CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-374

MEDICAL REVIEW

OTC Medical Officer's Review

NDA 21-374
Drug Name: Advil® Cold & Sinus Liqui-Gel®
Sponsor: Whitehall –Robins Healthcare
Pharmacologic Category: Internal Analgesic and Decongestant
Proposed Indication: Temporary Relief of Symptoms of the Common Cold, Sinusitis, and Flu, Including Nasal Congestion, Headache, Fever, and Body Aches
Dosage Form/Route of Administration: Liqui-Gel/ Oral
Submission Dates: July 24, 2001 and November 21, 2001
Review Date: January 10, 2002
Reviewer Name: Andrea Leonard-Segal, M.D., M.S.

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Executive Summary

I. Recommendations:

A. Advil® Cold and Sinus Liqui-Gels® could be approved. The data suggest that this product should be safe for Over-the-Counter (OTC) availability if consumers use it in accordance with the directions and warnings on the product label.

B. Based upon the data Phase 4 studies should not be necessary.

C. The proposed label should be modified in the following ways:

- The label states, "relieves sinus — nasal congestion, and fever." —
- Delete the statement, —
- The label states "take with food or milk if stomach upset occurs." —

D. —

II. Summary of Clinical Findings:

A. Brief Overview of the Clinical Program

The product under review in NDA 21-374 is Advil® Cold & Sinus Liqui-Gels®, a new formulation containing solubilized ibuprofen (IBU) 200 mg and pseudoephedrine hydrochloride (PSE) 30 mg. Advil® Cold & Sinus tablets containing the same concentrations of these two active ingredients are sold OTC. Advil® Cold & Sinus Liqui-Gels®, like Advil® Cold & Sinus tablets, are intended for the temporary relief of symptoms associated with the common cold, sinusitis or flu including nasal congestion, headache, fever, body aches and pain in people 12 years of age or older.

This review is a safety update in the population ≥ 12 years of age who have used the marketed combination product containing IBU and PSE (IBU/PSE), used IBU and PSE concomitantly, or used either, IBU as a single ingredient or PSE as a single ingredient. The safety of combined ibuprofen/pseudoephedrine hydrochloride in children < 12 years old is being reviewed separately under NDA 21-373.

The clinical development program in support of this NDA consists of:

1. Two pharmacokinetic studies of a new Liqui-Gel formulation containing solubilized IBU 200 mg and PSE 30 mg:
   - AB-00-04 – Advil® Cold & Sinus Liqui-Gel® Relative Bioavailability Study
   - AB-00-05 – Advil Cold & Sinus Liqui-Gel Food Effects Bioavailability Study

2. Safety data from post-marketing surveillance reports concerning the IBU/PSE combination and for the single ingredients IBU and PSE in the Whitehall-Robins Healthcare (WHR) database (since 1997). (After May, 2000, the WHR reports are from the Wyeth-Ayerst Global Safety Surveillance and Epidemiology (GSSE) database.)

3. Safety data concerning the combination and the single ingredients from:

- The FDA Spontaneous Reporting System (SRS) and the FDA Adverse Event Reporting System (AERS) (1989 – December 31, 2000)
- The American Association of Poison Control Centers (AAPCC) database (1994-December 31, 2000)
- The Drug Abuse Warning Network (DAWN) (1994-2000). (The DAWN data for the year 2000 includes Emergency Department Data published by the Substance Abuse and Mental Health Service Administration (SAMHSA) but the Medical Examiner section of the DAWN for 2000 was not published in time for this November 21, 2001 submission update.)
- Safety Update submitted November 21, 2001.

4. Articles discussing IBU/PSE combination products or the concomitant use of IBU and PSE combinations resulting from a search of the MEDLINE, EMBASE, Alert, BIOSIS PREVIEWS, Derwent Drug File, Toxline, and SciSearch databases for the years 1984-2001.

The worldwide safety review for this NDA comprises a review of the spontaneous adverse experience reports, the literature search, and a report of the marketing experience with similar products in countries outside the United States.

B. Efficacy

There were no efficacy studies in this NDA because this is a line-extension of a marketed product. The sponsor provided studies to prove that this new formulation is bioequivalent to the already approved formulation.

C. Safety

The data does not suggest new significant safety signals associated with the use of IBU/PSE, concurrent use of the two medications, or single use of IBU or PSE. The data suggest that deaths and serious adverse events are more common with the use of IBU or PSE as single ingredients, than with their combined use. The data does not suggest a significant problem with abuse of IBU/PSE.

The data does not suggest that IBU/PSE, when taken according to the directions, is unsafe for OTC availability.

D. Dosing

The proposed dosing regimen is one liqui-gel every 4 – 6 hr while symptoms persist. If symptoms do not respond to one liqui-gel, two may be used, not to exceed six in any

Clinical Review

I. Introduction and Background:

Ibuprofen, a propionic acid nonsteroidal anti-inflammatory drug, and pseudoephedrine hydrochloride, a sympathomimetic decongestant, have lengthy histories of safe and effective use, in combination and as single ingredients. IBU 200 mg as a single ingredient, OTC, analgesic/fever reducer has been available for use in adults since 1984 as Advil (Whitehall-Robins Healthcare, NDA 18-989). Nuprin (McNeil 19-012 001 and 002), Motrin IB (McNeil, 19-012 003), and Motrin Migraine Pain (McNeil 19-012 004). It is also available OTC in numerous generic 200 mg IBU single products.

IBU is also marketed OTC for children. The pediatric products include Children's Motrin and Junior Strength Motrin (McNeil NDAs 20-601, 20-602, 20-603, 20-516), Pediatric Advil (Whitehall Robins, NDA 20812), Children's Advil (Whitehall Robins NDA 20-589), and Junior Strength Advil (Whitehall Robins NDAs 20-944, 20-267).

During the lengthy clinical experience with IBU as a prescription and then an OTC drug, a vast array of serious and non-serious adverse events (AE) have been identified with product use. Gastrointestinal AEs are commonly reported (e.g., epigastric pain, dyspepsia, nausea, vomiting, heartburn, sensations of "fullness" in the gastrointestinal tract, peptic ulcer disease, and gastrointestinal bleeding), some of which can be serious. Among other recognized serious and non-serious AEs are:

- Renal toxicity (e.g., impaired function; acute failure)
- Allergic reactions (e.g., skin rashes, hives, facial swelling, asthma, anaphylactic shock) cardiovascular toxicity (e.g., fluid retention, congestive heart failure, hypertension, edema, hypotension, bradycardia, tachycardia, atrial fibrillation)
- Metabolic acidosis
- Thrombocytopenia
- Central nervous system (CNS) toxicity (e.g., headaches, dizziness, lethargy, drowsiness, sweating, fatigue, tinnitus, seizures, CNS depression, aseptic meningitis, coma)
- Visual changes (e.g., blurred; scotomata; changes in color vision, toxic amblyopia)
- Liver toxicity (e.g., enzyme abnormalities, jaundice, fatal hepatitis)
- Apnea
- Death

Ibuprofen is classified as a Pregnancy Category B drug. The IBU prescription label states that use is not recommended during pregnancy because it may cause problems in the unborn child, and that if taken during the last 3 months of pregnancy it may cause complications during delivery and may interfere with closure of the ductus arteriosus. A pregnancy warning in consumer friendly language is on the OTC IBU labels. Ibuprofen is also not recommended for use by nursing mothers because of insufficient safety data.

Drug interactions of concern are that ibuprofen:

- May enhance the toxicity of methotrexate.

- May increase bleeding when administered with coumarin-type anticoagulants.
- May diminish the antihypertensive effect of angiotensin converting enzyme inhibitors.
- Reduces the natriuretic effect of furosemide and thiazide diuretics
- Elevates plasma lithium levels and reduces lithium clearance, thus increasing the risk of lithium toxicity.

Pseudoephedrine hydrochloride received OTC Monograph status in 1976 but has been sold in OTC nasal decongestant products since the 1960s. In 1982, Afrinol (Shering-Plough, NDA 18-191), an extended release PSE tablet, was approved and in 1992, Efidac 24 Pseudoephedrine HCl (Alza, NDA 20-021) was approved. PSE is also marketed generically as an extended release tablet.

