European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London 12 April 2010
EMA/CHMP/239978/2010

WITHDRAWAL ASSESSMENT REPORT FOR

IBUPROFEN/DIPHENHYDRAMINE HYDROCHLORIDE WYETH

International Nonproprietary Name (INN): (ibuprofen and diphenhydramine hydrochloride)

EMEA/H/C/1108

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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LIST OF ABBREVIATIONS

4-IBAP	4-Isobutylacetophenone
AE	Adverse Event
AF	Assessment Factor
APAP	Paracetamol/Acetaminophen
AUCinf	Area under the plasma concentration vs. time curve extrapolated to infinity
BA	Bioavailability
BBB	Blood-Brain Barrier
BW	Body Weight
CHMP	Committee for Medicinal Products for Human Use
Cmax	Maximum plasma concentration
CMC	Carboxymethylcellulose
CNS	Central Nervous System
COX	Cyclooxygenase
CYP	Cytochrome P450
DOSEai	Maximum Daily Dose Consumed per Inhabitant
DPH	Diphenhydramine hydrochloride
DPMA	Diphenyl Methoxy Acetic Acid
DSM	Diagnostic and Statistical Manual of Mental
DT_{90}	Dissipation time 90%
EC_{10}	Effect Concentration 10 %
EC_{50}	Effect Concentration 50 %
ECOSAR	Ecological Structure Activity Relationship
ED_{50}	Effective Dose 50 %
EEA	European Economic Area
EMEA	European Medicine Agency
ERA	Environmental Risk Assessment
E_rC_{50}	Effect Concentration 50 % based on growth rate
EU	European Union
EU PV HQ	European Regional Pharmacovigilance
E_yC_{50}	Effect Concentration 50 % based on yield
FDA	Food and Drug Administration
Fpen	Percentage of Market Penetration
GABA	Gamma-Aminobutyric Acid
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMOs	Genetically Modified Organisms
HCl	Hydrochloride
HED	Human Equivalent Dose
hERG	Ether-a-go-go Related Gene
HMDB	Human Metabolome Database

HPLC	High-Performance Liquid Chromatography
HSDB	Hazardous Substances Data Bank
IBU	Ibuprofen
IBU-PEG	Ibuprofen-Polyethylene Glycol
IC_{50}	Inhibition Concentration 50 %
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Reports
inh	Inhabitant
ISO	International Organization for Standardization
IUCLID	International Uniform Chemical Information Data Base
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	Organic Carbon Sorption Coefficient
K_{ow}	Partition Coefficient octanol/water
LC_{50}	Lethal Concentration 50 %
LD_{50}	Median Lethal Dose 50 %
LSSU	Local Safety Surveillance Units
MAA	Marketing Authorisation Application
MIC	Microbial Inhibitory Concentration
MNNG	N-methyl-N'-nitro-N-nitrosoguanidine
MP	Medicinal Product
MTD	Maximum Tolerated Dose
NEL	No Effect Level
NMDA	N-Methyl-D-Aspartate
NOAEL	No Observable Adverse Effect Level
NOEC	No Observable Effect Concentration
NOEL	No Observable-Effect Level
NRP	National Responsible Person
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSAID	Nonsteroidal anti-inflammatory drug
OECD	Organisation for Economic Co-operation and Development
OSPAR	Convention for the Protection of the Marine Environment of the North East Atlantic
OTC	Over-the-Counter
PBO	Placebo
PD	Pharmacodynamic
PEC	Predicted Environmental Concentration
$PEC_{GROUNDWATER}$	Predicted Environmental Concentration in Groundwater
$PEC_{SURFACE\ WATER}$	Predicted Environmental Concentration in Surface Water
PEG600	Polyethylene glycol 600
PG	Prostaglandin
PGR	Population Growth Rate
PIL	Patient Information Leaflet
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PK_a	Acid Dissociation Constant
PK_b	Base Dissociation Constant

PNEC	Predicted No Effect Concentration
PSG	Polysomnography
QPPV	Qualified Person for Pharmacovigilance
RA	Regulatory Authority
RC	Relative Humidity
RQ	Risk Quotient (PEC/PNEC)
S3	Safety Surveillance System
SD rats	Sprague Dawley rats
SPC	Summary of Product Characteristics
TdP	Torsades de Pointes
TGD	Technical Guidance Document
tid	Three-time-a-day
t_{max}	Time to Peak Concentration
TRS	Total Related Substances
TSCATS	Toxic Substance Control Act Test Submission
UK	United Kingdom
US	United States
US EPA	Environmental Protection Agency of America
USA	United States of America
UV	Ultra-Violet
WasteWinhab	Amount of Waste Water per Inhabitant per Day
WCH	Wyeth Consumer Healthcare

I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for Ibuprofen/Diphenhydramine Hydrochloride Wyeth 200 mg/25 mg Capsules for the short-term treatment of mild to moderate pain in adults who have a history of experiencing difficulty in getting to sleep and staying asleep as a result of the pain is not approvable since "major objections" still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the list of outstanding issues (Section VI).

The major objections precluding a recommendation of marketing authorisation or the granting of OTC status, pertain to the following principal deficiencies:

Efficacy:
The submitted dossier and the response to the list of questions were not sufficient to meet the EU requirements for demonstrating a clinically relevant advantage of the combination of IBU/DPH compared to the single substances, in particular to IBU. In the opinion of the CHMP the monotherapy with IBU was as effective as the combination for reducing pain and inducing sleep:

• The efficacy of Ibuprofen/Diphenhydramine Hydrochloride Wyeth versus IBU has only been investigated in a patient population with a median age of approximately 20 years. For older patients no conclusion concerning an advantage of Ibuprofen/Diphenhydramine Hydrochloride Wyeth versus IBU is possible, due to a complete lack of data. The company tries to overcome this problem by discussing data for the combination in younger and older patients and by quoting the literature of DPH in the elderly. However a direct comparison of the combination versus the mono components for the target population for the entire adult population is required.

• There are no data available to demonstrate a possible advantage of Ibuprofen/Diphenhydramine Hydrochloride Wyeth versus IBU beyond a single dose application, rendering any posology recommendation of more than one day of treatment arbitrary. The view of the CHMP is that the literature quoted to overcome this problem cannot replace missing data.

• The CHMP concluded that the only shown apparent benefit of Ibuprofen/Diphenhydramine Hydrochloride Wyeth compared to IBU is a minimal increase in sleep duration. An investigation of sleep architecture and of next day functioning as required by the EMA guideline on hypnotic medicinal products has not been performed. Therefore, it can not be excluded at present that any prolongation of sleep duration is invalidated by a negative change in sleep architecture or by a deteriorated next day functioning. Ibuprofen alone has already an impressive effect versus placebo on sleep duration. It is questionable whether in patients without primary sleep disturbances a further extension of sleep duration by the addition of DPH () is desirable. It might have a negative effect by unnecessary sedation. With DPH/IBU a larger proportion of patients sleep more than 9 hours when compared with IBU alone.

• The view of the CHMP was that it has not been established that secondary insomnia due to pain is a truly existing condition to be treated. The data from the literature and the discussion by the company do not convincingly demonstrate that insomnia caused by pain should be treated by a hypnotic.

Safety:
The submitted dossier and the response to the list of questions was considered insufficient to provide the requested clear definition of the safety profile of the combination of IBU/DPH compared to the single substances, in particular to IBU:

- The first major deficiency, disregarding the EMA guideline on fixed combination medicinal products, is the complete lack of an adequate comparative safety profile of IBU 400/DPH 50 to IBU 400 in a representative patient population (older patients).
- Furthermore, there is no safety data coming from a direct comparison of IBU 400/DPH 50 vs IBU 400 following repeated use (more than 1 day).

- The second major deficiency is the lack of data to completely meet the EU guideline on clinical investigation of hypnotic medicinal products, particularly in relation to any potential next day effects.. Ibuprofen/Diphenhydramine Hydrochloride Wyeth is intended to be used by a patient population that suffers from mild to moderate pain, which interferes with falling asleep at night. But that target population is expected to resume all their normal activities of daily living in the morning. These activities will include driving, working mentally and manually and operating machinery. As the administration of IBU alone facilitates falling asleep, this absence of data presents a major obstacle for any benefit-risk assessment, because any beneficial effects of Ibuprofen/Diphenhydramine Hydrochloride Wyeth on the duration of sleep could be outweighed by impaired next day functioning

The attempt by the company to replace the missing data by discussing pharmacovigilance data from the United States and by quoting papers from the literature is considered by the CHMP to be insufficient The major problem of the lack of data for a direct comparison between the combination and the monocomponents remains. The same is true for the lack of data on sleep architecture and next day functioning.

Legal Status
Self-assessment
• Although a positive readability study had been completed on the proposed package leaflet, concerns remain in connection with the OTC status applied for (see e.g. first criterion of guideline on "Changing the classification for the supply of a medicinal product for human use" 1.3 Self-assessment). The CHMP considered that this criterion had not been met.

Direct danger/safety profile
• The interaction potential of DPH with widely used medications, e.g. allergy medication or psychotropic substances are of concern in connection with the desired OTC status. The Company is asked to provide further data on adverse events suspected of occurring due to drug interactions.
The Applicant should address the issues mentioned above together with the various criteria for classifying a medicinal product as subject to a medical prescription or not, to support the effective and safe use of the product in accordance with the European Commission guideline on “Changing the classification for the supply of a medicinal product for human use”, without the need for consulting a physician.

In their response the company failed to adequately address the raised concerns about legal status in order to be in accordance with the European Commission guideline “Changing the classification for the supply of a medicinal product for human use” with regard to self assessment and safety profile.

Proposal for Questions to be posed to additional Experts
None.

Inspection issues
None.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Pain and sleeplessness are two distinct, very common medical problems, that can be closely interrelated. Insomnia, or sleeplessness, is defined as the inability to fall asleep, stay asleep, or get adequate duration or quality of sleep necessary for optimal functioning and well being. Sleep problems may include one or more of the following: difficulty in falling sleep, difficulty in maintaining sleep, waking up too early and complaints of non-restorative (poor quality) sleep. Acute, transient insomnia is defined as sleeplessness lasting from 1 to 3 weeks. It may have a number of underlying causes, including pain.

While sleep problems are the most frequently reported complaint accompanying pain syndromes such as neuropathy, they can also occur in virtually every pain disorder, such as headache, backache, dysmenorrhoea, post-surgical pain, and osteoarthritis.

Today, the bidirectional influence of chronic pain on sleep quality and disturbed sleep on pain intensity is increasingly recognized. The importance of treating insomnia as well as pain in chronic pain syndromes and thereby avoiding initiation of a vicious circle, in which pain increases insomnia and insomnia in turn increases pain, is currently entering into pain management guidelines.
For acute pain, no similar evidence base exists. If for a benign, self-limiting cause of pain the symptoms are adequately relieved, a pattern of persistent sleep problems is extremely unlikely to establish itself.

The Company decided to develop Ibuprofen/Diphenhydramine Hydrochloride Wyeth for the treatment of minor aches and pains, which are associated with short-term sleeplessness. Ibuprofen/Diphenhydramine Hydrochloride Wyeth is intended to be sold OTC.

II.2 About the product

Ibuprofen/Diphenhydramine Hydrochloride Wyeth is a combination product containing 200 mg of ibuprofen and 25 mg of diphenhydramine. The recommended dose is 2 capsules in the evening before going to bed.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

CHMP guidelines:

- Draft Guideline on Fixed Combination Medicinal Products: CPMP/EWP/240/95 Rev. 1;
- Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain: CPMP/EWP/612/00;
- Clinical Investigation of Hypnotic Medicinal Products

Guideline recommendations were disregarded for the fixed combination guidance (proof that the combination is superior to its substances for repeat administration and a target population that is over a mean age of 20 years) and the hypnotic medicinal products guideline (no sleep laboratory

studies/ no separate studies in elderly patients/ no evaluation of improved daytime functioning/ no investigation of hang-over effects/ no investigation of sustained therapeutic efficacy). The justifications provided for these deviations are not regarded as satisfactory.

EMEA Scientific Advice:

No scientific advice was requested by the Applicant.

II.4 General comments on compliance with GMP, GLP, GCP

GMP:
The Rapporteurs have been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the Rapporteurs have accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For the authorised manufacturer responsible for the batch release in the EEA of the above mentioned product the qualified person states that both active substances, Ibuprofen and Diphenhydramine Hydrochloride used in the product are produced in accordance with the detailed European guidelines on good manufacturing practice for starting materials.

GLP:
According to the Applicant, all pre-clinical toxicology studies of the combination ibuprofen/diphenhydramine were performed in accordance with GLP.

GCP:
The Applicant states that all studies conducted as part of this program were performed and analyzed in accordance with all applicable regulations, laws and guidelines. These include formal regulatory guidance documents from the European Medicines Agency/Committee for Medicinal Products for Human Use (EMEA/CHMP), International Conference on Harmonization (ICH) and the U.S. Food and Drug Administration (FDA). All studies were conducted according to Good Clinical Practice and followed the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

II.5 Type of application and other comments on the submitted dossier

- *Legal basis*

This application concerns a centralised procedure according to Regulation (EC) No 726/2004, optional scope in accordance with Article 3(2)(a), New active substance.
This dossier includes complete administrative and complete quality, pre-clinical and clinical data on the combination only, in accordance with Article 10b fixed combination application.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Introduction:
The medicinal product applied in this centralised application are soft gelatin capsules combining the two active substances Ibuprofen and Diphenylhydramine- HCl (in the ratio 200mg IBU : 25mg DPH).

Drug substance

Characteristics
IBU: The drug substance Ibuprofen (IBU) is characterised by a CEP. All parts of 3.2.S. are referring to the CEP including also the re-test period of 3 years if stored in lock –rim fibre drums – which has been stated in the CEP.

