mg	Atrial fibrillation	Resolved w/Tx
60209	ACT 1000mg/DPH 50mg	Rash	Persisted
		Rash	Resolved wo/Tx
40075	IBU 400mg/DPH 50mg	Somnolence	Resolved wo/Tx
		Sweating	Resolved wo/Tx
		Face edema	Resolved w/o Tx
		Dry mouth	Resolved wo/Tx
		Tremor	Resolved wo/Tx
40112	IBU 400mg/DPH 50mg	Dry mouth	Persisted
		Somnolence	Resolved wo/Tx
		Nervousness	Persisted
		Pain	Resolved wo/Tx
50130	IBU 400mg/DPH 50mg	Nausea	Resolved wo/Tx
60011	IBU 400mg/DPH 50mg	Headache	Resolved w/Tx
		Taste perversion	Resolved wo/Tx
60016	IBU 400mg/DPH 50mg	Dystonia	Resolved wo/Tx
50121	IBU 200mg/DPH 25mg	Somnolence	Resolved wo/Tx
		Taste perversion	Resolved wo/Tx
60181	IBU 200mg/DPH 25mg	Insomnia	Resolved wo/Tx
		Insomnia	Resolved wo/Tx
20095	Placebo	Asthenia	Resolved wo/Tx
40326	Placebo	Palpitation	Resolved wo/Tx
		Hypertension	Resolved wo/Tx
		Diarrhea	Resolved wo/Tx
		Dry mouth	Resolved wo/Tx
		Dizziness	Resolved wo/Tx

IBU=ibuprofen DPH=diphenhydramine HCl

The most frequent adverse events in subjects treated with ibuprofen 400mg/ diphenhydramine 50mg were headaches (11.5%) and somnolence (8.7).

Number (%) of Subjects with Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	ACT 1000/DPH 50 N=326	IBU 400/DPH 50 N=323	IBU 200/DPH 25 N=158	Placebo N=167
	N (%)	N (%)	N (%)	N (%)
All Events	201 (61.7)	181 (56.0)	85 (53.8)	80 (47.9)
Body as a Whole				
Headache	28 (8.6)	37 (11.5)	12 (7.6)	17 (10.2)
Pain	17 (5.2)	10 (3.1)	2 (1.3)	4 (2.4)
Back pain	5 (1.5)	8 (2.5)	5 (3.2)	8 (4.8)
Common cold		5 (1.5)	3 (1.9)	3 (1.8)
Flu syndrome			2 (1.3)	
Cardiovascular				
Migraine	4 (1.2)			
Palpitation				2 (1.2)
Digestive				
Dyspepsia	25 (7.7)	16 (5.0)	11 (7.0)	15 (9.0)
Dry mouth	5 (1.5)	7 (2.2)		
Abdominal pain	4 (1.2)	6 (1.9)		
Nausea	6 (1.8)	5 (1.5)		
Diarrhea	6 (1.8)	4 (1.2)	3 (1.9)	3 (1.8)
Flatulence	4 (1.2)			3 (1.8)
Constipation	4 (1.2)			
Musculosketal				
Leg cramps	4 (1.2)			
Myalgia			3 (1.9)	
Nervous				
Somnolence	25 (7.7)	28 (8.7)	14 (8.9)	4 (2.4)
Dizziness	9 (2.8)	5 (1.5)		2 (1.2)
Respiratory				
Rhinitis	7 (2.1)	7 (2.2)	5 (3.2)	5 (3.0)
Cough increased			2 (1.3)	
Sinusitis				2 (1.2)
Skin and Appendages				
Pruritis	4 (1.2)			
Special Senses				
Taste perversion			2 (1.3)	

IBU=ibuprofen DPH=diphenhydramine HCl

Reviewer's Summary of Efficacy and Safety

The effect on sleep duration for the ibuprofen 400mg/diphenhydramine 50mg fixed combination was statistically superior to the acetaminophen 1000mg/diphenhydramine 50mg fixed combination.

The pain relief effect of the ibuprofen 400mg/diphenhydramine 50mg fixed combination was numerically better than but not statistically superior to the acetaminophen 1000mg/ diphenhydramine 50mg fixed combination.

Adverse events were numerically greater but not statistically significantly higher for the acetaminophen 1000mg/diphenhydramine 50mg fixed combination as compared to the ibuprofen 400mg/diphenhydramine 50mg fixed combination.

VII. Integrated Review of Safety

No new issues of safety have been identified. The combination has the same safety profile as ibuprofen and diphenhydramine administered separately.

VIII. Dosing, Regimen, and Administrative Issues – N/A

IX. Use in Special Populations – N/A

X. Labeling

Labeling for NDA 21-393 is deferred until efficacy has been demonstrated.

Labeling for NDA 21-394 is deferred until efficacy for NDA 21-393 and bioequivalence between ibuprofen 200mg/diphenhydramine citrate 38mg tablet and ibuprofen 200mg/diphenhydramine HCl 25mg liquid filled capsule have been demonstrated.

XI. Conclusions and Recommendations

Conclusions

1) The submitted studies in NDA 21-393 and NDA 21-394 demonstrate no new safety findings for the use of ibuprofen 400mg/diphenhydramine 50mg fixed combination oral liquid filled capsule in the relieving occasional sleeplessness when associated with —→ minor aches and pain.

2) The submitted studies in NDA 21-393 and NDA 21-394 are not sufficient to establish efficacy for the use of ibuprofen 400mg/diphenhydramine 50mg fixed combination oral liquid filled capsule in relieving occasional sleeplessness when associated with —— minor aches and pain:

   a) The difference in effect on sleeplessness of the fixed combination compared to ibuprofen monotherapy is not statistically and clinically significant.

      Neither Study AE-97-01, AE-98-01, nor AE-98-02 demonstrates statistically nor clinically significant contribution of the diphenhydramine component of the proposed combination drug product in the oral surgery acute pain model.

   b)

Recommendations

1) The sponsor should submit additional information to support the efficacy of ibuprofen 400mg/diphenhydramine 50mg fixed combination oral liquid filled capsule in relieving occasional sleeplessness when associated with [redacted] minor aches and pain.

Lucious Lim, M.D., M.P.H.

NDA 21-393
NDA 21-394
HFD-550/Div/Files
HFD-550/MO/Lim
HFD-550/Biopharm/Adebowale
HFD-550/Biopharm/Lee
HFD-550/Biostats/Lu
HFD-550/Chem/Ho
HFD-550/Pharm/Rivera
HFD-550/PM/Dean
HFD-550/SMO/Chambers
HFD-550/Div Director/Simon

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Lucious Lim
3/15/02 04:07:16 PM
MEDICAL OFFICER

Wiley Chambers
3/18/02 03:56:03 PM
MEDICAL OFFICER

James Witter
4/2/02 12:34:34 PM
MEDICAL OFFICER

Lee Simon
4/2/02 01:00:57 PM
MEDICAL OFFICER