PSE is recognized to have many serious and non-serious adverse events among which are hypertension, cardiac arrythmias including tachycardias, bradycardia, cardiovascular collapse with hypotension, shock, CNS depression, hallucinations, seizures, coma, anxiety, insomnia, nervousness, dizziness, excitability, tremor, restlessness, sweating, depression, pallor, anorexia, nausea, vomiting, dry mouth, and urinary retention. Death has been reported in association with overdose. Pseudoephedrine is classified as a Pregnancy Category C drug. It is not recommended for women who are nursing a baby and for anyone with hyperthyroidism, diabetes mellitus, cardiovascular disease, prostatic hypertrophy, and hypertension. It may cause ocular hypertension.

Known drug interactions are that pseudoephedrine:
- May cause a hypertensive crisis when given with monoamine oxidase inhibitors
- May cause hypertension when given with furazolidone, guanethidine, or methyldopa
- Elimination is increased when given with urinary acidifiers (e.g., ammonium chloride)
- Elimination is decreased when given with urinary alkalinizers (e.g., sodium bicarbonate)

On September 19, 1989 (Whitehall Labs' NDA 19-771), a combination ibuprofen and pseudoephedrine hydrochloride (IBU/PSE) tablet (containing IBU 200 mg and PSE 30 mg) was approved for OTC sale. Initially, IBU/PSE was marketed under the name CoAdvil®. In 1991, the name was changed to Advil® Cold and Sinus. Over [redacted] tablets/caplets of IBU/PSE have been sold. Other OTC products combining IBU 200 mg and PSE 30 mg are marketed as Sine-Aid IB, Motrin IB Sinus, and Ibuprohm Cold and Sinus (a generic product). A product combining 100 mg IBU/5 ml and 15 mg /5 ml PSE is marketed by McNeil Consumer Healthcare (NDA 21-128) for children as Children's Motrin Cold.

The product under review in NDA 21-374 is Advil® Cold & Sinus Liqui-Gels®, a new adult formulation containing solubilized IBU 200 mg and PSE 30 mg. A liqui-gel 200 mg ibuprofen formulation, Provel, approved by the FDA for Sandoz Pharmaceutical in 1994 and marketed as Advil Liqui-Gels by Whitehall-Robins Healthcare in 1998 (NDA 20-

402) has a faster rate but equivalent extent of absorption compared to the reference standard tablet (Nuprin® 200 mg). Consequently, the sponsor hypothesized that a Liqui-Gel formulation of IBU/PSE would provide for a faster rate but equivalent extent of absorption compared to the tablet Advil Cold & Sinus formulation.

Advil® Cold & Sinus Liqui-Gels®, like Advil® Cold & Sinus tablets, is intended for the temporary relief of symptoms associated with the common cold, sinusitis or flu including nasal congestion, headache, fever, body aches and pain in people 12 years of age or older.

This is a safety update review of the use of IBU/PSE, IBU as a single ingredient, and PSE as a single ingredient in people ≥ 12 years of age. The safety of IBU/PSE in children < 12 years old is being reviewed separately under NDA 21-373. There were no efficacy studies submitted as part of this application.

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

There were no clinically relevant findings noted in the chemistry review (See Chemistry review for specifics). The pharmacology /toxicology review concluded that there were no safety issues relevant to clinical use or other clinically relevant issues. (See Pharmacology/Toxicology review for specifics.)

This submission did not require a microbiology or statistical review.

III. Human Pharmacokinetics and Pharmacodynamics

Study AB-00-05 demonstrated that the extent of absorption of ibuprofen from the combination liqui-gel was similar to that from the individual component and the combination tablet. However, the rate of absorption was between that of the individual component and the combination tablet. The 90% confidence intervals for Cmax were outside the accepted limits for bioequivalence (80-125%) being lower (~0.16% outside the accepted limits) than that of Advil® Liqui-Gels® and higher (~ 13.5% outside the accepted limits) than that for Advil® Cold and Sinus tablet.

For pseudoephedrine the rate and extent of the combination liqui-gel was similar to that of the combination tablet. The extent of absorption of the combination liqui-gel was similar to that of the individual component but not the rate. The Cmax of the combination liqui-gel was higher (~1.2% outside the accepted limits for bioequivalence) when compared to the individual component.

Study AB-00-05 results demonstrated that in the presence of food the rate of absorption of ibuprofen from Advil® Cold and Sinus Liqui-gels® was decreased (Cmax was lower ~24% outside the accepted limits for bioequivalence), but not the extent of absorption. For pseudoephedrine the rate and extent of absorption from Advil® Cold and Sinus Liqui-gel® was similar in both the fed and fasted state. (See Human Pharmacokinetics Review).

IV. Description of Clinical Data and Sources

The clinical development program in support of this NDA consists of:

1. Two pharmacokinetic studies of a new liqui-gel formulation containing solubilized IBU 200 mg and PSE 30 mg:
   - AB-00-04 – Advil® Cold & Sinus Liqui-Gel® Relative Bioavailability Study
   - AB-00-05 – Advil® Cold & Sinus Liqui-Gel® Food Effects Bioavailability Study

2. Safety data from post-marketing surveillance reports concerning the IBU/PSE combination and for the single ingredients IBU and PSE in the Whitehall-Robins Healthcare (WHR) database (since 1997). (After 5/2000, the WHR reports are from the Wyeth-Ayerst Global Safety Surveillance and Epidemiology (GSSE) database.)

3. Safety data concerning the combination and the single ingredients from:
   - The FDA Spontaneous Reporting System (SRS) and the FDA Adverse Reporting System (AERS) (1989 – 12/31/2000)
   - The American Association of Poison Control Centers (AAPCC) database (1994-December 31, 2000)
   - The Drug Abuse Warning Network (DAWN) (1994-2000). (The DAWN data for the year 2000 includes Emergency Department Data published by the Substance Abuse and Mental Health Service Administration (SAMHSA) but the Medical Examiner section of the DAWN for 2000 was not published in time for this November 21, 2001 submission update.)
   - Safety Update submitted November 21, 2001

4. Articles discussing IBU/PSE combination products or the concomitant use of IBU and PSE combinations resulting from a search of the MEDLINE, EMBASE, Alert, BIOSIS PREVIEWS, Derwent Drug File, Toxline, and SciSearch databases for the years 1984-2001.

The worldwide safety review for this NDA comprises a review of the spontaneous adverse experience reports, the literature search, and a report of the marketing experience with similar products in countries outside the United States.

V. Clinical Review Methods

A complete review of the safety data from the two pharmacokinetic studies, data from the post-marketing data bases, data from DAWN and data from the AAPCC for subjects ≥ 12 years of age or listed as "age unknown" submitted by the sponsor was conducted. The articles submitted by the sponsor that pertained to subjects ≥ 12 years of age from the medical literature were also reviewed.

No DSI audit was conducted. WHR stated in Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) they did not enter into any financial arrangement with the clinical investigators and that the investigators did not disclose proprietary interests or equity in WHR. No investigator received significant payments of other sorts all as defined by the Code of Federal Regulations.

VI. Integrated Review of Efficacy

The efficacy of the proposed combination as well as of PSE and IBU as single ingredients have been established through extensive clinical evaluation and marketing experience. There was no new efficacy data submitted as part of this NDA.

VII. Integrated Review of Safety

A. Clinical Trials AB-00-04 and AB-00-05. (See Human Pharmacokinetics Review for a complete review and analysis of these two studies.)

Study AB-00-04 (Advil® Cold & Sinus Liqui-Gel® Relative Bioavailability Study) was a single-center, randomized, open-label, single-dose 4-way crossover study. The objective was to compare the rate and extent of absorption of IBU and PSE from an Advil®.Cold and Sinus Liqui-Gel® formulation (IBU 200 mg/PSE 30 mg/Liqui-Gel) to Advil® Liqui-Gels® (IBU 200 mg/liqui-gel), Children's Sudafed® Nasal Decongestant Liquid Medication (PSE 15 mg/5 ml) and Advil® Cold and Sinus tablets (IBU 200 mg/PSE 30 mg/tablet). Subjects underwent a medical history, physical examination, fasting laboratory studies (hematology, biochemistry, urinalysis, drugs of abuse screen, HIV screen and for females, a pregnancy test). Treatment was administered on 4 distinct occasions separated by 7 days. The order of treatments was randomly chosen. During all treatment periods, blood was drawn before dosing and at specified intervals up to 24 hours following dosing. At the conclusion of the study, the physical examination was repeated. All AEs during and within 15 days of completing the study were recorded. Twenty-eight subjects enrolled and 27 completed the 4 treatment periods.