DPH: The manufacturer of the drug substance, in accordance with the "Guideline on Active Substance Master File Procedure" (CPMP/QWP/227/02). The specification provided is according to the Ph.Eur Monograph test methods and limits for Diphenylhydramine including an additional method for detection of residual solvents by HS- GC method which is regarded suitable.
In the batch analysis report three batches of the drug substances were tested showing acceptable results.

DPH - Stability
Data of three months` stability trials at accelerated conditions have been submitted. The remaining 6 months` test results of the current stability studies for the drug substance DPH at accelerated conditions should be provided ASAP by the DS manufacturer .

Drug Product

Development pharmac. & Manufacture
All important excipients influencing the quality and acceptability of the product (in the meaning of the size of the capsule and its suitability for oral administration) are discussed in this chapter..
The manufacturing process in total is described in a sufficient way and considered to be suitable for producing capsules of good quality according to the description.

Specification & Control test
The drug substance specification is regarded acceptable in general including all important test parameters as well as test methods intended for the product. has been justified by in a study provided by the Applicant. Concerning the microbial tests, the applicant has provided a detailed study taking into account all possible ways and sources of bacterial contamination for the product accompanied by a risk assessment for each potential factor which is regarded acceptable in general.
The parameter microbial quality should be therefore tested on a non routine base which should be indicated in the finished product specification.

Stability- conclusion

Based on the stability results of the US formulation a shelf life of 24 °C , "store below 25°C" has been proposed..

The required stability data covering a storage period of 12 months are currently available. Based on these data a shelf life the proposed shelf-life is 24 months with storage precaution "Store below 25ºC" can be accepted.

III.2 Non clinical aspects

Pharmacology

Ibuprofen and diphenhydramine are both well established drugs. Ibuprofen has analgesic properties with anti-inflammatory and antipyretic effects by inhibiting prostaglandin synthesis, whereas diphenhydramine functions as antihistamine. The combination of a sleep-aid with an analgesic should facilitate a better night's sleep.

Previous studies with single entities showed that diphenhydramine produces bradycardia, hypotension and increases the PR and QRS intervals at very high doses, whereas Ibuprofen was not associated with direct cardiac effects. No additional pharmacodynamic and safety pharmacology studies with the fixed combination have been submitted.

According to the *Guideline CHMP/EMEA/CHMP/SWP/258498/2005* (from 24 January 2008), safety pharmacological studies with fixed combination should be considered. However, need for (combination) studies depends on anticipated interactions between the agents and on the range of concentrations and exposures covered in the available studies with the single components.

Interference of the two drugs is not to be expected due to distinct pharmacological properties of them. According to the applicant, since its first approval in UK in 1966, IBU has been subject of hundreds of preclinical studies covering safety and mechanistic studies. Also diphenhydramine has extensively studied in the past. In addition, Advil® tablet was launched in the USA in 2006, and the liquigel capsule (containing a fixed combination of IBU (200 mg)/DPH (25 mg)) was launched in 2007. Based on existing preclinical, but also on clinical experience, lack of additional safety pharmacology studies seems to be justified.

* *Guideline on the non-clinical development of fixed combinations of medicinal products (CHMP/EMEA/CHMP/SWP/258498/2005, from 24 January 2008)*

Pharmacokinetics

Provided that the pharmacokinetics of the single components are adequately characterised in animals, including the profile for enzyme induction and inhibition and drug-drug interactions, additional non-clinical documentation on pharmacokinetic interactions is generally not needed for fixed combinations *(CPMP/EWP/240/95).*

The table below summarises clinical pharmacology data (human profile)

Parameter	**IBU**	**DPH**
Bioavailability	>80%	43% to 72% (extensive first pass metabolism
Peak plasma concentration	< 0.5 - 2 hours	< 1.5 - 4 hours

Plasma half-life	1.5 - 2 hours	3 - 9 hours
Volume of distribution	0.1 - 0.2 L/kg	3.3 - 14.6 L/kg
Protein binding	~ 99%	85%
Metabolites	2-hydroxy IBU, 2- carboxy IBU	Diphenylmethane (inactive)
Metabolic pathway	CYP2C9 (major)	CYP2D6

A comparison of the two entities shows that both display many differences. Whereas ibuprofen is largely metabolized via CYP2C9, metabolism of diphenhydramine occurs mainly via CYP2D6. Time to onset of effect of ibuprofen is less than 30 minutes, whereas it takes one to two hours until effects from diphenhydramine may be expected. Otherwise, half-life of ibuprofen is much shorter than that of diphenhydramine (1.5- 2 hours versus 3-9 hours).
With regard to this application, no separate preclinical studies have been submitted. On one hand, the PK profiles of the two active substances have been well characterized in the past and on the other hand, Ibuprofen and diphenhydramine belong to two different drug classes, with low likelihood of pharmacokinetic interaction. The fact that metabolism occurs via separate enzymatic systems was confirmed by one clinical Study (WM-716) which clearly demonstrated bioequivalent plasma levels after simultaneous application of both components in comparison with single administration of the compounds.
Interactions of ibuprofen or diphenhydramine with other drugs have not been adequately addressed by the applicant.

Toxicology

According to the *Guideline on the non-clinical development of fixed combinations of medicinal products,* toxicity studies with fixed combination should be considered. The use of one species may be sufficient.
With regard to this application no unexpected results distinct from either component alone were seen in the animals treated with the combinations. This suggests that interaction between the two drugs does not take place. The toxicology program consisted of single-dose, repeat-dose, reproductive/developmental and genotoxicity studies. One local tolerance study has been conducted to investigate the potential irritant effects of injecting the liquid fill of the product.

Single dose toxicity

Single dose toxicity studies were conducted in rats. The two active substances ibuprofen and diphenhydramine were administered either as single agents or in combinations at ratios of 2:1, 4:1, and 8:1 (IBU:DPH). The LD_{50} values for rats receiving ibuprofen alone was 1225 mg/kg and 275 mg/kg for diphenhydramine. The LD_{50} value for the combination of both entities was 880 mg/kg for the 8:1 ratio.
No unexpected toxicological events as compared to effects derived from single compound application have been reported.

The table below depicts the outcome of the LD_{50} Studies:

Study report/ Duration GLP	**Species Sex Group size**	**Substance oral**	**LD_{50} (mg/kg)**
BRT-84-24 Single dose yes	SD rats 5M/5F	IBU DPH IBU:DPH (2:1) IBU:DPH (4:1) IBU:DPH (8 :1)	1225 275 700 840 880

Repeat-dose toxicity

Additional Repeat-dose toxicity studies have been performed in rats and dogs by using the combination IBU/DPH. Considering the short duration of the intended clinical use (maximum 5 days), the length of the preclinical studies (14 days and 13 weeks) is regarded as sufficient. The dose of ibuprofen and diphenhydramine at the same ratio as foreseen for the marketing authorization was 150 and 18.75 (ratio 8:1; 14 days study), respectively. Ratio 8:1 was not foreseen for the 13 weeks studies. The NOEL in rats was 25 mg IBU/6.25 mg DPH/kg/day. For calculation of the human equivalent dose, this dose has to be divided by 6,2 (allometric correction factor for the rat) suggesting a dose of 4.03 mg/kg IBU and 1 mg diphenhydramine /kg/day. For a patient with a bodyweight of 60 kg, the HED corresponds approximately a dose of 241.8 mg IBU and 60 mg diphenhydramine / patient/day (whereas the proposed therapeutic dose is 400mg IBU/50 mg DPH). The indicated safety margins are therefore not correctly calculated.
A well-known pathologic effect of ibuprofen is the ulceration of GI tract, a property shared with other NSAIDs. With regard to combination of ibuprofen with diphenhydramine, observed organic toxicities in rats could be mainly attributed to ibuprofen, since toxic effects of the combination were similar to those on the ibuprofen-only groups. There was no clear signal that a combination of ibuprofen and diphenhydramine potentiates single-agent effects.
Concerning the studies in dogs, the used doses (up to IBU/DPH at 16/4 mg/kg BW) were too low for estimation of the NOAEL. No relevant findings were observed. In addition, the number of experimental animals (n = 2-4) was a limiting factor for interpretation of the study.

The repeat-dose toxicity studies are summarized in the table below:

Study Report Species Group size GLP	**Daily Dose IBU/DPH (mg/kg/d) Ratio**	**Duration**		**NOEL IBU/DPH (mg/kg/day)**	**Major findings**
BRT8432 CD Rats 5M/5F yes	**Dose** 0/0 24/6 60/15 150/37.5 150/18.75 0/37.5 0/100	**Ratio** 0:0 4:1 4:1 4:1 8:1 0:37.5 0:100	14-d	24/6 (NOEL)	Test article-related changes were noted in higher dose combination groups or DPH alone (100): decreased body weight and food consumptio

Study Report Species Group size GLP	Daily Dose IBU/DPH (mg/kg/d) Ratio	Duration		NOEL IBU/DPH (mg/kg/day)	Major findings
BRT8509 CD Rats 15M/15F yes	**Dose** 0/0 25/6.25 50/12.5 <u>100/25</u> <u>100/0</u> 0/25	**Ratio** 0:0 4:1 4:1 4:1 100:1 0:25	13-wk	25/6.25 (NOEL	Macroscopic changes in 2/1 males and 2/15 females of <u>100/25</u> group • GI irritation (ulcers, diverticuli, mucosal necrosis of the jejunum, erosions of stomach mucosa) • Renal papillary necrosis (1M)
BRT8433 Beagle Dogs 2M/2F yes	**Dose** 0/0 4/1 8/2 16/4 16/2 0/4 16/0 0/20	**Ratio** 0:0 4:1 4:1 4:1 <u>8:1</u> 0:4 16:0 0:20	14 day	n.t.	No test article-related effects determined
BRT8512 Beagle Dogs 4M/4F yes	**Dose** 0/0 4/1 8/2 16/4 0/4 16/0	**Ratio** 0:0 4:1 4:1 4:1 0:4 16:0	14 day	n.t.	No test article-related effects determined

NOEL = No-observed- effect level

<u>Genotoxicity and carcinogenicity studies</u>

The mixture of Diphenhydramine-HCl and Ibuprofen was negative in Salmonella typhimurium strains TA98, TA100, TA102, TA1535, and TA1537 up to 5000 µg/plate. In addition, from a clinical perspective, there are no signals for genotoxic or carcinogenic potential of the two marketed ingredients. In vivo genotoxicity and carcinogenicity studies are therefore not required.

<u>Reproductive toxicology</u>

Both, ibuprofen and diphenhydramine cross the placenta and have been detected in breast milk.
With regard to the submitted preclinical studies, no embryotoxic, fetotoxic or teratogenic effects could be identified in rats at concentrations up to 100 mg/19mg IBU/DPH. The only adverse event was markedly decreased maternal bodyweight gain during the first subinterval of gestation in rats.

The no-observable-effect level (NOEL) for maternal toxicity in rats was 10 mg IBU/2 mg DPH/kg/day.

Range-finding teratology studies in rats and rabbits (see table below)

Study type Study ID GLP	Species Number/group Route	Dose (mg/kg/day)		Treatment (days of gestation)	Major findings	NOEL
Range-finding BRT8435 yes	Rats 5 oral	**IBU/DPH** 0/0 7.5/1.9 20/5 60/15 7.5/0,95 20/2,5 60/7,5 0/15 60/0 0/60	**ratio** 0:0 4:1 4:1 4:1 8:1 8:1 8:1 0:15 60:0 0:60	6-15	Maternal observations: 60 mg/kg (IBU and DPH respectively): markedly ↓ BW gain during first subinterval	n.d.
Range-finding teratology studies BRT8436 yes	Rabbits 5 oral	**IBU/DPH** 0/0 7.5/1.9 20/5 60/15 7.5/0,95 20/2,5 60/7,5 0/15 60/0	**ratio** 0:0 4:1 4:1 4:1 8:1 8:1 8:1 0:15 60:0	6-18	Maternal observations: No consistent weight gain inhibition Caesarean Section: IBU/DPH 60/15, 20/2,5 & 60/7.5: Slightly ↑ pre- and postimplantation loss ↓ number of viable foetuses Foetal morphological observations: Group 7 (60/7.5): **2**/5 Group 9 (60/0): **1**/5	n.d.

Rabbits displayed a slight increase in the rates of preimplantation and postimplantation loss at doses of 20/2.5, 60/15, and 60/7.5 mg/kg IBU/DPH. However, this was not the case in study BRT 8508, where the same dose levels have been used.

Embryo Foetal Development Studies in rats and rabbits (see table below)

Study type Study ID GLP	Species Number group Route	Dose (mg/kg/day)		Treatment Days of gestation	Major findings	NOEL (IBU/DPH) mg/kg
		IBU/DPH	**ratio**			
		0/0	0:0			
Teratology study	Rats	7.5/1.9	4:1		Maternal observations:	n.d.
	25	20/5	4:1		• markedly ↓ BW gain during first subinterval	
BRT8507	oral	60/15	4:1	6 - 15	Caesarean Section and foetal morphological observations:	
yes		60/0	60:0		no meaningful findings	
		0/15	0:15			
		IBU/DPH	**ratio**			
		0/0	0:0			
Teratology study		7.5/1.9	4:1		Maternal observations:	n.d.
		20/5	4:1		Slight reduction in the maternal body weight gain at 60/1 (IBU/DPH)	
BRT 8508	New Zealand White Rabbits	60/15	4:1			
yes		60/0	60:0			
	14	0/15	0:15	6 - 18	Caesarean Section & foetal morphological observations:	
	oral				no meaningful findings	
		IBU/DPH	**ratio**			
		0/0	0:0 5:1		Maternal observations:	NOEL maternal toxicity: 10/2
Teratology study	Albino rats	10/2	6:1		↓ of mean weight gain from day 6-9 (II-IV)	
		60/11	5:1			
934058	24	100/19	0:19	6 - 15	No embryotoxic, fetotoxic or teratogenic effects	
yes	oral	0/19				

↓ decrease
↑ increase
NOEL: no-observable-effect level
The minimum concentration resulting in decrease in the mean number of viable foetuses (in study BRT 8436) was 20 mg IBU/2,5 mg DPH/kg/day (Study BRT 8436). This dose is equivalent to a human dose (HED) of 387 (= 6.45 x 60) mg IBU/48 (= 0.8 x 60) mg DPH/60 person by using a correction factor of 3.1***. This corresponds approximately the therapeutic dose in humans (400 mg IBU/50 mg DPH/60 kg person).