Study AB-00-05 (Advil® Cold & Sinus Liqui-Gel® Food Effects Bioavailability Study) sought to compare the rate and extent of absorption of IBU and PSE from an Advil® Cold & Sinus Liqui-Gel® formulation under fed and fasted conditions. Subjects underwent a medical history, physical examination, fasting laboratory studies (hematology, biochemistry, urinalysis, drugs of abuse screen, HIV screen and for females, a pregnancy test). They received one of two treatments:

- Treatment A: Two Advil® Cold & Sinus Liqui-Gels® under fasted conditions
- Treatment B: Two Advil® Cold & Sinus Liqui-Gels® under fed conditions

on two separate occasions, the order of which was randomly chosen.

During both treatment periods, blood was drawn before dosing and at specified intervals up to 24 hours following dosing. At the conclusion, the physical examination was repeated. All adverse experiences during and within 15 days of completing the study were recorded. Twenty-eight subjects enrolled and 27 completed both treatment periods.

Safety Results of Both Pharmacokinetic Studies Combined:

A total of 56 healthy participants (34 males and 22 females) ages 18 – 44 years received Advil® Cold & Sinus Liqui-Gels® in these 2 pharmacokinetic studies. There were 36 (64.3%) Caucasians, 10 (17.9%) Blacks, 9 (16.1%) Hispanics, and 1 (1.8%) Asian enrolled. No participants took a placebo. Eight participants reported 13 AEs (See **Table 1**). The sponsor states that subjects in Study AB-00-04 were presumed to be fasting per protocol and they were reported accordingly.

Table 1. AE Reported in Studies AB-00-04 and AB-00-05*

Study	AE	Gender/Age	Treatment	Relationship to Treatment
AB-00-04	Tired	M/39	Advil Liqui-Gels (Fasted)	Remote
AB-00-04	Nausea	F/44	Advil Cold & Sinus Liqui-Gels (Fasted)	Remote
AB-00-05	Sore Throat	F/27	Advil Cold & Sinus Liqui-Gels (Fasted)	Possible
AB-00-05	Drowsiness	M/18	Advil Cold & Sinus Liqui-Gels (Fasted)	Probable
AB-00-05	Headache	F/29	Advil Cold & Sinus Liqui-Gels (Fasted)	Probable
AB-00-05	Nausea	F29	Advil Cold & Sinus Liqui-Gels (Fasted)	Probable
AB-00-05	Headache	F/25	Advil Cold & Sinus Liqui-Gels (Fasted)	Probable
AB-00-05	Nasal Congestion Lightheadedness	F/31	Advil Cold & Sinus Liqui-Gels (Fasted) Advil Cold & Sinus Liqui-Gels (Fed)	Remote Probable
AB-00-05	Drowsiness Menstrual Cramps Drowsiness Abdominal aches ("knot in stomach")	F/29	Advil Cold & Sinus Liqui-Gels (Fasted) Advil Cold & Sinus Liqui-Gels (Fed) Advil Cold & Sinus Liqui-Gel (Fed) Advil Cold & Sinus Liqui-Gel (Fed)	Probable Remote Probable Remote

*No participant receiving Sudafed reported any adverse experiences

Seven of the 13 AEs were judged by the investigator to be "probably" related to the treatment, one "possibly," and the remainder "remotely" related. All AEs were characterized as mild; none were serious and there were no deaths. No participant withdrew because of an adverse event. There were no abnormal physical examination or laboratory findings at the end of either study.

B. Postmarketing Surveillance Overview

The WRH database (including GSSE between May and December, 2000), SRS, and AERS were reviewed for reports concerning the ibuprofen/pseudoephedrine hydrochloride combination and for the single ingredients, ibuprofen and pseudoephedrine hydrochloride (see **Table 2**). The sponsor states that the reports submitted from their database do not overlap the reports from the SRS and AERS databases.

Table 2. Distribution of All Spontaneous Domestic and International AE Reports According to Report Type and Reporter Classification.

Report Source	Initial Reports from 8/1/89-12/31/00	Serious Reports[+++]			Non-Serious Reports			Total Events Reported[+]
		HP*	NHP**	UN***	HP	NHP	UN	
SRS Database[++]								
PSE	872	113	61	1	118	572	7	1833
IBU	7387	1895	175	216	2041	2602	458	15013
IBU + PSE	40	2	1	0	5	31	1	81
AERS Database[++]								
PSE	398	49	13	3	64	269	0	1016
IBU	1002	244	37	86	103	518	0	4801
IBU + PSE	87	7	4	2	1	73	0	202
WHR Database								
PSE	28	0	1	0	0	27	0	43
IBU	2401	254	117	0	216	1819	0	4008
IBU + PSE	411	42	11	0	41	316	0	699

*HP = Reporter was a health professional.
**NHP = Reporter was a non-health professional.
***UN = Reporter was unidentified as being either an HP or NHP.
+A number of adverse event reports contain more than one reported event hence the number of reports is not equal to the sum of the individual events.
++Reports transmitted to FDA by WHR for the existing, marketed, solid dosage form product, have been excluded from these tabulations.
+++Serious Reports equate to one of the following outcomes: death, hospitalization, disability, intervention required, life threatening, congenital anomaly.

Comment: The sponsor does not specifically state the ages of the subjects that are reported. Thus it is not clear that this data reflects only subjects aged ≥ 12 years.

As **Table 2** indicates, compared with the single ingredient products, the number of reports associated with the combination product was consistently one to two orders of magnitude lower across the databases. Compared to the number of reports for IBU or PSE single-ingredient products, the number of serious reports for IBU/PSE was consistently lower across all databases. A total of 67 serious reports were associated with the use of the combination product. Fifty-three (79%) of these reports were reported to WHR and the remaining 14 (20%) were directly transmitted to the FDA.

Comment: The quantity of each product sold or taken by consumers (the denominator) is not available against which to compare the number of serious reports per product.

IBU/PSE Serious and Non-Serious Adverse Event Data

WHR and GSSE IBU/PSE- All AEs

WHR states they received 411 initial reports describing 699 adverse events with IBU/PSE between August 1, 1989 and December 31, 2000 (Refer to **Table 2**). However, there were 706 adverse events reported. **Table 3** displays the adverse events associated with the 411 initial reports.

Table 3. All Adverse Events Associated with IBU/PSE from WHR and GSSE from August 1, 1989 through December 31, 2000 (COSTART Term) in Descending Order of Frequency. (Where there is no number listed in the column, there were zero events reported for that category.)

Adverse Event	Total Events	Events in Subjects Known to be ≥ 12 Years of Age	Events in Subjects Age Unknown
No Drug Effect	132		
Rash	30	8**	1***
Dizziness	29	2	
Insomnia	26		
Pruritis	22	8**	
Nervousness	16		
Nausea	15		
Urticaria	15	4**	
Edema Face	14	4	
Somnolence	13		
Allergic Reaction	13	3	
Rash Mac Pap	12	8**	
Vasodilatation	12	3	
Asthenia	11	2	
Dyspepsia	11	1	
Pain, Abdominal	10		
Dyspnea	10	2	
Rhinitis	10		
Headache	9		
Angioedema	9	5**	
Reaction Unevaluable	9		
Hypertension	8		
Pain	7	2	
Reaction, Aggravation	6		
Palpitations	6		
Diplopia	6		3***
Twitching	6	3	
Fever	5	3	
Tachycardia	5	1	
Epistaxis	5		
Sweat	5		
Malaise	4	2	
Hypertension	4		
Vasodilatation	4	1	
Melena	4	1	
Nausea Vomiting	4		
Vomiting	4	1	
Thrombocytopenia	4*	3	2***
Euphoria	4		
Paresthesia	4		
Urinary Retention	4		
Anaphylaxis	3	2	
Atrial Fibrillation	3	1	
Diarrhea	3	1	
Purpura, Thrombopenic	3	2	
Edema, Peripheral	3		
Tremor	3		
Asthma	3	1	
Parosmia	3		

*** Fewer events reported in sponsors "All events reported" table than reported for at least age 12 and "age unknown."**

**** The sponsor's "all events for those at least 12 years of age" table mistakenly listed "serious" Skin and Appendages, Special Senses and Urogenital System events. There was no "all events" page provided for these categories.**

***** The sponsor did not include a table of "all events" for "age unknown" – only "all serious events" for "age unknown." However this "all serious events" for "age unknown" table was situated among the WHR "all events" tables in the submission.**

Table 3 (Continued). All Adverse Events Associated with IBU/PSE from WHR and GSSE from August 1, 1989 through December 31, 2000 (COSTART Term) in Descending Order of Frequency.