Based on literature data, an increased risk of miscarriage with the use of NSAIDs has been found. However, several other studies did not find an association. With regard to the preclinical findings in one study in rabbits, interference of the drug with implantation may be speculated. Nielsen et al, 2001 compared pregnancies where mothers had used NSAIDs (n = 1462) with pregnancies without use of NSAIDs (n = 17259). The main outcome measures were incidences of congenital abnormality, low birth weight, preterm birth, and miscarriage. It was concluded that the use of NSAIDs during pregnancy does not seem to increase the risk of congenital abnormality, low birth weight, or preterm birth. However, a significant association with miscarriage in the first trimester was demonstrated.
Potential effects of NSAIDs (including ibuprofen) during pregnancy were also addressed by Cappon et al., 2003. He demonstrated that the compounds, which are specific COX-1 or nonspecific COX inhibitors, show a greater potency to induce malformation during the sensitive periods for heart development and midline closure in rats and rabbits. Therefore, the selective COX-2 inhibitors pose minor risk of inducing heart anomalies even at the greater exposures.
According to the *FDA classification of drug safety during pregnancy*, ibuprofen falls into category B*/B/D** during the 1st, 2nd and 3rd trimester. DPH is allocated to category B. Its use is not recommended in nursing mothers, due to the risk of adverse effects, such as unusual excitement or irritability, in infants (Black and Hill, 2003).

According to the applicant, the use of IBU/DPH Wyeth 200 mg/25 mg capsules in third trimester of pregnancy is contraindicated. The use of IBU/DPH is not recommended during the first and second trimesters of pregnancy unless recommended by a doctor.
The possibility of unwanted, adverse events is explained by inhibition of prostaglandin synthesis which may adversely affect the pregnancy and/or the embryo/foetal development (including cardiopulmonary toxicity with premature closure of the ductus arteriosus and pulmonary hypertension and renal dysfunction). Furthermore, as stated by the applicant, at the end of pregnancy, prostaglandin synthesis inhibitors expose the mother and child to 1. possible prolongation of bleeding time, an anti-aggregating effect which may occur even after very low doses and to 2. inhibition of uterine contractions resulting in delayed or prolonged labour.
**** FDA Guidance for Industry; Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (July 2005)*

Local tolerance

Single dose intravenous irritation studies of the combination in rabbits have been performed in order to address the potential that recreational drug abusers might intravenously inject the liquid fill. It was shown that intravenous injection of the fill of IBU/DPH combination product would be significantly more irritating than injection of diphenhydramine as single agent (resulting in a lower likelihood of abuse).

The individual clinical observations were as follow:

Study type Study ID GLP	**Species Number per dose**	**Test Article Right Ear Vein (ml)**	**Major findings**
Phase I (range-finding phase)	Rabbits 1M	I: 0.1 ml DPH II: 0.2 ml DPH	I and IV: increased respiration II: 0,2 ml: seizures or convulsions

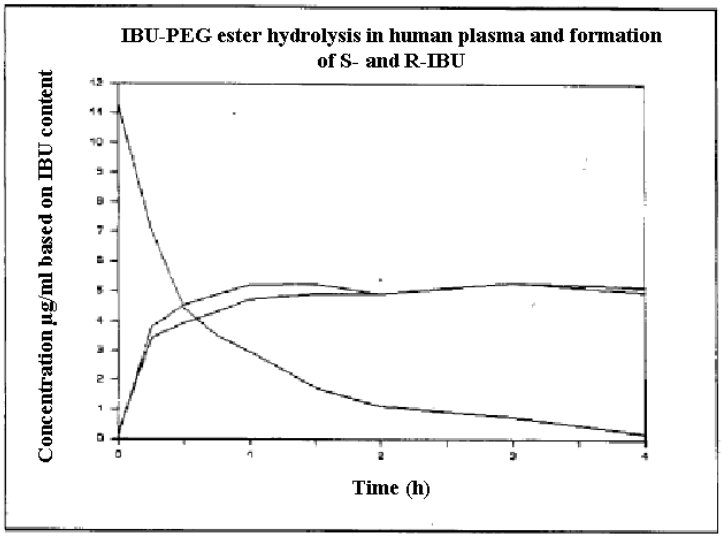
0530-07144 yes		III: 0.5 ml DPH IV: 0.1 ml DPH/IBU Saline control into contralateral ear	III: (0.5 ml): died immediately
Phase II (main study) **0530-07144** yes	Rabbits 9M	I: 0.1 ml DPH (~2.3 mg/kg) II: 0.1 ml DPH/IBU (~ 2.3 mg/kg DPH /16 mg/kg IBU)	I: 7/9 had increased respirations 4/9 hyperactivity 1/9 head bobbing, circling gait thrusting of a hind limb 1/9: shaking II: venous dilation of both ears evidence of pain greater microscopic evidence o tissue irritation

Dependence

No pre-clinical studies have been submitted which might be justified since clinical studies from the literature showed that diphenhydramine has a negligible risk of inducing dependence and has low abuse potential (Griffiths RR and Johnson MW, 2005). Physical dependence, which includes tolerance and withdrawal, on NSAIDs has not been reported and in addition it causes dermal irritation after injection (see above).

Studies on impurities

Several impurities have been identified for diphenhydramine (impurities A, B, C, D, E) and for ibuprofen (4-Isobutylacetophenone (4-IBAP) and Ibuprofen-PEG 600 ester (IBU-PEG ester).
Ibuprofen-PEG 600 ester occurs at concentrations up to 3.2% w/w relative to ibuprofen during the shelf life of the product. It results from the reaction of ibuprofen and polyethylene glycol 600, a gelling and stabilizing agent in the liquid portion of the capsule. These esters start to form after the ibuprofen is mixed with the PEG and slowly continue to form throughout the shelf-life of the product. Therefore, in order to characterize the IBU-PEG ester, hydrolysis studies, a fourteen-day safety study, and four-day ulcerogenicity study in Sprague-Dawley rats have been performed.
Hydrolysis studies of IBU-PEG ester in intestinal and gastric juice demonstrated that IBU-PEG ester is susceptible to rapid hydrolysis to yield ibuprofen and PEG after exposure to simulated gastric and intestinal juices. IBU-PEG ester is rapidly hydrolysed even in the presence of human plasma (see figure below). The greatest amount of IPEG degradation takes place in the intestine, the likely site of absorption, whereas the absorption of IPEG in vivo is minimal.
Figure below: Mean (n=3) decline of IBU-PEG ester in human plasma and rise of IBU enantiomers concentration in the presence of human plasma.



Fourteen Day Safety Study: IBU-PEG ester, at a dose of up to 100 mg/kg/day for 14 days, exhibited no potential to produce pharmacological and toxicological effects in SD rats.
Four-day ulcerogenicity study in SD rats (Study T-2812): The macroscopic observations of the gastrointestinal tract indicated that there was no evidence of ulcerogenic potential of IBU-PEG ester at concentrations of 5 and 100 mg/kg/day.
Finally, also the Ames test (Reverse Mutation Assay) which was conducted with concentrations up to 5000 µg/plate by using Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 did not reveal potential mutagenic activity of IBU-PEG ester (with and without the addition of a mammalian activation system).
Based on this, no deleterious findings have been identified.

Ecotoxicity/environmental risk assessment (ERA)

The predicted environmental concentrations in surface water ($PEC_{SURFACEWATER}$) were for both substances above 0.01 µg/L and therefore, Phase II of the ERA was triggered. The $PEC_{SURFACEWATER}$ for ibuprofen was calculated to be 2.0 µg/L and for diphenhydramine HCl to be 0.25 µg/L. The applicant was asked to provide calculations or estimations of the K_{oc} values for both ibuprofen and diphenhydramine HCl, an issue which has been answered adequately.
According to the guideline the risk assessment should focus on the long-term exposure of aquatic organisms to human medicines. However, for the active substance diphenhydramine HCl no data regarding long-term effects have been submitted by the applicant. The duration of the acute toxicity studies was not regarded sufficient to assess long-term effects on reproduction or effects on early life stages of fish and aquatic invertebrates. The applicant was therefore asked to evaluate the long-term effects to fish (reproduction, early life stages, OECD 210) and the long-term toxicity to Daphnia sp. (OECD 211) due to the exposure to the active substance diphenhydramine HCl.
A better elaboration of the long-term and delayed effects of diphenhydramine with regard to the environmental risk is still outstanding, whereas new laboratory studies might not be necessarily required. Literature data for ibuprofen and diphenhydramine HCl with focus on long-term exposure to fish and aquatic invertebrates should be sufficient to address the risk to aquatic organisms and to finalize the risk assessment.

Based on the available data the risk to aquatic organisms due to exposure to the product "Ibuprofen/Diphenhydramine Hydrochloride Wyeth" can be considered to be acceptable with respect to acute exposure. The long-term risk to aquatic organisms could not be finalised based on the actual available data.

III.3 Clinical aspects

Pharmacokinetics/Biopharmaceutic Studies

The biopharmaceutic program for the development of IBU/DPH soft capsules consisted of three studies conducted to establish the biopharmaceutic profile of the US marketed soft capsule formulation. These three studies are the following:

WM-716 - Single-dose, Open-label, Randomized, 3-way Crossover Pharmacokinetic Interaction Study Comparing an Ibuprofen/Diphenhydramine Combination to Individual Doses of Ibuprofen and Diphenhydramine - a drug interaction study to determine if there was a PK interaction when IBU and DPH are administered concomitantly in the fasted state.

Figure 1: Mean Diphenhydramine Concentrations Over Time (n=23)

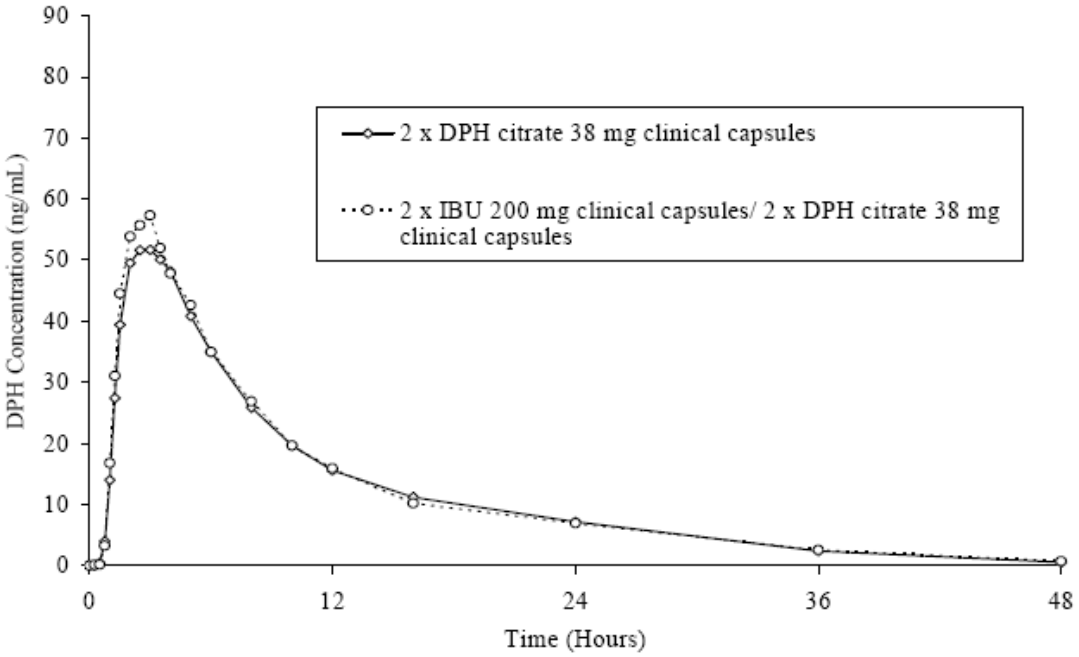
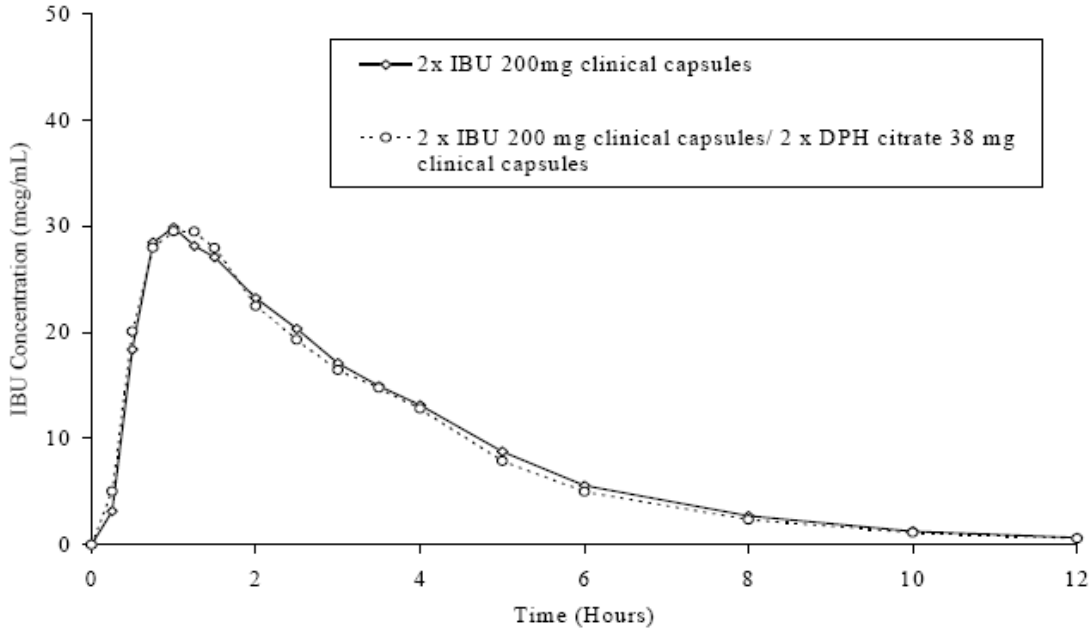


Figure 2: Mean Ibuprofen Concentrations Over Time (n=23)



Conclusions WM-716: The bioavailability of ibuprofen, when administered alone, is equivalent to the bioavailability of ibuprofen, when administered with diphenhydramine. Similarly, the bioavailability of diphenhydramine, when administered alone, is equivalent to the bioavailability of diphenhydramine, when administered with ibuprofen. Therefore, there is no evidence of a significant pharmacokinetic interaction when these drug products are administered together.

A post-hoc analysis of the data was completed which showed that there was a significant treatment-by-gender interaction ($p \leq 0.15$) for DPH, but not for IBU. The treatment-by-gender interaction was also significant ($p \leq 0.10$) for the weight adjusted parameters. To further examine the interaction, the primary PK parameters for DPH were analyzed within each gender.

In males, DPH administered simultaneously with IBU was bioequivalent to DPH administered alone. In females, DPH had a slightly faster rate, but equivalent extent of absorption when administered simultaneously with IBU, although the upper boundary of the 90% confidence interval for Cmax (125.9%) was just above the 125% required for bioequivalence (most likely due to the reduced sample size). For the most part, mean DPH PK parameter values were higher in females than in males when the two drugs were administered simultaneously, although these differences are not believed to be clinically meaningful.

Figure 3: Within Gender Comparisons of Diphenhydramine PK Parameters: Mean ± Standard Deviation

Treatment	C_{max} (ng/mL)		AUCI (ng-hr/mL)		T_{max} (hr)	
	Males (n=11)	Females (n=12)	Males (n=11)	Females (n=12)	Males (n=11)	Females (n=12)
DPH (A)	55.6 ± 17.5	57.0 ± 15.1	617.0 ± 230.1	581.9 ± 174.4	3.1 ± 1.3	2.8 ± 0.7
DPH + IBU (C)	54.0 ± 17.5	68.9 ± 27.5	577.1 ± 213.9	637.8 ± 215.2	3.0 ± 0.8	2.5 ± 0.5
C/A ratio (%)+	94.8	116.2	92.7	108.0	--	--
C/A 90% CI+	84.7 -106.1	107.3 - 125.9	86.4 - 99.5	101.4 -115.0	--	--

+ derived from log-transformed data
-- = Not Done

AE-97-02 – Advil PM Liquigels Bioequivalence/Food Effects Study - a food effect and formulation effect study of IBU/DPH liquigel fed and fasted, IBU liquigel fasted, and DPH liquigel fasted.

Figure 4: Mean Plasma Diphenhydramine Concentrations (n=25)

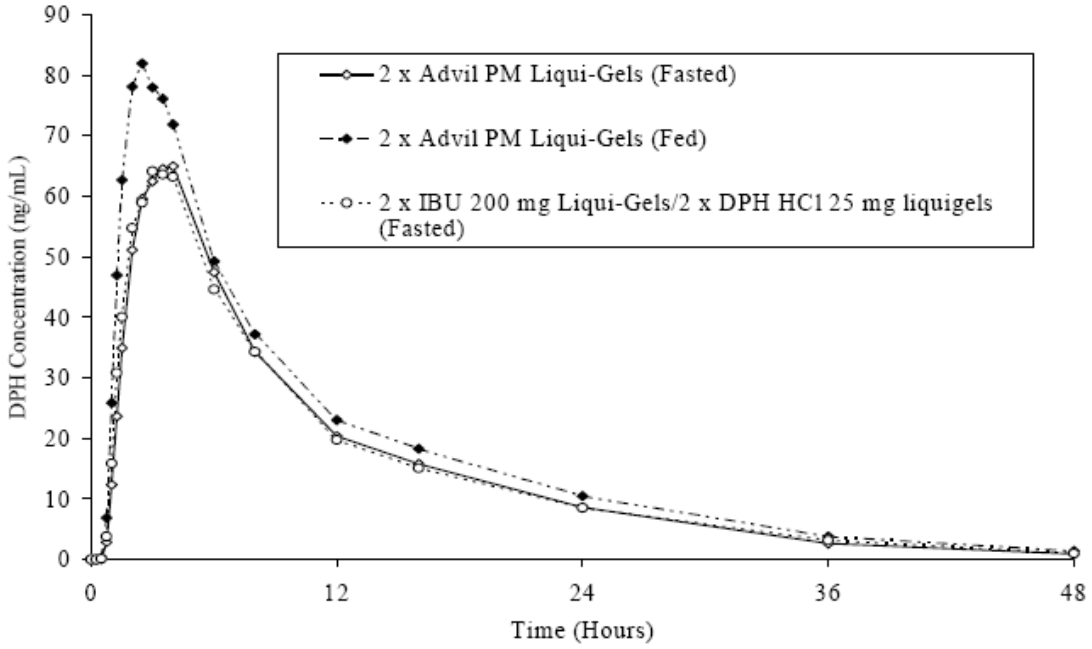
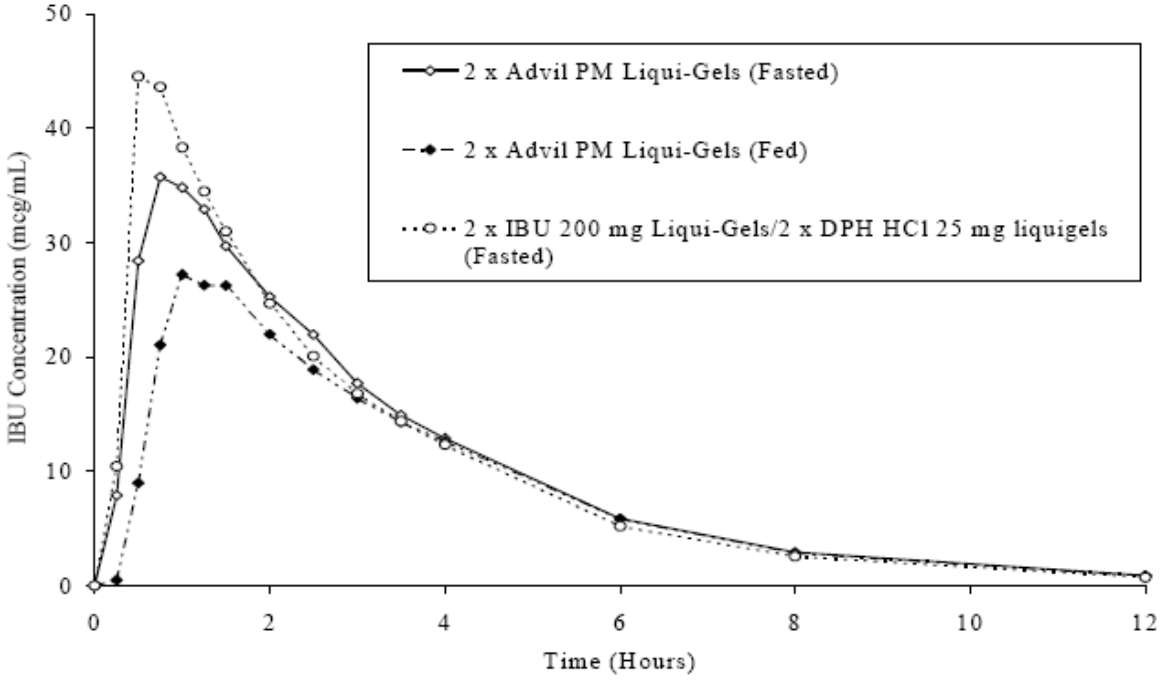


Figure 5: Mean Plasma Ibuprofen Concentrations (n=25)



Conclusions AE-97-02:
Food significantly **increased** the rate and extent of **diphenhydramine absorption** and significantly decreased the rate, and to the lesser degree, the extent of **ibuprofen** absorption from Ibu/DPHs. Under fasted conditions, diphenhydramine liquigels were bioequivalent to Ibu/DPHs. Also under fasted conditions, ibuprofen liquigels had a faster rate, but equivalent extent of absorption relative to the combination product.

AE-97-09 – Ibu/DPHLiqui-Gel Relative Bioavailability Study - a formulation effect study of IBU/DPH liquigels compared to marketed product, single-ingredient IBU liquigels and DPH liquigels in the fasted state.

Figure 6: Plot of Mean Diphenhydramine Plasma Concentrations versus Time (n=23)

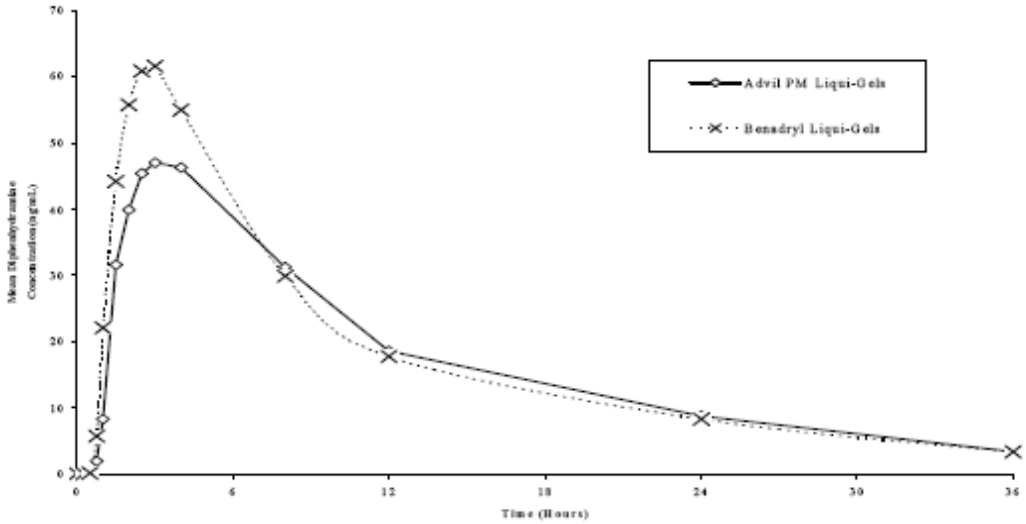
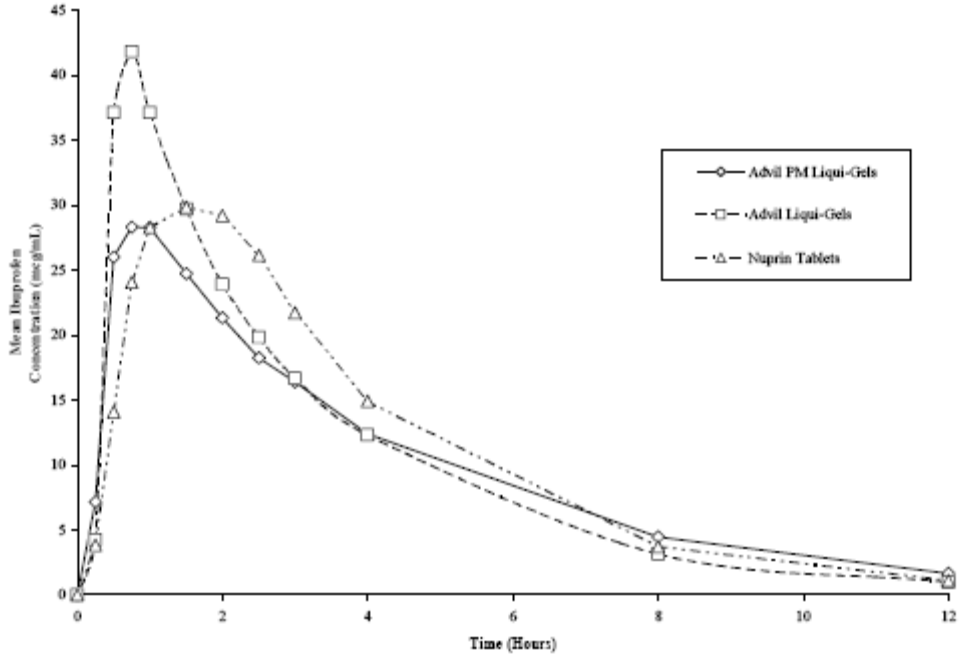


Figure 7: Plot of Mean Ibuprofen Plasma Concentration versus Time (n=23)



Conclusion AE-97-09: The results indicate that under fasted conditions, Ibu/DPH has a slower rate but equivalent extent of absorption of diphenhydramine and ibuprofen relative to the single entity marketed products containing either diphenhydramine or ibuprofen.. Consistent with the single entity products, Ibu/DPH provided therapeutic plasma concentrations of diphenhydramine and ibuprofen

Overall conclusions:
Study WM-716 showed that IBU and DPH do not influence each others kinetics when administered simultaneously.
Differences in the rate and extent of absorption of the combination product in contrast to the single substances are promoted by food and a treatment-by-gender effect. For the most part, mean DPH PK parameter values (e.g. Cmax, AUC) were higher in females than in males when the two drugs were administered simultaneously. The Applicant believed that these differences were not clinically meaningful. But a possible pronounced effect of DPH on females, making female patients more prone for next day hangover and other unwanted DPH effects could represent an important safety issue. The company showed in their response to the LoQ that although some studies detected gender differences of certain PK parameters, others did not, and these differences do not seem to impact on the safety of DPH in females in a relevant way.

PK differences of IBU vs Ibuprofen/Diphenhydramine Hydrochloride Wyeth, namely a slower rate of absorption, could translate to a slower onset of pain relief with Ibuprofen/Diphenhydramine Hydrochloride Wyeth than with IBU alone, indicating a disadvantage of the combination versus the single substance. The company could not provide an explanation for the slower IBU rate of absorption, but 2 clinical trials confirmed that the analgesic effect is essentially the same when the applicant's formulation is compared with the previously marketed individual dosage form of IBU and DPH.