Adverse Event	Total Events	Events in Subjects Known to be ≥ 12 Years of Age	Events in Subjects Age Unknown
Vision Abnormality	3		
Tinnitus	3		
Ischemia Cerebral	3	3	
Chills	2		
Overdose Intentional	2	1	
Pain, Back	2		
Pain, Chest	2	1	
Hypotension	2	1	
Purpura, Vascular	2	3*	
Syncope	2	1	
Dysphagia	2		
Glossitis	2	1	
Hemorrhage, Gastrointestinal	2	1	
Hemorrhage, Gum	2	1	
Agranulocytosis	2	2	
Ecchymosis	2		
Edema	2	2	
Agitation	2		
Arteriospasm	2		2***
Convulsion	2	2	
Depersonalization	2		
Dry Mouth	2		
Hemorrhage Cerebral	2		2***
Hyperkinesia	2		
Speech Disorder	2	1	
Urinary Retention	2		
Bronchitis	2		
Cough Inc	2		
Laryngismus	2	1	
Rash, Vesiculo-Bullous	2		
Lacrimation Disorder	2		
Taste Perversion	2		
Dysuria	2	1**	
Kidney Failure Acute	2*	1**	2***
Cerebral Hemorrhage	2*		4***
Shock	2	2	
Drug Interaction	1		
Flu Syndrome	1		
Lab Test Abnormality	1		
Mucous Membrane Disorder	1	1	
Overdose	1		
Pyrexia	1	1	
Sepsis	1***		1***

*** Fewer events reported in sponsors "All events reported" table than reported for at least age 12 and "age unknown."**
**** The sponsor's "all events for those at least 12 years of age" table mistakenly listed "serious" Skin and Appendages, Special Senses and Urogenital System events. There was no "all events" page provided for these categories.**
***** The sponsor did not include a table of "all events" for "age unknown" – only "all serious events" for "age unknown." However this "all serious events" for "age unknown" table was situated among the WHR "all events" tables in the submission.**

Table 3 (Continued). All Adverse Events Associated with IBU/PSE from WHR and GSSE from August 1, 1989 through December 31, 2000 (COSTART Term) in Descending Order of Frequency

Adverse Event	Total Events	Events in Subjects Known to be ≥ 12 Years of Age	Events in Subjects Age Unknown
Angina Pectoris	1	1	
Arteriospasm	1		1***
Bradycardia	1	1	
Hemorrhage	1	1	
Hypotension NOS	1	1	
Infarct Myocardial	1	1	
Migraine	1		
Tachycardia Supraventricular	1		
Vascular Disorder Peripheral	1	1	
Anorexia	1		
Constipation	1		
Discolor Tongue	1		
Dry Mouth	1		
Edema Tongue	1	1	
Eructation	1		
Esophagitis	1		
Flatulence	1		
Gastritis	1	1	
Gastrointestinal Disorder	1		
Liver Function Abnormalities	1		
Nausea Vomiting Diarrhea	1		
Necrosis, Liver	1 (2***)		2***
Stomatitis	1		
Stomatitis Ulcer	1		
Stool Abnormal	1		
Tongue Disorder	1		
Ulcer, Esophageal	1		
Purpura, Fulminans	1 (2***)		2***
GGTP Increased	1	1	
SGOT Increased	1	1	
SGTP Increased	1	1	
Myalgia	1		
Neck Stiffness	1	1	
Amnesia	1		
Anxiety	1		
Coma	1		1***
Confusion	1		
Depression	1		
Dysarthria	1	1	
Hallucination	1		

*** Fewer events reported in sponsors "All events reported" table than reported for at least age 12 and "age unknown."**
**** The sponsor's "all events for those at least 12 years of age" table mistakenly listed "serious" Skin and Appendages, Special Senses and Urogenital System events. There was no "all events" page provided for these categories.**
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Table 3 (Continued). All Adverse Events Associated with IBU/PSE from WHR and GSSE from August 1, 1989 through December 31, 2000 (COSTART Term) in Descending Order of Frequency

Adverse Event	Total Events	Events in Subjects Known to be ≥ 12 Years of Age	Events in Subjects Age Unknown
Hemiplegia	1		1***
Hypertonia	1		
Hypokinesia	1		
Loss of Consciousness NEC	1	1	
Sleep Disorder	1		
Stupor	1	1	
Vertigo	1		
Apnea	1		
Dyspnea NOS	1	1	
Laryngitis	1		
Pharyngitis	1		
Respiratory Disorder	1		
Sputum Increased	1		
Acne	1		
Application Site Reaction	1		
Dermatitis, Exfoliative	1		
Eczema	1		
Erythema Multiforme	1	1**	
Rash Morbilliform	1	1	
Rash Pustular	1	1**	
Skin Disorder	1		
Vascular Purpura	1		
Accommodation Abnormal	1		
Conjunctivitis	1		
Ear Disorder	1		
Eye Disorder	1	1**	
Taste Loss	1		
Glomerulitis	1		
Kidney Function Abnormal	1		
Nephritis	1	1**	
Polyuria	1		
Urinary Abnormality	1		

*** Fewer events reported in sponsors "All events reported" table than reported for at least age 12 and "age unknown."**
**** The sponsor's "all events for those at least 12 years of age" table mistakenly listed "serious" Skin and Appendages, Special Senses and Urogenital System events. There was no "all events" page provided for these categories.**
***** The sponsor did not include a table of "all events" for "age unknown" – only "all serious events" for "age unknown." However this "all serious events" for "age unknown" table was situated among the WHR "all events" tables in the submission.**

Comment: The most common event (132) reported was "no drug effect." Aside from no drug effect, allergic reactions are most commonly reported. This data does not suggest new safety concerns.

SRS Database IBU/PSE - All AEs (Excluding WHR AE Reports)

There were 81 total reported adverse events for the IBU/PSE combination product reported to the SRS Database (See **Table 2**). Of these, 34 were in people ≥ 12 years of age and 41 were in subjects of "age unknown." **Table 4** presents all AEs in the SRS database (01/01/89 – 10/31/97).

Table 4. All Adverse Events in Descending Order of Frequency in the SRS Database (Excluding WHR and GSSE Reports) for IBU/PSE Combination

Adverse Events	Total Events	Events in Subjects Known to be ≥ 12 Years of Age
No Drug Effect	14	4
Saliva, Increased	6	0
Dry Mouth	4	2
Rash	3	3
Urticaria	3	2
Pruritus	2	1
Fever	2	1
Headache	2	2
Dry Mouth	2	1
Dyspepsia	2	0
Arthralgia	2	1
Insomnia	2	1
Confusion	2	1
Thinking Abnormality	2	1
Dyspnea	2	0
Vasodilatation	2	0
Laryngismus	2	0
Taste Perversion	2	0
Lab Test Abnormality	1	0
Allergic Reaction	1	1
Asthenia	1	0
Drug interaction	1	1
Pain	1	1
Reaction Aggravation	1	1
Reaction Unevaluable	1	0
Hemorrhage*	1	1
Syncope*	1	1
Tachychardia (Ventricular)	1	0
Vasodilatation	1	0
Eosinophilia*	1	1
Purpura, Thrombocytopenic*	1	1
Thrombocytopenia*	1	1
Anxiety*	1	1
Convulsion*	1	1
Depression	1	1
Hyperkinesia	1	0
Paresthesia, Circumoral	1	1
Somnolence	1	0
Stupor	1	0
Asthma	1	0
Hyperventilation*	1	1
Rhinitis	1	0
Sweating	1	0

* 8 Serious adverse events for age ≥ 12 years (in a total of 3 patients – see **Table 7**).

AERS – All AEs for IBU/PSE Excluding WHR-GSSE Reports (11/1/1997 –9/30/2000)

For those ≥ 12 years, there were 51 reports associated with IBU/PSE in the AERS Database. There were 36 reports for IBU/PSE in subjects of unknown age. There were 13 serious reports in the AERS database for IBU/PSE; five were in the group ≥ 12 years where IBU/PSE was the primary suspect drug and 5 where IBU/PSE was the secondary suspect drug. The remaining 3 were in the "age unknown" group where IBU/PSE was the primary suspect drug. The sponsor states that there were 202 AEs in the AERS database, but the submission listed 198. **Table 5** lists all 198 AEs associated with IBU/PSE from the AERS database from November 1, 1997 – September 30, 2000.