Clinical efficacy

Wyeth submits 9 clinical studies supporting Ibuprofen/Diphenhydramine Hydrochloride Wyeth 200mg/25mg as a pain reliever/night time sleep aid in a fixed dose combination drug product. The suggested dose for adults is two capsules that contain solubilized ibuprofen (IBU) 200-mg and diphenhydramine (DPH) 25-mg [for a total dose of IBU 400-mg and DPH 50-mg].
Studies AE-98-03 and AE-97-08 use 2 dose regimens of IBU/DPH (200/25 or 400/50 mg) and are therefore considered dose response studies. AE-98-01, AE-98-02 and AE-04-14A are the main pivotal trials. The other 4 submitted trials are supportive trials not adding crucial information to the clinical efficacy overview. Therefore these, as well as the second dose response trial AE-98-03 are not discussed in detail.

The clinical efficacy studies are denominated:
• AE-95-01 - IBU vs. placebo polysomnographic study in healthy volunteers (age 18-45)
• AE-97-01 - Oral Surgery Pilot Study
• **AE-98-01** - Oral Surgery Pivotal Study I; single dose efficacy
• **AE-98-02** - Oral Surgery Pivotal Study II; single dose efficacy
• **AE-04-14A** - Oral Surgery Pivotal Study using actigraphy to measure sleep efficacy
• AE-98-03 - Oral Surgery Dose-Response Study
• AE-01-11 - IBU/DPH vs. Acetaminophen/DPH Oral Surgery Study
• AE-97-08 - Ten-Day Safety, First-Dose Efficacy Study; stratified by age/gender
• AE-98-04 - Inpatient Headache Study (age 18-64; 96% caucasian)

Demographic Data

Study	Sample Size	Male/ Female (%)	Ethnicity %C/B/A/H/O*	Mean Age	Mean Weight**	Mean Height+
AE-97-01	105	40/60	74/7/4/15/0	23.8	157.6	67.1
AE-98-01	280	44/56	72/4/4/19/1	21.4	154.5	67.7
AE-98-02	282	49/51	95/1/1/3/0	20.0	150.3	68.1
AE-04-14A	329	49/51	91/1/2/5/1	18.9	153.2	67.6
AE-98-03	284	51/49	56/36/4/2/2	24.1	168.1	67.3
AE-01-11	350	46/54	96/1/2/1/0	20.0	153.3	67.5

*C/B/A/H/O = Caucasian/Black/Asian/Hispanic/Other
**measured in pounds
+measured in inches

Dose-response studies and main clinical studies

AE-97-08

This was a randomized (stratified by age and gender), double-blind, parallel group, placebo-controlled, outpatient, multicenter, multiple dose safety, first dose efficacy study. The objective of the study was to compare the safety of IBU/DPH 200 mg/25 mg, IBU/DPH 400 mg/50 mg, APAP/DPH 1000 mg/50 mg and PBO when administered for 10 consecutive days. In addition, efficacy was evaluated after the first dose of medication was taken. Males and females 12 years of age and older who 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 prior to study entry and who were able to read, comprehend, and sign the informed consent form were included. The primary efficacy parameters were: pain relief (sum of pain intensity difference plus pain relief score after two hours; SPRID-2) and Sleep Duration (categorical).

AE-97-08 - Age and Gender Distributions, 75% caucasian / 15 % non caucasian

Age-Group	Gender	Total n (%)	IBU 200 mg/ DPH 25 mg n (%)	IBU 400 mg/ DPH 50 mg n (%)	APAP 1000 mg/ DPH 50 mg n (%)	PBO n (%)
All Evaluable Subjects						
<45 yrs	Male+	90 (31)	15 (31)	28 (29)	30 (30)	17 (35)
	Female+	204 (69)	33 (69)	69 (71)	70 (70)	32 (65)
	Total^	294 (31)	48 (31)	97 (31)	100 (31)	49 (31)
45-64 yrs	Male+	105 (27)	18 (28)	32 (25)	38 (28)	17 (27)
	Female+	285 (73)	47 (72)	97 (75)	96 (72)	45 (73)
	Total^	390 (41)	65 (43)	129 (41)	134 (42)	62 (40)
65 yrs or older	Male+	85 (33)	13 (33)	23 (26)	32 (37)	17 (38)
	Female+	173 (67)	27 (68)	64 (74)	54 (63)	28 (62)
	Total^	258 (27)	40 (26)	87 (28)	86 (27)	45 (29)
All Ages	Male+	280 (30)	46 (30)	83 (27)	100 (31)	51 (33)
	Female+	662 (70)	107 (70)	123 (74)	220 (69)	105 (67)
	Total^	942 (100)	153 (100)	313 (100)	320 (100)	156 (100)

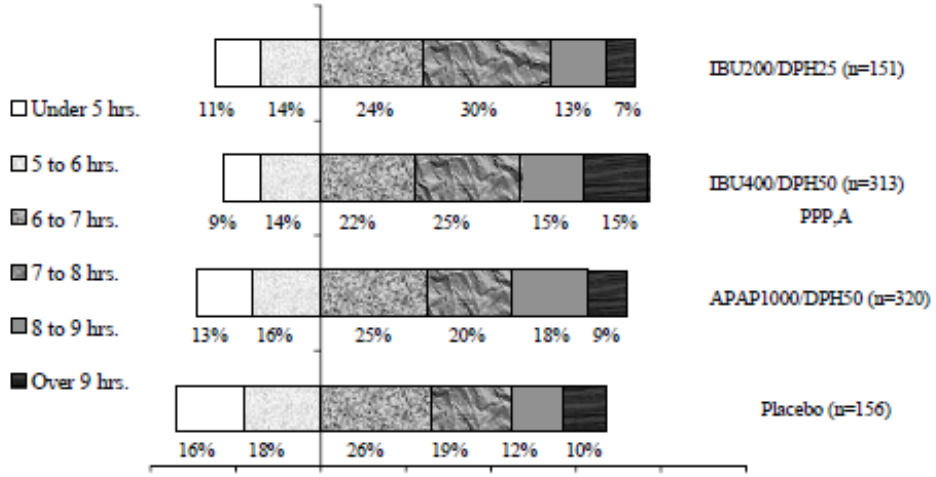
+: Percentages are based on the total within each age group, and each treatment group.
^: Percentages are based on the total within each treatment group.

AE 97-08 Key efficacy parameters

Efficacy Parameter	Treatment Groups				Pairwise Comparisons (Δ, p-value)				
	IBU 200 mg/ DPH 25 mg n= 153	IBU 400 mg/ DPH 50 mg n = 313	APAP 1000 mg/ DPH 50 mg n = 320	PBO n = 156	2 IBU/DPH vs. PBO	1 IBU/DPH vs. PBO	2 IBU/DPH vs. 1 IBU/DPH	2 IBU/DPH vs. APAP/DPH	APAP/DPH vs. PBO
Pain Parameters									
@Pain Relief ^^ - mean (s.d.)	2.1 (1.0)	2.4 (1.1)	2.2 (1.1)	2.0 (1.2)	0.4 <0.001*	0.1 0.243	0.3 0.043*	0.2 0.136	0.2 0.028*
Sleep Parameters									
@Sleep duration (Cat.) # -mean (s.d.)	2.4 (1.4)	2.7 (1.5)	2.4 (1.5)	2.2 (1.5)	0.5 <0.001*	0.2 0.162	0.3 0.097	0.2 0.020*	0.3 0.154
Sleep duration (hours slept) -mean (s.d.) hrs	7.0 (1.6)	7.3 (1.8)	7.0 (1.7)	6.5 (2.1)	0.8 <0.001*	0.5 0.029*	0.3 0.096	0.5 0.046*	0.3 0.009*
Sleep latency median (mins)	27.2	28.5	29.3	42.2	1.5 <0.001*	1.4 0.002*	1.1 0.466	1.2 0.034*	1.3 0.009*
Sleep quality^ mean (s.d.)	2.7 (1.0)	3.1 (1.2)	2.8 (1.1)	2.5 (1.2)	0.6 <0.001*	0.2 0.021*	0.4 0.004*	0.3 0.005*	0.3 0.001*

@ Primary efficacy endpoints.
mins. = minutes; s.d. = standard deviation
Δ is the observed difference between the pair (first –second) of treatments, except for sleep latency. For sleep latency, Δ is the hazard ratio of the first treatment vs. the second treatment; * p ≤ 0.05 in favor of the first treatment listed.
Based on a categorical scale 0 (<5 hours) to 5 (> 9 hours).
^ Based on a categorical scale 0 (very poor) to 5 (excellent).
^^ Based on a categorical scale 0 (no relief) to 4 (complete relief).

AE-97-08 Duration of Sleep, evaluable subjects



PPP: Significantly better than placebo at 0.001 level
A: Significantly better than APAP1000/DPH50 at 0.05 level

AE-97-08 Subgroup analysis for age

Efficacy Parameter	Treatment Groups									Pairwise Comparisons (Δ, p-value)				
	IBU 200 mg/ DPH 25 mg			IBU 400 mg/ DPH 50 mg		APAP 1000 mg/DPH 50 mg		PBO		2 IBU/ DPH vs. PBO	1 IBU/ DPH vs. PBO	2 IBU/ DPH vs. 1 IBU/ DPH	2 IBU/ DPH vs. APAP/ DPH	APAP / DPH vs. PBO
Sleep Parameters	Age Group													
Sleep duration (hrs. slept) -mean (s.d.) hrs.	<45 yr	31%	7.4 (1.6)	31%	7.6 (1.8)	31%	7.6 (1.6)	31%	7.0 (2.7)	0.6 0.040*	0.4 0.214	0.2 0.532	0.0 0.886	0.6 0.083
	45-64 yr	43%	6.8 (1.7)	41%	7.2 (1.8)	42%	6.8 (1.6)	40%	6.2 (1.8)	1.0 <0.001*	0.6 0.055	0.4 0.113	0.4 0.065	0.6 0.020*
	≥ 65 yr	26%	6.8 (1.4)	28%	7.0 (1.8)	27%	6.6 (1.8)	29%	6.5 (1.8)	0.5 0.103	0.3 0.462	0.2 0.464	0.4 0.128	0.1 0.709

hrs. = hours; s.d. = standard deviation

Δ is the observed difference between the pair (first –second) of treatments, except for sleep latency. For sleep latency, Δ is the hazard ratio of the first treatment vs. the second treatment.

* $p \leq 0.05$ in favor of the first treatment listed.

Efficacy Parameter	Treatment Groups									Pairwise Comparisons (Δ, p-value)			
	IBU 200 mg/ DPH 25 mg			IBU 400 mg/DPH 50 mg		APAP 1000 mg/DPH 50 mg		PBO		2 IBU/ DPH vs. PBO	1 IBU/ DPH vs. PBO	2 IBU/ DPH vs. 1 IBU/ DPH	2 IBU/ DPH vs. APAP/ DPH	APAP / DPH vs. PBO
Pain Parameters	Age Group													
Pain Relief ^^ -mean (s.d.)	<45 yr	31%	2.2 (1.0)	31%	2.4 (1.1)	31%	2.3 (1.1)	31%	2.1 (1.3)	0.3 0.106	0.1 0.673	0.2 0.258	0.1 0.330	0.2 0.406
	45-64 yr	43%	2.1 (1.0)	41%	2.4 (1.1)	42%	2.2 (1.0)	40%	2.0 (1.2)	0.4 0.015*	0.1 0.440	0.3 0.113	0.2 0.190	0.2 0.158
	≥ 65 yr	26%	2.1 (1.1)	28%	2.3 (1.1)	27%	2.2 (1.1)	29%	1.9 (1.0)	0.4 0.082	0.2 0.334	0.2 0.563	0.1 0.963	0.3 0.088

s.d. = standard deviation

Δ is the observed difference between the pair (first –second) of treatments, except for sleep latency. For sleep latency, Δ is the hazard ratio of the first treatment vs. the second treatment; * $p \leq 0.05$ in favor of the first treatment listed.

^^ Based on a categorical scale 0 (no relief) to 4 (complete relief).

AE-98-01

This was a randomized, stratified (by baseline pain and gender), inpatient, placebo-controlled, partial factorial, single-dose, double blind, 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 ibuprofen 400 mg/diphenhydramine hydrochloride 50 mg, ibuprofen liquigels (400 mg) or placebo in a 3:3:1 ratio and were required to go to bed for the evening. Sleep was evaluated by an observer at regular intervals over 3 hours post-dosing. Subjects were wakened and provided pain assessments at 90 and 120 minutes post-dosing. Subjects also provided subjective assessments of sleep efficacy as well as global assessments of the study medication as a sleep-aid and as an analgesic the next morning (or at the time rescue medication was used). All of the 281 subjects who were enrolled were included in the safety analysis. Since one subject had no post-baseline efficacy assessments, 280 were included in the intent-to-treat efficacy analysis: 40 received placebo, 122 received ibuprofen/diphenhydramine, and 118 received ibuprofen.