Table 5. All AEs Associated with IBU/PSE from FDA AERS from November 1, 1997 through September 30, 2000 (MedDRA Term) in Descending Order of Frequency.

Adverse Event	Total Events	Events in Subjects ≥ 12 Years	Events in "Age Unknown"
Drug Ineffective	36	12	24
Dyspepsia*	7	5	2
Dyspnea NOS*	6	4	2
Face Edema*	6	5	1
Abdominal Pain NOS	5	3	2
Anaphylactoid Reaction*	4	3	1
Pruritus NOS*	4	3	1
Dizziness (Exc Vertigo)*	4	4	
Paresthesia NEC*	4	2	2
Urticaria NOS*	4	4	
Edema NOS*	3	1	2
Palpitations NOS	3	3	
Hypersensitivity NOS	3	3	
Edema Lower Limb*	2	1	1
Tachycardia NOS	2	1	1
Gastrointestinal Hemorrhage*	2	2	
Glossitis	2	2	
Intestinal Ulcer*	2	2	
Chest Pain NEC*	2	2	
Vomiting NOS*	2	1	1
Drug Hypersensitivity*	2	2	
Headache NOS*	2	2	
Sedation*	2	2	
Anxiety NEC*	2	2	
Alopecia	2	2	
Dermatitis NOS	2	1	1
Hypertension NOS	2		2
Vasodilation*	2		2
Disseminated Intravascular Coagulation*	1		1
Bradycardia NOS*	1	1	
Cyanosis NOS*	1	1	
Myocardial Infarction*	1	1	
Edema Upper Limb*	1		1
Feeling Hot	1		1
Sinus Tachycardia*	1	1	
Amblyopia NOS	1		1
Diplopia *	1	1	
Papilledema*	1	1	
Vertigo NEC*	1	1	
Photopsia	1	1	
Vision Blurred*	1	1	
Abdominal Pain Upper*	1	1	
Diarrhea NOS	1	1	
Dry Mouth	1	1	
Dysphagia*	1		1
Esophageal Disorder*	1		1

*AEs in the serious reports for those ≥ 12 years and "age unknown." See Table 8.

Table 5 (continued). All AEs Associated with IBU/PSE from FDA AERS from November 1, 1997 through September 30, 2000 (MedDRA Term) in Descending Order of Frequency.

Adverse Event	Total Events	Events in Subjects ≥ 12 Years	Events in "Age Unknown"
Tongue Disorder*	1		1
Hemorrhage NOS*	1	1	
Malaise*	1	1	
Nausea*	1	1	
Pain NOS	1		1
Swelling NOS	1		1
Drug Interaction NOS*	1		1
Feeling Jittery*	1	1	
Hepatocellular Damage*	1		1
Anaphylactic Shock*	1	1	
Infection NOS*	1		1
Meningitis Herpes*	1	1	
Meningitis NOS*	1	1	
Meningitis Viral NEC*	1	1	
Sinusitis NOS	1	1	
Upper Respiratory Infection NOS	1		1
Accidental Overdose (Therapeutic Overdose*	1	1	
Arterial Pressure Increased*	1	1	
Overdose NOS	1	1	
Drug Level NOS Above Therapeutic*	1	1	
Drug Level NOS Changed*	1	1	
Electrocardiogram Abnormal NOS*	1	1	
Gram Stain Positive*	1		1
Hematuria Present	1		1
Thrombocytopenia*	1		1
Weight Decreased	1		1
Pain in Limb*	1		1
Brain Herniation*	1		1
Coma NEC*	1	1	
Convulsions NOS*	1	1	
Hemorrhagic Stroke*	1		1
Hypoesthesia*	1	1	
Insomnia NEC	1	1	
Meningitis Aseptic*	1	1	
Speech Disorder NEC*	1	1	
Syncope*	1	1	
Tremor NEC*	1	1	
Agitation	1	1	
Depression NEC	1		1
Lack of Spontaneous Speech*	1		1
Dysuria	1	1	1
Renal Failure Acute*	1		1
Urinary Frequency	1	1	
Urinary Tract Disorder NOS	1	1	
Urine Abnormal NOS	1	1	
Cough*	1		1
Pharyngeal Disorder NOS*	1	1	
Rhinitis NOS*	1	1	
Throat Edema*	1	1	
Angioneurotic Edema*	1	1	
Dermatitis Exfoliative*	1		1
Dermatitis NOS Aggravated*	1	1	
Hair Disorder NOS.	1	1	
Purpura NOS*	1		1
Rash Erythematous	1		1
Skin Disorder NOS*	1		1
Sweating Increased	1	1	
Tongue Edema*	1		1
Collapse*	1	1	
Hypotension NOS*	1	1	
Vasculitis NOS*	1	1	

*AEs in the serious reports for those ≥ 12 years and "age unknown." See Table 8.

Comment: No information about causality was provided for the non-serious AE's in Tables 3, 4, and 5.

IBU/PSE Serious Adverse Event Data

The serious outcomes for the IBU/PSE are described in **Table 6 (WHR-GSSE database), Table 7 (SRS database),** and **Table 8 (AERs database).** The most frequently reported serious outcome for IBU/PSE was hospitalization (58 subjects, 14 in the United States). Forty-three of the 53 serious reports in the WHR Database (refer to **Table 2**) were from France where, the sponsor states, there is active national surveillance. Only 2 of the 53 WHR reports were "definitely" related to IBU/PSE use and 8 were "possibly" related. Causality was not available for the serious cases in the SRS or AERs databases or for 27 of the WHR reports. Many cases appear to be confounded by concomitant medications or underlying disorders.

There were 4 reports of death (3 in the AERS database, where the combination product was listed as a secondary suspect drug and 1 from the WHR database). Three death reports were from outside the United States and are confounded by the presence of concomitant medications. Two of the reports of death from the AERS database appear to be about the same consumer. In the WHR Database, the physician, who reported the death in France of a patient who used IBU/PSE, did not believe the death was associated with the product.

There were 3 reports of a drug interaction associated with the use of IBU/PSE. One report in the AERS database was of a patient who required hospitalization. The suspect drug was Lorabid and the combination product was listed as a secondary suspect drug. The other two reports of drug interaction (SRS and WHR databases) were not considered to be serious. One patient took IBU/PSE with fluoxetine. The second patient took IBU/PSE with lithium carbonate 600 mg/day plus fluoxetine 5 mg/day. The reporting physician for this patient thought there was a probable link between increased lithium levels and the IBU/PSE combination product.

There was one serious report of intentional overdose for IBU/PSE in the WHR-GSSE database. That consumer took 8 tablets of the combination product plus 24-30 tables of ES Tylenol. She required a 2-day hospitalization where she was treated with charcoal and Mucomyst. No sequelae were reported. (See **Table 6.**)

Table 6 displays the serious cases for IBU/PSE from the WHR- GSSE database (01/01/89-12/31/00). The original case reports were reviewed.

Table 6. Serious Cases for IBU/PSE from WHR-GSSE (01/01/89-12/31/00)

Nation	Age (Years)	Sex	Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Causal Relationship and (Relevant History)
US	51	M	6 (?*) Tabs/24 hrs	1 Dose	URI	Speech disorder Cerebral ischemia Muscle twitching	H	N/A (Diabetic, Prior Stroke)
US	45	M	2 caplets	1 Dose	URI	Pain NOS Vasodilatation	H, I	N/A (Strep Infection, Multiple Concomitant Medicines)
US	53	M	2 tablets daily	2 Days	URI	Dizziness (exc vertigo) Melena, Peptic Ulcer	H, I	N/A
US	73	M	1 tablet (4 years post expiration date)	1 Dose	Runny Nose Sore Throat	Hypersensitivity NOS	H	Possible
US	45	F	1 tab	1 Dose	URI	Fibrillation, atrial	H	Possible (Prior Atrial Fibrillation, Excessive Caffeine)
US	48	F	4 caplets/day	10 Days	URI	Hemoglobin Thrombocytopenia	L, H	N/A
US	17	F	8 tablets	1 Dose	Intentional Overdose	Non-accidental overdose	H, O	Related (Took 24-30 ES Tylenol®)
US	46	F	2 caplets	1 Dose	Unknown	Hypersensitivity NOS Dyspnea NOS Hypotension NOS	H	Possible (Aspirin Allergy, Asthma)
US	50	F	2 tablets daily	1 Dose	URI	Dyspnea NOS Face edema Eye disorder NOS Glossitis Pain NOS	I	N/A
US	60	F	1 tablet	1 Dose	Sinus Headache	Hypersensitivity NOS Tongue edema Laryngospasm Chest pain Dermatitis	H	N/A (Hyperten-sion, Mitral Valve Prolapse, Multiple Medications)
France	50	M	6 tabs/day	Unknown	URI	Mucous membrane disorder NOS	H	None
France	33	M	8 tabs	1 Day	URI	Myocardial infarction	H	None (Smoker, + Family History, MI Occurred Next Day)
France	52	M	Unknown	Unknown	Allergic rhinitis	Angina pectoris	H	N/A