The primary efficacy parameters were: pain relief (sum of pain intensity difference plus pain relief score after two hours;

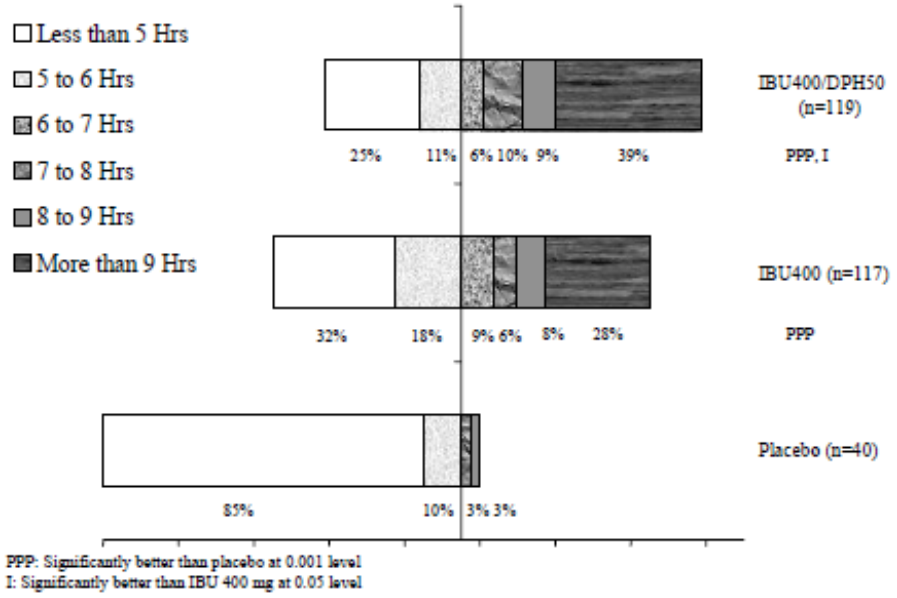
SPRID-2) and Cumulative percentage of patients asleep after 60 min.

AE-98-01 Efficacy outcome

Efficacy Parameter	Treatment Groups			Pairwise Comparisons (Δ, p- value)		
	IBU 400 mg/DPH 50 mg n= 122	IBU 400 mg n = 118	PBO n = 40	IBU/DPH vs. PBO	IBU/DPH vs. IBU	IBU vs. PBO
Pain Parameters						
@SPRID-2 – mean (s.d.)	7.7 (4.3)	7.6 (4.4)	1.3 (3.0)	6.4 <0.001*	0.1 0.952	6.3 <0.001*
Pain/Sleep Parameters						
Time to rescue-median, hrs	>12.0	>12.0	1.7	0.2 <0.001*	0.7 0.098	0.2 <0.001*
% needing rescue by wake-up time	36.9	48.3	85.0	-48.1 <0.001*	-11.4 0.071	-36.7 <0.001*
Sleep Parameters						
Sleep duration # -mean (s.d.)	2.8 (2.1)	2.3 (2.1)	0.3 (0.8)	2.5 <0.001*	0.5 0.022*	2.0 <0.001*
@Cumulative % asleep - 60 mins	63.9	64.4	40.0	23.9 <0.008*	-0.5 0.915	24.4 <0.006*
Sleep latency median (mins)	42.9	44.0	>180.0	2.7 <0.001*	0.9 0.688	2.8 <0.001*

hrs = hours; mins = minutes; s.d. = standard deviation
Δ is the observed difference between the pair (first –second) of treatments, except when medians are reported. In this case, Δ is the hazard ratio of the first treatment vs. the second treatment; * p ≤ 0.05 in favor of the first treatment listed.
Assessed using a categorical scale 0 (<5 hours) to 5 (> 9 hours).
@ - primary parameters

AE-98-01 Duration of Sleep, ITT



PPP: Significantly better than placebo at 0.001 level
I: Significantly better than IBU 400 mg at 0.05 level

AE-98-02

This study was identical in design to study AE-98-01. Of the 283 subjects randomized and receiving study medication, 282 were included in the ITT sample, 40 subjects in the PBO group, 119 subjects in the IBU 400 mg/DPH 50 mg group, and 123 subjects in the IBU 400 mg group. All treatment groups were comparable for demographic and surgical procedure characteristics, and baseline pain severity.

In the original study protocol the sponsor planned to analyse primary efficacy using the same endpoints as in study 98-01 (SPRID-2h and Cumulative percentage of patients asleep after 60 min, Cum%asleep60). During the conduct of the trial, the protocol/analysis plan was amended, also

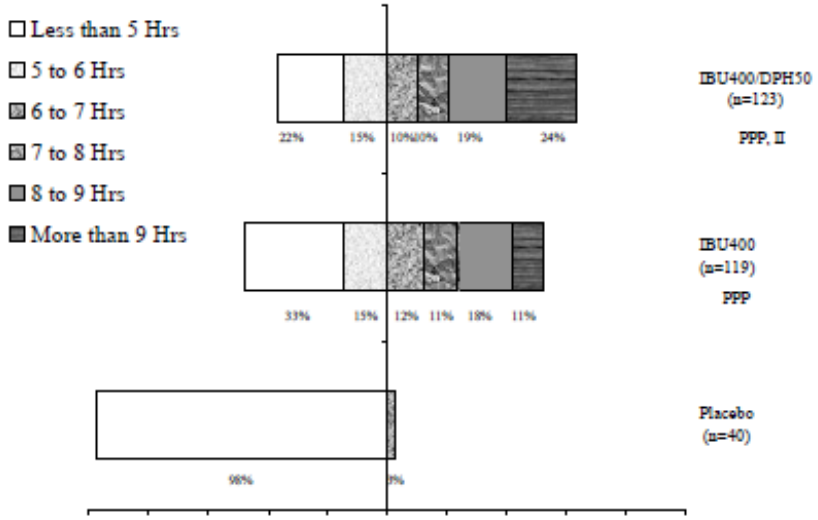
driven by the results of the AE-98-01 trial. According to this amendment, primary sleep evaluation was planned to be done by making use of a co-primary endpoint: Duration of sleep and Cum%asleep60. In contradiction to this definition of the co-primary endpoint, the Sponsor specified in the corresponding amended analysis plan a hierarchical testing procedure, starting with a statistical test for sleep duration followed by a test for Cum%asleep60 in case significance was reached (at 0.05) for sleep duration.

AE-98-02 Efficacy outcome

Efficacy Parameter	Treatment Groups			Pairwise Comparisons (Δ, p- value)		
	IBU 400 mg/ DPH 50 mg n= 119	IBU 400 mg n = 123	PBO n = 40	IBU/DPH vs. PBO	IBU/DPH vs. IBU	IBU vs. PBO
Pain Parameters						
@SPRID-2 –mean(s.d.)	7.0 (3.5)	7.8 (2.9)	0.3 (2.1)	6.7 <0.001*	-0.8 0.050§	7.5 <0.001*
Pain/Sleep Parameters						
Time to rescue	>12.0	>12.0	1.6	0.05 <0.001	0.6 0.195	0.07 <0.001*
% needing rescue by wake-up time	33.6	42.3	95.0	-61.4 <0.001*	-8.7 0.173	-52.7 <0.001*
Sleep Parameters						
@Sleep duration # -mean (s.d.)	2.6 (1.9)	2.0 (1.8)	0.1 (0.3)	2.5 <0.001*	0.6 0.005*	1.9 <0.001*
Cumulative % asleep - 60 mins	66.4	75.6	27.5	38.9 <0.001*	-9.2 0.112	48.1 <0.001*
Sleep latency median (mins)	45.0	36.5	>180.0	5.8 <0.001*	0.97 0.818	6.0 <0.001*

hrs = hours; mins = minutes; s.d. = standard deviation
@ Primary efficacy parameters
Δ is the observed difference between the pair (first –second) of treatments, except when medians are reported. In this case, Δ is the hazard ratio of the first treatment vs. the second treatment; * $p \leq 0.05$ in favor of the first treatment listed.; § $p \leq 0.05$ in favor of the second treatment listed.
Assessed using a categorical scale 0 (<5 hours) to 5 (> 9 hours).

AE-98-02 Duration of Sleep, ITT Subjects



PPP: Significantly better than placebo at 0.001 level
II: Significantly better than IBU 400 mg at 0.01 level

AE-04-14A

This was a randomized, stratified (by gender and baseline pain), inpatient, single-dose, double-blind, parallel group, single center confirmatory study. AE-04-14A compared IBU/DPH 400 mg/50 mg to IBU 400 mg in a study identical in design to AE-98-01 and AE-98-02 except no PBO

treatment group was included, subjects were not wakened to evaluate pain intensity and relief, and sleep efficacy was assessed using an actigraph (in addition to subjective assessments). This study was done to confirm the results of AE-98-01 and AE-98-02 (prolongation of sleep duration), and to determine whether awakening subjects in those studies had any impact on the assessment of sleep duration. Three hundred twenty-nine subjects were randomized and included in the intent-to-treat analysis: 165 received IBU/DPH 400 mg/50 mg and 164 received IBU 400 mg alone. The treatment groups were comparable for demographic and surgical procedure data, as well as baseline pain severity. The sole primary endpoint was Sleep Duration, no pain assessments were done.

AE-04-14A, Efficacy outcomes

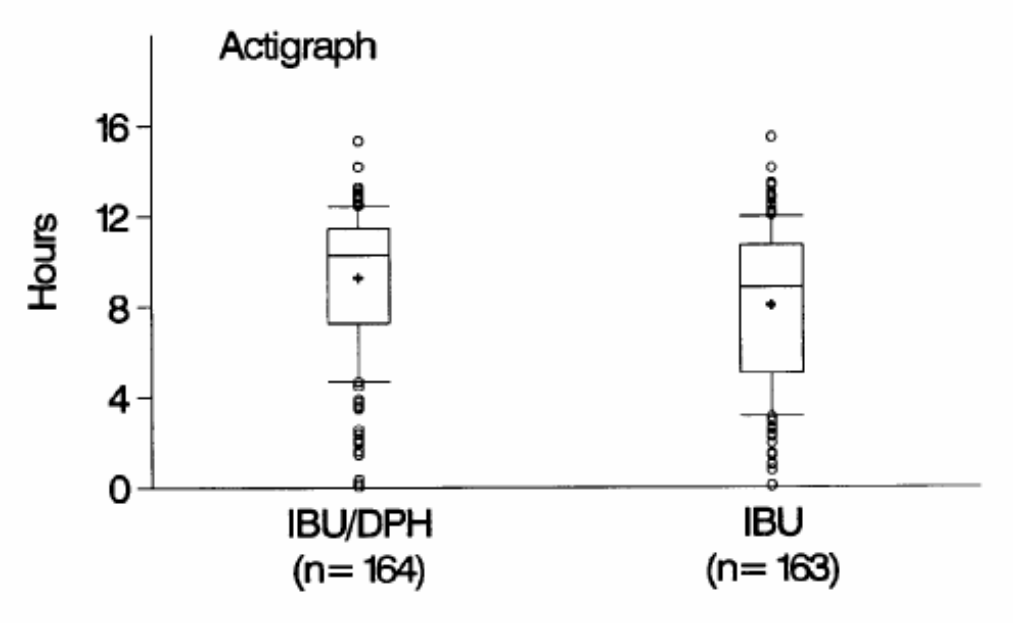
Parameter	Summary Statistic	IBU 400 mg/DPH 50 mg (n=165)	IBU 400 mg (n=164)	Δ, p-value
@Sleep Duration-Actigraph	Mean (s.d.) -hr	9.3 (3.2)	8.1 (3.5)	1.2 <0.001*
Sleep Duration - Subjective	Mean(s.d.) - hr	7.9 (3.0)	6.9 (3.3)	1.0 0.003*
Sleep Efficiency - Actigraph	Mean (s.d.) -%	75.9 (24.9)	65.7 (27.5)	10.2 <0.001*
Wake After Sleep Onset -Actigraph	Mean (s.d.) - hr	2.3 (2.9)	3.6 (3.5)	-1.3 <0.001*
Sleep Latency - Actigraph	Median (min)	23.3	22.5	1.04 0.731
Sleep Latency - Observer based	Median (min)	17.6	17.6	1.04 0.751
Time to rescue	Median (hr)	>12.0	>12.0	0.64 0.020*
% taking rescue	%	28.5	39.6	-11.1 0.031*

@Primary efficacy parameter

Δ IBU 400 mg/DPH 50 mg - IBU 400 mg difference (observed); for parameters showing medians it is the hazard ratio of IBU 400 mg/DPH 50 mg vs. IBU 400 mg.

* IBU 400 mg/DPH 50 mg group was significantly better than the IBU 400 mg group; $p \leq 0.05$.

AE-04-14A Duration of sleep, Actigraph assessment, The boxes show the 75th and 25th percentiles, the line in the box the 50th, + depicts the mean, top (bottom) lines represent 90th (10th) percentiles.



Clinical studies in special populations

No studies in special populations have been submitted.

Analysis performed across trials (pooled analyses AND meta-analysis)
Supportive study(ies)

Wyeth performed an across study comparison of demographic and outcome measures of the oral surgery trials as well as a pooled analysis of the key efficacy parameters.

Demographic characteristics across study comparison of oral surgery studies

Treatment Group	Study	n	Demographic Characteristics					
			Age (yrs)		Gender n (%)		Race n (%)	
			Mean±s.d.	Range	Male	Female	Cauc	Non-Cauc
IBU 400 mg/ DPH 50 mg	97-01*	29	23.9±7.5	16-42	12 (41)	17 (59)	24 (83)	5 (17)
	98-01	122	21.5±4.7	16-39	54 (44)	68 (56)	91 (75)	31 (25)
	98-02	119	19.7±4.1	16-40	58 (48)	61 (51)	114 (96)	5 (4)
	98-03	123	24.5±5.6	16-41	63 (51)	60 (49)	65 (53)	58 (47)
	01-11^	155	19.8±3.1	16-31	72 (47)	83 (54)	148 (96)	7 (4)
	04-14A	165	18.7±2.4	16-28	81 (49)	84 (51)	149 (90)	16 (10)
IBU 400 mg								
	97-01	31	23.5±7.2	16-44	12 (39)	19 (61)	24 (77)	7 (23)
	98-01	118	21.1±4.5	16-36	51 (43)	67 (57)	78 (66)	40 (34)
	98-02	123	20.2±4.3	16-39	59 (48)	64 (52)	118 (96)	5 (4)
	98-03	-	-		-	-	-	-
	01-11^	-	-		-	-	-	-
	04-14A	164	19.0±3.1	16-37	81 (49)	83 (51)	151 (92)	13 (8)
PBO	97-01	14	24.2±9.7	16-44	6 (43)	8 (57)	11 (79)	3 (21)
	98-01	40	21.8±4.9	16-34	17 (43)	23 (58)	32 (80)	8 (20)
	98-02	40	20.0±5.0	15-39	20 (50)	20 (50)	37 (93)	3 (7)
	98-03	41	23.0±4.8	16-37	21 (51)	20 (49)	26 (63)	15 (37)
	01-11^	37	19.9±3.7	16-31	17 (46)	20 (54)	36 (97)	1 (3)
	04-14A	-	-	--	-	-	-	-

* Ibuprofen 400/diphenhydramine citrate 76 mg

^ Based on per-protocol subject sample, excluding one ITT subject from the placebo group.

Demographic characteristics pooled oral surgery studies, ITT

Treatment Group	No. Subjects	Age (yrs.) Mean (s.d) Range	Gender n (%) Male/Female	Race n (%) Cauc/non-Cauc
IBU 400/DPH 50 mg	713	20.8 (4.7) 16-42	340 (48)/373 (52)	591 (83)/122 (17)
IBU 400 mg	436	20.2 (4.4) 16-44	203 (47)/233 (53)	371 (85)/65 (15)
Placebo	173	21.4 (5.4) 15-44	81 (47)/92 (53)	143 (83)/30 (17)

s.d. = standard deviation; yrs. = years

Key pain efficacy parameters across study comparison of oral surgery studies

Efficacy Parameter		Treatment Groups			Pairwise Comparisons (Δ, p-value)		
		IBU/DPH 400/50 mg	IBU400 mg	PBO	IBU/DPH vs. PBO	IBU/DPH vs. IBU	IBU vs. PBO
Pain Parameters	**Study**						
SPRID-2 - mean (s.d)	97-01	8.3 (3.5)	9.1 (4.4)	0.9 (3.8)	7.4 (<0.001)	-0.8 (0.381)	7.2 (<0.001)
	98-01	7.7 (4.3)	7.6 (4.4)	1.3 (3.0)	6.4 (<0.001)	0.1 (0.952)	6.3 (<0.001)
	98-02	7.0(3.5)	7.8 (2.9)	0.3(2.1)	6.7 (<0.001)	-0.8 (0.050)	7.5 (<0.001)
	98-03	9.2 (3.5)	NA	1.7 (3.2)	7.5 (<0.001)	NA	NA
	01-11^	6.5 (3.5)	NA	1.2 (2.7)	5.3 (<0.001)	NA	NA
Pain/Sleep Parameters	**Study**						
Time to rescue (median in hours)	97-01	>12.0	>10.0	1.2	0.1 (<0.001)	1.0 (0.839)	0.1 (<0.001)
	98-01	>12.0	>12.0	1.7	0.2 (<0.001)	0.7 (0.098)	0.2 (<0.001)
	98-02	>12.0	>12.0	1.6	0.1 (<0.001)	0.6 (0.195)	0.1 (<0.001)
	98-03	>12.0	NA	1.8	0.1 (<0.001)	NA	NA
	01-11^	>12.0	NA	2.1	0.11 (<0.001)	NA	NA
	04-14A	>12.0	>12.0	NA	NA	0.64 (0.020)	NA
% needing rescue by wake-up time	97-01	48.3	45.2	92.9	-44.6 (0.005)	3.1 (0.879)	-51.6 (0.001)
	98-01	36.9	48.3	85.0	-48.1 (<0.001)	-11.4 (0.071)	-36.7 (<0.001)
	98-02	33.6	42.3	95.0	-61.4 (<0.001)	-8.7 (0.327)	-52.7 (<0.001)
	98-03	34.1	NA	80.5	-46.4 (<0.001)	NA	NA
	01-11^	45.8	NA	91.9	-46.1 (<0.001)	NA	NA
	04-14A	28.5	39.6	NA	NA	-11.1 (0.031)	NA

^ Based on per-protocol subject sample, excluding one ITT subject from the placebo group

Key sleep efficacy parameters across study comparison of oral surgery studies

Efficacy Parameter		Treatment Groups			Pairwise Comparisons (Δ, p-value)		
		IBU/DPH 400/50 mg	IBU400 mg	PBO	IBU/DPH vs. PBO	IBU/DPH vs. IBU	IBU vs. PBO
Sleep Parameters	**Study**						
Sleep duration (categorical^^) -mean (s.d.)	97-01	3.3 (1.9)	2.7 (2.1)	0.4 (1.3)	3.0 (<0.001)	0.6 (0.131)	2.3 (<0.001)
	98-01	2.8 (2.1)	2.3 (2.1)	0.3 (0.8)	2.5 (<0.001)	0.5 (0.022)	2.0 (<0.001)
	98-02	2.6 (1.9)	2.0 (1.8)	0.1 (0.3)	2.5 (<0.001)	0.6 (0.005)	1.9 (<0.001)
	98-03	3.1 (1.9)	NA	0.6 (1.3)	2.5 (<0.001)	NA	NA
	01-11^	2.2 (1.9)	NA	0.1 (0.5)	2.1 (<0.001)	NA	NA
	04-14A	7.9 (3.0)	6.9 (3.3)	NA	NA	1.0 (0.005)	NA
Cumulative % asleep by 60 mins	97-01	89.7	77.4	57.1	32.6 (0.009)	12.3 (0.183)	16.1 (0.096)
	98-01	63.9	64.4	40.0	23.9 (0.008)	-0.5 (0.915)	24.4 (0.006)
	98-02	66.4	75.6	27.5	38.9 (<0.001)	-9.2 (0.112)	48.1 (<0.001)
	98-03	88.6	NA	48.8	39.8 (<0.001)	NA	NA
	01-11^	71.0	NA	40.5	30.5 (<0.001)	NA	NA
	04-14A	NA	NA	NA	NA	NA	NA
Sleep latency (observed) – median in mins	97-01	36.3	25.0	30.0	2.1 (0.068)	0.9 (0.675)	2.4 (0.033)
	98-01	42.9	44.0	>180.0	2.7 (<0.001)	0.9 (0.688)	2.8 (<0.001)
	98-02	45.0	36.5	>180.0	5.8 (<0.001)	1.0 (0.818)	6.0 (<0.001)
	98-03	30.8	NA	63.8	3.3 (<0.001)	NA	NA
	01-11^	43.2	NA	70.5	2.7 (<0.001)	NA	NA
	04-14A	17.6	17.6	NA	NA	1.0 (0.751)	NA

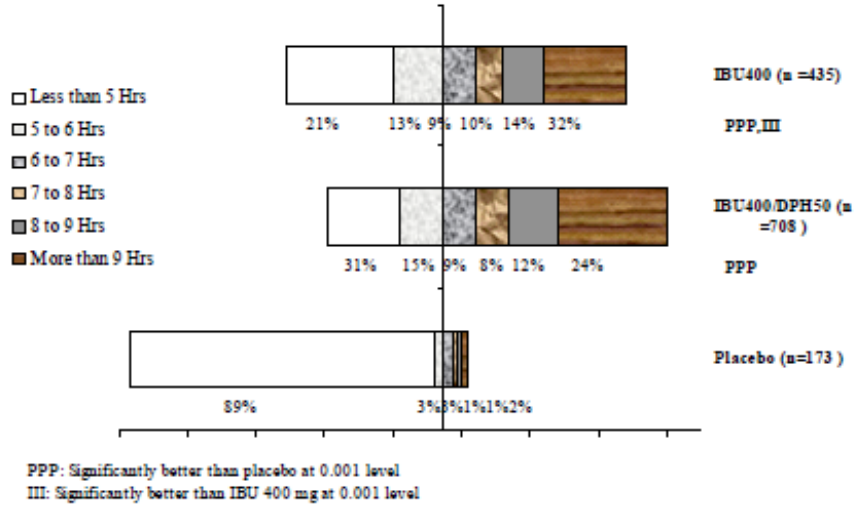
^ Based on per-protocol subject sample, excluding one ITT subject from the placebo group.
^^ except in Study AE-04-14a, where the subjective assessment of sleep duration of was the number of hours slept.

Key efficacy parameters pooled oral surgery studies, ITT

Efficacy Parameter	Treatment Groups			Pairwise Comparisons (Diff./p-value)		
	IBU 400 mg/ DPH 50 mg	IBU 400 mg[b]	PBO[c]	2 IBU/DPH vs. PBO	1 IBU/DPH vs. IBU	IBU vs. PBO
Sleep Duration[a] (categorical) (mean [s.d])	2.8 (2.0) n=708	2.3 (2.0) n=435	0.3 (0.9) n=173	2.5 <0.001*	0.5 <0.001*	2.0 <0.001*
Sleep Duration (actigraph)[d] mean[s.d] (hr)	9.2 (3.1) n=187	7.9 (3.5) n=184	1.8 (3.3) n=10	7.4 <0.001*	1.3 <0.01*	6.1 <0.001*
Cum. % Asleep at 60 mins.	78.5 n=713	79.6 n=436	40.5 n=173	38.0 <0.001*	-1.1 0.644	39.1 <0.001*
Sleep Latency (obs.) (median) (mins)	34.3 n=713	30.1 n=436	>180 n=173	3.2 <0.001*	1.0 0.822	3.3 <0.001*
SPRID2 mean (s.d)	7.6 (3.8) n=547	7.9 (3.8) n=272	1.1 (2.9) n=173	6.5 <0.001*	-0.3 0.112	6.8 <0.001*
Time to Rescue Med (hrs.)	>12 n=713	>12 n=436	1.9 n=173	0.1 <0.001*	0.8 0.020*	0.1 <0.001*
% Needing Rescue by Wake-up Time	36.3 n=713	43.1 n=436	87.9 n=173	-51.6 <0.001*	-6.8 0.003*	-44.8 <0.001*

hrs. = hours; mins. = minutes; obs. = observed; s.d. = standard deviation
Diff Is the observed difference between the pair (first-second) of treatments, except when medians are reported. In that case diff is the hazard ratio of the first treatment vs. the second treatment.
* p≤0.05 in favor of the first treatment listed
[a] Assessed using a categorical scale of 0=<5 hrs to 5=>9 hrs.
[b] Treatment group not evaluated in AE-01-11.; [c] Treatment group not evaluated in AE-04-14a.
[d] AE-97-01 and AE-04-11A only

Sleep duration, pooled oral surgery studies, ITT



PPP: Significantly better than placebo at 0.001 level
III: Significantly better than IBU 400 mg at 0.001 level

Overall conclusions on clinical efficacy

In the CHMP's opinion, there are no prospective, well-designed, adequately controlled studies in this submission that stand on their own as convincing that the IBU/DPH fixed combination is superior to its components in the treatment of night time pain associated with sleeplessness.

The EMA guideline for fixed combination medicinal products requests an improvement in benefit or compliance over the single substances. Each substance of the fixed combination must have a documented contribution within the combination. If the duration of action of the used substances differ significantly, combinations, in principle, may not be considered rational unless pre-eminently justified. None of the above can be seen in the dossier due to a lack of methodically correct assessment of sleep architecture and next day functioning improvement, rendering the only significant effect not interpretable.
The EMA hypnotic guideline recommends that sleep efficacy be assessed in at least one study using polysomnography (PSG). The sponsor used this state of the art method only in one study in 30 healthy volunteers, not assessing a comparison between IBU/DPH vs. at least IBU. The mentioned guideline also requires measurement of improvement in next daytime functioning, being the ultimate goal of influencing sleep architecture in a desired way. Such data are completely missing. Patient selection according to DSM criteria for insomnia is also normally required when studying hypnotics.
The pain assessments submitted are acceptable and in line with the nociceptive pain guideline but are afflicted with questionable external validity since study populations comprised patients with a median age around 20 years. Six studies evaluated the efficacy of the combination product in subjects who had undergone oral surgery and were phase advanced, one study was conducted in subjects with night time headache who were phase advanced and study AE-97-08 enrolled subjects who had a history of experiencing night time pain and sleeplessness, the latter being the only one reflecting the targeted population in terms of age, but lacks to provide a comparison between IBU/DPH vs. IBU. No data are available beyond first dose efficacy, rendering any possible conclusion of multiple use effectivity anchorless. Moreover, the clinical relevance of a 30-70 min. longer sleep duration cannot be discussed at all without the missing data demanded in the sleep guideline.

In the answer to the list of questions the applicant did not provide further data. The attempt to fill the gap of missing data with results from the literature cannot be considered adequate.

The CHMP concluded that major objections remain and further studies are deemed necessary to reliable evaluate the effect of the proposed fixed combination product.
An adequately powered two arm trial comparing IBU/DPH vs. IBU in a representative patient population in terms of age should be submitted.

Clinical safety

Subjects in the clinical study program were typically exposed to a **single** dose of IBU 400/DPH 50, except in the multiple dose study AE-97-08, where study medication was administered for 10 consecutive days. Adverse events were coded in the COSTART terms, and a reference table to the MedDRA preferred terms was provided.

The 10 single dose studies generally enrolled a patient population with a **median age of around 20 years**. Even in this young and basically healthy population, **adverse event incidence** in the IBU 400/DPH 50 group (8.1%) was about **twice** as high as incidence in the IBU 400 group (4.5%). **No data on next day function** or presence/absence of negative effects of Ibuprofen/Diphenhydramine Hydrochloride Wyeth on the next day were collected. Any advantage of the combination product as far as efficacy is concerned has to be seen in context with these safety issues.

In the multiple dose study, **88** subjects were **over 65 years** of age, and 134 were between 45 and 64. In this study, **no comparison** of the effects of **IBU 400/DPH 50** to **IBU 400** alone was undertaken

Although a positive readability study had been completed on the proposed leaflet, concerns remain in connection with the OTC status applied for (see e.g. first criterion of guideline on "Changing the classification for the supply of a medicinal product for human use" 1.3 Self-assessment). The CHMP considered that this criterion had not been met. Comparing the safety data of placebo to IBU 400/ DPH 50, a fourfold increase of adverse events (3.6% to 12.4%) pertinent to the nervous system is notable. This increase is similar to that observed with the single entities.