N/A = Not available; H = Hospitalized; I = Intervention; L = Life threatening; NOS = Not otherwise specified; D = Death; U = Unknown

Table 6 (Continued). Serious Cases for IBU/PSE from WHR-GSSE (01/01/89-12/31/00)

Nation	Age (Years)	Sex	Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Causal Relationship
France	N/A	M	Unknown	5 Days	Unknown	Arterial spasm NOS Hemiplegia	H	N/A (acute alcohol intoxication)
France	15	M	Unknown	Unknown	Unknown	Idiopathic thrombocytopenic purpura	H	Doubtful (Concomitant Medication)
France	35	M	2 tablets twice/day	6 Days	Unknown	Peripheral vascular disease NOS (Arterial Spasm in Leg)	H	Possible (AIDS, Multiple Concomitant Medications)
France	42	M	3 tablets daily	2 Days	Rhinitis and Pharyngitis	Urticaria NOS	I	N/A (Concomitant Medicines)
France	60	M	Unknown	Unknown	Unknown	Angioneurotic Edema	H	N/A
France	59	M	1 tablet	1 Dose	Unknown	Angioneurotic edema	H	N/A (Concomitant Medications)
France	31	M	1 tablet	1 Dose	Unknown	Face edema Urticaria NOS	H	Possible (Allergic to aspirin, topical NSAIDs, Concomitant Medications)
France	33	M	3 daily	5 Days	Rhino-pharyngeal Episode	Renal failure, acute Nephritis NOS	H	N/A (Concomitant medication)
France	18	M	Unknown	Unknown	Rhino-pharyngitis	Idiopathic thrombocytopenic purpura	H	Doubtful (Concomitant Medications)
France	18	M	Unknown	5 Days	Rhino-pharyngitis	Asthenia Thrombocytopenia	H	N/A (Concomitant Medications)
France	36	M	1 Tablet	1 Day	Rhino-pharyngitis	Anaphylactic reaction	L,H	Doubtful (Concomitant Amoxicillin, Allergy to Amoxicillin)
France	37	M	2 Tablets	7 Days	Unknown	Agranulocytosis	H	Doubtful
France	37	M	2 Tablets daily	6 Days	Sore Throat	Agranulocytosis Pyrexia SGOT increased SGPT increased GGT increased	L, H	N/A (Concomitant Medications)
France	28	M	Unknown	3 Days	Unknown	Rash, Lymphadenopathy	H	"Likely" (+ skin test to Rhinadvil, Multiple Drug Allergies, Concomitant Medications)
France	U	F	1 caplet 3 X/day	1 Dose	Influenza	Coma	L, H	None
France	25	F	2 tablets	1 Dose	Rhinitis	Convulsions NOS	H, I, O	N/A
France	63	F	Unknown	4 Days	Unknown	Dysarthria Gastritis NOS Gastric hemorrhage	H	N/A (Concomitant Medication)

N/A = Not available; H = Hospitalized; I = Intervention; L = Life threatening; NOS = Not otherwise specified; D = Death; U = Unknown; O = Other

Table 6 (Continued). Serious Cases for IBU/PSE from WHR-GSSE (01/01/89-12/31/00)

Nation	Age (Years)	Sex	Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Causal Relationship
France	N/A	F	3 tablets daily	1 Week	Unknown	Diplopia (persisted after medicine stopped)	A	N/A
France	N/A	F	Unknown	Unknown	Rhinitis	Renal failure, acute Hepatic necrosis Dermatitis Disseminated intravascular coagulation Sepsis, Staphylococcal Thrombocytopenia Hemorrhagic stroke	D, H	None (Concomitant medicines)
France	57	F	3 tablets	1 Day	Influenza Sinusitis	Convulsions NOS Stupor	L, H	N/A (Hypertension,concomitant medications, underlying cerebrovascular disease)
France	21	F	Unknown	10 Days	Tonsillitis	Pruritus NOS Rash, papular	H	Possible (Concomitant Medication)
France	49	F	1 tablet	1 Dose	Acute Rhinitis	Asthma NOS	L, H, I	N/A
France	38	F	1 tablets	1 Dose	Sore Throat	Angioneurotic edema Dermatitis NSO	H, O	N/A (Concomitant Medication)
France	23	F	400 mg/60 mg daily	24 Days	Rhinopharyngitis	Gingival bleeding Thrombocytopenia	H	N/A (Concomitant Medication)
France	61	F	3 tablets daily	1 Dose	Acute Nasopharyngitis	Edema NOS Pyrexia Rash, papular	H	"Believed to be related" (Concomitant Medications)
France	21	F	1 tablet 3 x Daily	2 Days	Acute rhinitis Pharyngitis	Rash, papular	H	N/A (Allergic Urticaria, Concomitant Medicines)
France	45	F	3 tablets/day	7 Days	Rhinitis	Rash, papular	H	Doubtful (Atopy, Asthma, Concomitant Medications)
France	54	F	2 tablets/day	7 days	Sore throat Ear pain	Face edema Pruritis NOS Rash papular Syncope	H	Possible (Concomitant Medications)
France	27	F	2 tablets	1 day	Unknown	Angioneurotic edema	H	Doubtful
France	48	F	3 tablets/day	8 Days	Unknown	Vascular purpura	H	Doubtful (Concomitant Medications)
France	39	F	1 Dose	1 Dose	Acute Bronchitis	Malaise Tachycardia NOS	H	N/A (Chronic Bronchitis, Peptic Ulcer, Tachycardia, Concomitant Medication)

N/A = Not available; H = Hospitalized; I = Intervention; L = Life threatening; NOS = Not otherwise specified; D = Death; U = Unknown; O = Other

Table 6 (Continued). Serious Cases for IBU/PSE from WHR-GSSE (01/01/89-12/31/00)

Nation	Age (Years)	Sex	Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Causal Relationship
France	36	F	1 Dose	2 Days	Unknown	Bradycardia NOS Dizziness (exc vertigo) Dyspepsia Pruritis NOS Acute circulatory failure Urticaria NOS	L	Possible (Concomitant amoxicillin)
France	16	F	2 Tablets	1 Day	Headache	Edema NOS Pruritis NOS Dermatitis NOS Urticaria	H	N/A (Concomitant Medications)
France	32	F	Unknown	1 Day	Influenza	Angioneurotic edema	H	N/A (Concomitant Medications)
France	27	F	3 tablets/day	4 Days	Rhinitis	Pyrexia Pruritis NOS Dermatitis NOS Rash, papular	H	Doubtful
France	52	F	3 tablets	2 days	Rhino-pharyngitis	Pruritis NOS Dermatitis NOS Rash, papular	H	Possibly (Recurrent Urticaria, Concomitant APAP)
France	34	F	1 tablet twice daily	2 Doses	Unknown	Anaphylactic reaction Diarrhea NOS Vomiting NOS	H	N/A (Concomitant Medications)
France	22	U	3 Tablets	6 Days	Unknown	Dysura Asthenia Loss of consciousness Malaise Stiff neck Rash, morbillform	H	N/A (Systemic Lupus Erythema-tosus)
France	N/A	U	Unknown	Unknown	Unknown	Dermatitis NOS	H	"Doubtful" (Prior Similar Reaction to Advil)
France	U	U	Unknown	4 Days	Fever Cough	Erythema multiforme Pruritis NOS Vascular purpura Rash, pustular	H	Likely

N/A = Not available; H = Hospitalized; I = Intervention; L = Life threatening; NOS = Not otherwise specified; D = Death; U = Unknown; O = Other

The sponsor did not provide separate data about pregnancy, abuse, overdose, or long-term use from the WHR-GSSE database for IBU/PSE.

Table 7 lists the patients with serious outcomes reported in the FDA SRS database (excluding the WHR and GSSE data) from 01/01/89 – 10/31/97 who took IBU/PSE. There were 3 serious cases and all occurred in subjects ≥ 12 years of age. No assessment of causality was provided, and there is no information about duration of use or indication. There were no fatalities.

Table 7. Serious Cases for IBU/PSE in the FDA SRS Database (01/01/89 – 10/31/97)

Nation	Age in Years	Sex	Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Causal Relationship
US	30	F	N/A	Unknown	Unknown	Syncope Hyperventilation Convulsion Anxiety	H	N/A
US	48	F	4 tablets	Unknown	Unknown	Thrombocytopenia Hemorrhage	H, L	N/A
US	32	F	1*	Unknown	Unknown	Purpura, thrombocytopenic Eosinophilia	H, I	N/A

N/A = not available; H = hospitalized; I = intervention; L = life threatening
* No additional information provided

There were no reports of death, drug overdose, abuse, or reports associated with pregnancy in the SRS database for IBU/PSE. The sponsor recorded that here were 3 patients who experienced serious AEs associated with long-term use. It is not clear if these are the 3 patients reported in the table above where the duration of use is unknown.

Table 8 lists the serious cases for IBU/PSE in FDA AERS database (11/01/97 – 9/30/00) for subjects ≥ 12 years of age and subjects of unknown age. There were 13 reports listed in AERS; the sponsor provided details about eleven.

There were 2 deaths in the group 12 years and older. The sponsor states that these reports may have been describing the same patient. The MedDRA primary terms describing both of these 60-year-old patients were "Gastrointestinal hemorrhage," "Hemorrhage NOS," and "Intestinal ulcer." "Rhinitis NOS" was listed as an AE for one of the two reports. There was one non-fatal overdose reported in the AERS database for this age group with IBU/PSE.

For consumers of "age unknown" there was one death. That patient had the following MedDRA Primary Terms to describe adverse events: disseminated intravascular coagulation; thrombocytopenia; hepatocellular damage; gram stain positive; brain herniation; hemorrhagic stroke; renal failure, acute; dermatitis, exfoliative NOS; and purpura NOS. There is no information about the age, sex, dose, duration of use, indication, concomitant medications, medical history or causal relationship between the drug and AEs in this patient. No conclusion about causality can be determined. (See **Table 8**.)

Table 8. Serious Cases for IBU/PSE in FDA AERS (11/01/97 – 9/30/00).

Nation	Age in Years	Sex	Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Causal Relationship
US	U	F	1 Caplet	U	N/A	Paresthesia Vasodilatation Face edema Dyspnea NOS Cough Anaphylactoid reaction Drug interaction NOS Vomiting NOS	H	N/A
US	U	F	2 Tablets	2 Days	N/A	Dysphagia Skin disorder NOS Pruritus Pain in limb Esophageal disorder NOS Edema, upper limb Edema NOS Lack of spontaneous speech Dyspnea NOS Tongue disorder NOS Tongue edema Infection NOS	I	N/A
US	49	F	2 Caplets twice daily	U	N/A	Pruritis Hypersensitivity NOS Syncope Throat edema Urticaria NOS Feeling jittery Myocardial infarction Vision blurred Accidental overdose (therapeutic agent) Sedation Face edema Anaphylactic shock Collapse Dizziness (exc vertigo) Drug level NOS changed Dyspnea NOS Electrocardiogram abnormal (NOS)	L	N/A
US	35	F	200 mg/dose	U	N/A	Accidental overdose (therapeutic agent) Depressed level of consciousness	H, I	N/A
Foreign	36	M	U	1 Day	N/A	Dyspnea NOS Face Edema Arterial Pressure NOS decreased	L	N/A
Foreign	60*	M	U	N/A	N/A	Gastrointestinal hemorrhage NOS Intestinal ulcer Rhinitis NOS	H, D	N/A
Foreign	60*	M	3/day	6 Days	N/A	Gastrointestinal hemorrhage NOS Intestinal ulcer	D	N/A
Foreign	36	F	U	2 days	N/A	Vertigo, NEC Abdominal pain, upper Bradycardia NOS Dyspepsia Hypotension Pruritis Urticaria NOS	H, L	N/A

*Likely the same case

NOS = Not otherwise specified; U = Unknown; H = Hospitalization; D = Death; L = Life Threatening; N/A = Not available

Table 8 (Continued). Serious Cases for IBU/PSE in FDA AERS (11/01/97 – 9/30/00).

Nation	Age in Years	Sex	Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Causal Relationship
Foreign	39	F	1 unit/day	1 day	N/A	Anxiety Malaise Sinus tachycardia	H	N/A
Foreign	35	F	1 tablet	U	N/A	Dermatitis, atopic Hypersensitivity NOS Palpitations Pruritus	I	N/A
Foreign	U	U	U	U	N/A	Dermatitis, exfoliative Brain herniation Renal failure, acute Purpura NOS Hepatocellular damage Hemorrhagic stroke Gram stain positive Disseminated intravascular coagulation Thrombocytopenia	H, D	N/A

NOS = Not otherwise specified; N/A = not available; H = hospitalized; I = Intervention; D = death; U = unknown

There were 2 cases of accidental overdose listed among the serious reports in **Table 8**. It is unclear, from the reported information, why they were categorized that way.

OTC IBU/PSE is indicated for up to 7 days. The AERS Database contained 30 total reports of adverse events associated with long-term use of IBU/PSE, 4 of which were serious, in those at least 12 years of age. For the "age unknown" category there were 32 reports, 2 of which were serious (one death), associated with long-term use. There were no reports associated with pregnancy or drug abuse for IBU/PSE in the AERs Database.

Serious AE Reports on Concomitant Use of Single Ingredient IBU and PSE

There were two serious reports in the WHR-GSSE database associated with concomitant use of IBU and PSE single products.

- A 21-year-old female from France took 5 days of an unknown dose of Advil, an unknown quantity of Sudafed for an unknown duration of time, and had a Hepatitis B vaccine. She required hospitalization when she developed aplastic anemia, purpura and a "mucous membrane disorder." There was no assessment of causal relationship available and the final outcome was not provided.

- A 15-year-old female took one dose of Advil, one dose of CoTylenol, and 2 doses of Sudafed over a 2-day period for nasal congestion and diarrhea. She experienced cerebral edema, diarrhea and a cardiac arrest and died. There is no further information about this patient, so causality cannot be determined.

In the SRS database there were 8 serious reports of concomitant use IBU and PSE. These are described in **Table 9**. One patient died, but it is unclear if this death was causally related to the use of either product.

Table 9. Serious Cases for Concomitant Use of IBU and PSE Single Ingredient Products in FDA SRS (01/01/89 – 10/31/97)

Nation	Age in Years	Sex	Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Causal Relationship
US	71	M	Advil – U Sudafed 2 TB	U 3 Days	N/A	Hypertonia No drug effect Syncope	H	N/A
US	15	F	Advil 400 mg Sudafed - U	U U	N/A	Brain syndrome, acute Edema, brain Heart arrest NPN inc	D, H	N/A
US	19	F	Advil - U PSE - U	1 Day 1 Day	N/A	Overdose, intentional	H	N/A
US	68	F	Nuprin 400mg Sudafed	U U	N/A	Gastritis Hematemesis Melena	H	N/A
US	36	F	Advil – U Sudafed 2 TB	U U	N/A	Syncope	H	N/A
US	40	F	IBU – U PSE – U	U U	N/A	Arrhythmia Coma Diabetes insipidus Overdose, intentional	H	N/A
US	36	F	IBU – U Sudafed – U	U U	N/A	Agranulocytosis LE syndrome Pain Stomatitis	H	N/A
Foreign	21	F	IBU – U Sudafed – U	6 Days 6 Days	N/A	Fever Infection, super Marrow depression Pancytopenia Cough increase Pharyngitis	H	N/A

N/A = not available; H = hospitalized; D = death; U = unknown dose or duration of dose where applicable

Table 10 displays the serious cases for concomitant use of single agent IBU and single agent PSE in the FDA AERS database from 11/01/97 to 9/30/00. There were no deaths among these cases.