Patient exposure

Figure a): Studies Included in the Clinical Summary of Safety

Type of Study	Study Number	IBU/DPH^ n	IBU/DPH^ Dose (mg)	Comparator(s) n	Comparator(s) Dose (mg)	PBO n
Multiple Dose (parallel)						
	AE-97-08	481	400/50[1], 200/25[1]	326	APAP[3]/DPH[1] 1000/50	167
Single Dose (parallel)						
	AE-97-01	29	400+76[2]	31 31	IBU 400 DPH 76[2]	14
	AE-97-05	49	400+76[2]	51	IBU 400	52
	AE-98-01	122	400/50[1]	119	IBU 400	40
	AE-98-02	120	400/50[1]	123	IBU 400	40
	AE-98-03	243	400/50[1], 200/25[1]	NA	NA	41
	AE-98-04	81	400/50[1]			81
	AE-01-11	155	400/50[1]	158	APAP/DPH[1] 1000/50	38
	AE-04-14a	165	400/50[1]	164	IBU 400	NA
	AE-05-15	172	400/76[2]	173	APAP/DPH 1000/50	58
	AE-05-16	184	400/76[2]	178	APAP/DPH 1000/50	63
Pharmacokinetic (single dose, x - over)						
	WM-716	23	400+76[2]	23	IBU 400, DPH 76[2]	NA
	AE-97-02	27	400/50[1] (fed), 400/50 (fasted) 400+50 (fasted)	NA	NA	NA
	AE-97-09	25[3]	400/50[1]	25-27	IBU400 (LG & tablet), DPH 50[1]	NA
	AE-00-10	42	400/50[1], 400/76[2]		NA	NA
	AE-01-12	26	400/50[1], 400/76[2]		NA	NA
Total		1944		1404		594

^ Dose amounts separated by '/' indicate that the combination was administered in tablets (or soft gelatin capsules) containing both ingredients; '+' indicate that the two components were administered as clinical capsules, tablets or soft gelatin capsules containing individual ingredients.
[1] DPH HCl; [2] DPH Citrate [3] paracetamol (acetaminophen)
[3] two subjects discontinued prior to IBU/DPH 400/50 mg treatment period in the cross-over study.
Note: DPH HCl 50 mg and DPH Citrate 76 mg are considered equivalent

Figure b): Summary of Exposure to IBU/DPH in the Clinical Database

Type of Study	IBU/DPH HCl 400/50 mg IBU/DPH Citrate. 400/76 mg	IBU/DPH HCl 200/25 mg IBU/DPH Citrate. 200/36 mg	Total
Multiple Dose	323	158	481
Single Dose (efficacy)	1200	120	1320
Pharmacokinetic	143	-	143
Total	1666	278	1944

Adverse events

Figure c): Multiple Dose Data – AEs with Incidence Rates ≥ 2% in Any Treatment:

	Number (%) of Subjects			
Body System/ COSTART Term	IBU/DPH 400/50 mg (n = 323)	IBU/DPH 200/25 mg (n = 158)	APAP/DPH 1000/50mg (n = 326)	Placebo (n = 167)
Nervous	40 (12.4)	20 (12.7)	41 (12.6)	6 (3.6)
Somnolence	28 (8.7)	14 (8.9)	25 (7.7)	4 (2.4)
Dizziness	5 (1.5)	1 (0.6)	9 (2.8)	2 (1.2)
Digestive	39 (12.1)	16 (10.1)	50 (15.3)	21 (12.6)
Dyspepsia	16 (5.0)	11 (7.0)	25 (7.7)	15 (9.0)
Dry Mouth	7 (2.2)	1 (0.6)	5 (1.5)	1 (0.6)
Body as a Whole	57 (17.6)	25 (15.8)	50 (15.3)	30 (18.0)
Headache	37 (11.5)	12 (7.6)	28 (8.6)	17 (10.2)
Pain	10 (3.1)	2 (1.3)	17 (5.2)	4 (2.4)
Back Pain	8 (2.5)	5 (3.2)	5 (1.5)	8 (4.8)
Respiratory	9 (2.8)	9 (5.7)	10 (3.1)	7 (4.2)
Rhinitis	7 (2.2)	5 (3.2)	7 (2.1)	5 (3.0)

Figure d): Single Dose Data – AEs with Incidence Rates ≥ 2% in Any Treatment Group:

BODY SYSTEM COSTART TERM	IBU/DPH Total (n=1320)	IBU/DPH 400/50mg$ (n=1200)	IBU/DPH 200/25mg (n=120)	IBU 400mg (n=488)	DPH 76mg+ (n=31)	APAP/DPH 1000/50 mg (n=509)	Placebo (n=427)	All Subjects (n=2775)
ANY AE	132 (10.0)	97 (8.1)	35 (29.2)	22 (4.5)	3 (9.7)	25 (4.9)	44 (10.3)	226 (8.1)
DIGESTIVE	60 (4.5)	54 (4.5)	6 (5.0)	17 (3.5)	1 (3.2)	14 (2.8)	25 (5.9)	117 (4.2)
NAUSEA	30 (2.3)	24 (2.0)	6 (5.0)	15 (3.1)	0 (0.0)	7 (1.4)	10 (2.3)	62 (2.2)
DRY MOUTH	19 (1.4)	19 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	9 (2.1)	30 (1.1)
VOMITING	15 (1.1)	12 (1.0)	3 (2.5)	5 (1.0)	1 (3.2)	4 (0.8)	5 (1.2)	30 (1.1)
BODY AS A WHOLE	45 (3.4)	25 (2.1)	20 (16.7)	6 (1.2)	1 (3.2)	2 (0.4)	12 (2.8)	66 (2.4)
HEADACHE	38 (2.9)	22 (1.8)	16 (13.3)	6 (1.2)	0 (0.0)	1 (0.2)	10 (2.3)	55 (2.0)
CELLULITIS	1 (0.1)	0 (0.0)	1 (0.8)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	2 (0.1)
NERVOUS	24 (1.8)	17 (1.4)	7 (5.8)	2 (0.4)	1 (3.2)	5 (1.0)	7 (1.6)	39 (1.4)
DIZZINESS	12 (0.9)	10 (0.8)	2 (1.7)	2 (0.4)	1 (3.2)	5 (1.0)	1 (0.2)	21 (0.8)
PARESTHESIA	4 (0.3)	0 (0.0)	4 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	6 (0.2)
RESPIRATORY	15 (1.1)	8 (0.7)	7 (5.8)	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.7)	21 (0.8)
PHARYNGITIS	10 (0.8)	3 (0.3)	7 (5.8)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.5)	13 (0.5)

$: Includes IBU/DPH Citrate 400/38 mg treatment group in AE-97-01, AE-97-05, AE-05-15 and AE-05-16
+: 2 X DPH Citrate 38 mg tablets, considered equivalent to 2 X DPH HCl 25 mg.

Serious adverse events and deaths

No deaths were reported in any of the studies. The serious adverse events recorded during the development programme occurred either in the control groups and/or were not related to treatment.

Laboratory findings

Clinical laboratory evaluations were not performed in any of the multiple-dose or single dose studies. Pre- and post-laboratory evaluations were only performed in two of the PK studies (WM-716 and AE-97-02). No significant findings were noted in these two studies.

Safety in special populations

The Applicant provided subgroup analyses according to age group, gender, race and concomitant disease. Due to the inadequate numbers of patients, many of these analyses do not provide meaningful results. In the presented data, no safety signals emerged.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

PK study WM-716 demonstrated that there are no drug interactions if IBU and DPH are administered together. IBU administered alone was shown to be bioequivalent to IBU administered simultaneously with DPH with respect to both the rate and the extent of drug absorption. Likewise, DPH administered alone was shown to be bioequivalent to DPH administered simultaneously with IBU. Given the well known PK and safety profiles of IBU and DPH, no other specific drug interaction studies with IBU/DPH were conducted.
The interaction potential of IBU and DPH with widely used medications, e.g. Aspirin, other NSAID's or psychotropic substances are of concern in connection to OTC status.

Discontinuation due to AE'S

Multiple Dose Study AE-97-08:
In all, twenty subjects (5, 2, 11 and 2 in the IBU/DPH 400/50 mg, IBU/DPH 200/25 mg, APAP/DPH 1000/50 mg and placebo groups, respectively), discontinued due to an AE.

Single Dose Studies:
Six subjects discontinued due to an adverse event.

Biopharmaceutic Studies
Two subjects discontinued due to AEs.

Pharmacovigilance system

The Rapporteurs consider that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

Table 3.2.1: Safety Concern and Planned Pharmacovigilance Actions

Important identified risks	**Planned action(s)**
Anaphylaxis	Routine pharmacovigilance activities as in Section 3.1
Gastrointestinal effects	
Pregnancy and lactation	Monthly cumulative internal review of cases
Sedative effects	
Anticholinergic effects	6-monthly PSURs
Renal and urinary adverse events	
	Routine pharmacovigilance is adequate based on the long history of OTC use for both ibuprofen and diphenhydramine and the known safety profile of these individual ingredients.
Important potential risks	
Cardiovascular events	
Abuse potential	

Conclusions:

The pharmacovigilance plan is endorsed; the aspects such as sedative effects, anticholinergic effects as well as abuse potential warrant close monitoring. The Applicant is requested to re-evaluate these issues within the first PSUR.

The column “proposed Risk Minimisation Activities” has been revised accordingly to reflect the respective safety concern i.e. to refer only to the parts of the SPC directly related to the respective safety concern

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

V.1 Benefits

Compared to placebo, sufficient pain relief could be demonstrated for the combination product. However, in one of the pivotal studies there was a trend for the single ingredient ibuprofen to be better than the combination for pain relief and sleep latency. For all sleep efficacy parameters investigated (sleep latency, cumulative % asleep at 60 min, and sleep duration) only sleep duration showed a significant difference to monotherapy

V.2 Risks

As regards the comparison IBU400/DPH50 vs IBU400, pivotal study AE-98-01 formally fails to meet both predefined primary efficacy endpoints (SPRID-2h and Cumulative percentage of patients asleep after 60 min). In the framework of secondary efficacy evaluation, a signal for sleep prolongation under IBU400/DPH50 was observed. Awakening of subjects for pain assessment is considered an unfavourable design aspect. Whether or not awakening subjects to record pain could principally create an artificial bias in favour of the combination product remains debateable. Ultimately 39 % of the patients receiving IBU400/DPH50 slept for more than 9 hours, which could be an artefact of the study design, however could be an indication for oversedation that unfortunately can not be ruled out as this parameter was not studied (i.e. next daytime functioning, vigilance indicative variables, etc.) in accordance with the EU guideline.
In pivotal study AE-98-02 the amended co-primary endpoint was also not met formally. Furthermore, point estimates for Cumulative percentage of patients asleep after 60 min indicate a trend for an advantage of the IBU-monotherapy. IBU alone is superior to IBU/DPH with respect to pain relief in this study. 24 % of the patients receiving IBU400/DPH50 slept for more than 9 hours, possibly being oversedated.
The study population of the pivotal trials consists of young patients, being approximately 20 years of age on average. The only study reflecting in any way the targeted population in terms of age is AE-97-08 (a dose response trial), including also elderly patients above 65 years (participants were 12 years of age or older, 70% were female). Although stratified for age subgroups, the study is generally underpowered for robust statistical conclusions in the different age strata, especially in the smallest subgroup 65y+. Moreover, it has to be noted that the only relevant pairwise comparison, which is IBU/DPH 400/50 vs. IBU 400 lacks in this protocol.

No multiple dose efficacy data have been submitted to support the dossier, which consists of only single dose efficacy assessments.

No studies in special populations have been submitted.

The next-day sedative effects and associated diminishment of both mental alertness and motor performance following the night time administration of DPH in an anti-histamine dosing regime have been well characterized in the literature. Sedative effects of DPH administered once nightly as a sleep aid have not been adequately addressed in the response to the LoQ. Sedative effects of DPH may be potentiated by alcohol and other sedatives/hypnotic agents.

Regarding the submitted safety data in this dossier and the response to the LoQ, the following concerns still remain:
It is doubtful if the safety population is representative for the target population (median age of 20 years in single dose studies, unspecific and extensive exclusion criteria in multiple dose study).
A comparative safety profile of IBU/DPH vs IBU was not established in the so called "real life-like" population of AE-97-08.
The safety profile of IBU/DPH vs IBU is incomplete in all age sets and patient populations, due to complete lack of data on next day effects.
A doubling of adverse event incidence in the young and healthy patient population of the single dose studies with IBU/DPH vs IBU was observed.
A fourfold increase of AEs pertinent to the nervous system for Ibuprofen/Diphenhydramine Hydrochloride Wyeth versus PBO has been shown in the multiple dose study.
These issues add up to an incomplete safety database that still precludes a meaningful benefit-risk assessment.

V.3 Balance

With respect to preclinical data no additional studies in experimental animals are required. From a preclinical point of view, the safety profile of the combination IBU/DPH as compared to the single entities may be regarded as sufficiently characterized.

The absence, when assessed against EU guidelines, of indispensable efficacy and safety data presents a major obstacle for a meaningful benefit-risk assessment. Any effects of Ibuprofen/Diphenhydramine Hydrochloride Wyeth on the duration of sleep could be outweighed by impaired next day functioning and an inferior safety profile in comparison to IBU.
As the administration of IBU alone rapidly mitigates pain and allows falling asleep, for the IBU/DPH combination in the opinion of the CHMP, based on the limited data presented, the increase of adverse event incidence, even in the young study population, together with the questionable benefit of a slightly longer sleep duration tips the benefit risk balance in an unfavourable direction.

First line treatment of minor aches and pains is the administration of a pain killer, a considerable variety of which are already available OTC. For mild insomnia, several different sleep aids are available OTC as well. Based on the data reviewed, the combination product has at the most a clinically questionable effect of sleep prolongation compared to the single components, therefore the single substances represent first line treatment and are already available on the market as OTC products.

V.4 Conclusions

The overall B/R of Ibuprofen/Diphenhydramine Hydrochloride Wyeth is considered by the CHMP to be negative.