Table 10. Serious Cases for Concomitant Use of Single Agent IBU and PSE in FDA AERS (11/01/97 – 9/30/00)

Nation	Age in Years	Sex	Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Causal Relationship
US	36	M	IBU 22400 mg PSE 12 tablets***	1 Day	N/A	Vomiting NOS Hyperkalemia Hypoventilation Mydriasis Myoglobinuria Overdose NOS Respiratory rate increased Sedation Convulsions NOS Tachycardia NOS Acidosis NOS Electrocardiogram (EKG) ST segment depression EKG T-wave inversion Blood creatine phosphokinase increased	H	N/A
US**	U	F	U	73 days for both IBU and PSE	N/A	Atrial fibrillation Sinusitis NOS Tachycardia NOS	H	N/A
US**	U	F	U	73 days for both IBU and PSE	N/A	Tachycardia NOS Atrial fibrillation Sinusitis NOS	H	N/A
US	42	F	IBU PSE	1 Day Both	N/A	Bronchospasm NOS Uterine fibroids Urticaria NOS Tachycardia NOS Anxiety Serotonin syndrome Ovarian cyst Polyuria Arrythmia NOS Panic disorder Chest pain Drug interaction NOS Fatigue Flushing Hypersensitivity NOS Influenza like illness Intermenstrual bleeding Mouth ulceration Muscle cramps Myoclonic jerks	H	N/A
US	U	F	IBU Sudafed	72 Days Both	N/A	Atrial fibrillation	H	N/A
US	21	F	Motrin 200 mg PSE 150 mg	U	N/A	Accidental overdose (therapeutic agent) Mental impairment NOS	H, I	N/A
Foreign	42	M	Advil Sudafed	U	N/A	Aplastic Anemia Mucous membrane disorder NOS Purpura NOS	H	N/A

**Likely the same case. ***Dose unknown

No conclusion about causality in the SRS and AERS concomitant use serious AE cases can be drawn because of incomplete information about total doses of medication used and/or duration of therapy, concomitant therapy and underlying medical conditions.

IBU Single Ingredient Adverse Event Data

This section contains a review of AE data for IBU as a single agent from the SRS, WHR-GSSE, and AERS databases. The data was presented as tables of adverse events, tables enumerating the number of reports from each type of reporting source (health professional, non-health professional, and not specified), and tables listing numbers of subjects. These tables were not integrated so it was difficult, for example, to discern how many subjects were represented by the number of reports.

Table 11 displays the summary of total reports, deaths, and hospitalizations for ibuprofen as a single ingredient received by SRS, and WHR.

Table 11 (See *Comment* below). Summary of SRS and WHR Data for IBU as a Single Ingredient.

	All Spontaneously Reported Events	Serious AEs	Serious AEs OD	Reports of Deaths	Reports of Hospitalizations
Age ≥ 12 years					
SRS*	11342	6079	509	198	1766
WHR (8/1/1989 – 12/31/2000)	3264	630	78	11	238
Age Unknown					
SRS*	4746	724	45	55	231
WHR (8/1/1989 – 12/31/2000)	569	62	2	2	27

*Excludes WHR Supplied Reports. The number of serious AEs exceeds the number of reports.
** OD = overdose

SRS AE data for IBU Single Ingredient

Table 12 (See Appendix I) is a listing of serious AEs for those age ≥ 12 years and those "age unknown" from the SRS Database for single ingredient IBU in COSTART Terms.

Table 13 (See Appendix I) lists the AEs associated with fatalities for those age ≥ 12 years and those "age unknown" from the SRS Database for single ingredient IBU in COSTART Terms. There were 253 reports of death for both populations combined, yet, the sponsor provided a demographics table of fatalities that shows 47 patients died.

Comment: The sponsor's fatalities table may be mislabeled because it appears to be identical to a table that reports the number of patients who experienced a drug interaction.

In the SRS database there were 12 reports of serious outcome (2 deaths) associated with IBU use in pregnancy for those at least 12 years of age and 27 (10 deaths) in the "age unknown" group. It is unclear if all deaths were fetal deaths, however 2 stillbirths and 4 abortions were reported in the former group and 4 stillbirths and 6 abortions reported in

the latter. It is unclear if the abortions were spontaneous or induced. Among the 74 pregnancy adverse events reported for both age categories, 25 reports were of congenital anomaly. This was the most common serious pregnancy adverse event reported.

In the SRS database, there were 142 serious overdoses in people ≥ 12 years, of which 19 were associated with fatality. There were 14 serious overdoses in the "age unknown" population, 4 of which were associated with fatality. There were 3 reports of serious outcome from abuse in the population over 12 years of age and none in the "age unknown" category (which corresponds with a total of 3 patients who abused IBU).

The SRS data for IBU reveals 41 reports of serious outcomes from drug interaction (3 reports of death) in people at least 12 years of age. There were 6 such reports of drug interaction (3 reports of death) in those "age unknown." These reports were from 47 people, but the specific drug interaction information was not provided.

SRS data for long-term IBU use contains 1535 reports of serious outcomes of which 153 are reports of deaths in people at least 12 years of age. There were 244 reports of serious outcomes with 50 reports of deaths for those "age unknown."

WHR-GSSE AE data for IBU Single Ingredient
Table 14 (See Appendix I) lists serious AEs in the WHR-GSSE Database for IBU.

Adverse events associated with fatalities from the WHR Data (single ingredient IBU) are listed in **Table 15.**

Table 15. Adverse Events Associated With Fatalities in Subjects ≥ 12 Years of Age and Age Unknown from the WHR Database (Single Ingredient IBU) – COSTART Terms

COSTART Body System Category	Adverse Event	Total Events	AE in Subjects ≥ 12
Body as a Whole	Allergic reaction	1	1
	Asthenia	1	1
	Death	3	3
	Fever	1	1
	Reaction Unevaluable	1	0
Cardiovascular System	Hemorrhage, Intracranial*	1	1
Digestive System	Hemorrhage, Gastrointestinal	2	1
	Hemorrhage, Gum	1	1
	Hemorrhage, Rectal	1	1
	Hepatitis	1	1
	Jaundice	1	1
	Liver Damage	1	1
	Melena	1	1
	Nausea, Vomiting	1	1
	Ulcer, Duodenal Hemorrhage	1	1
	Ulcer, Stomach	1	0
Hemic and Lymphatic	Ecchymosis	1	1
	Purpura	1	1
	Thrombopenic purpura	3	3
Metabolism and Nutrition	Hyperkalemia	1	1
Nervous System	Central Nervous System Depression	1	1
	Coma	1	1
	Encephalopathy	1	0
	Intracranial Hemorrhage*	2	2
	Meningism	1	1
Respiratory System	Dyspnea	1	1
	Epistaxis	1	1
Skin and Appendages	Rash	1	1
Urogenital System	Kidney Failure	1	1
	Kidney Failure, Acute	1	1

* This AE was listed under both cardiovascular and nervous systems. It is unclear if the total AEs numbered 3 or whether 2 AEs were in the same person.

In the WHR data indicated that there were 11 reports of fatalities in the ≥ 12 years group and 3 reports for those "age unknown." There were 14 total fatalities.

There were 26 reports of serious outcomes associated with overdose in the ≥ 12 years group and 2 for those in the "age unknown" group. There were 1 death and 25 hospitalizations from overdose. There were 2 suicide attempts. The sponsor states that there were 3 reports of drug interactions, the specifics of which were not provided.

Among the WHR cases, there were 11 reports of serious outcomes associated with long-term use (2 deaths) in the ≥ 12 years group and 19 reports (2 deaths) for those "age unknown."

The WHR database did not present data about serious outcomes associated with use in pregnancy or with IBU abuse.

AERS AE Data for IBU Single Ingredient
Table 16 shows AERS Data for IBU as a single drug.

Table 16. AERS Data for IBU (11/01/1997 – 9/30/2000)

	# Total Reports	# Serious Reports	# Serious Reports OD	Deaths	# Serious Abuse Reports	# Serious Reports Associated with Pregnancy
Age ≥ 12 years						
AERS	1053	605	51	93	4	2
(IBU 1°Suspect Drug)	(758)	(392)	(25)	(54)	4	0
(IBU 2° Suspect Drug)	(295)	(213)	(26)	(39)	0	2
Age Unknown						
AERS	385	120	5	7	None Reported	2
(IBU 1°Suspect Drug)	(316)	(78)	(1)	(3)		1
(IBU 2° Suspect Drug)	(69)	(42)	(4)	(4)		1

Table 17 (See Appendix I) lists serious AEs for IBU as single drug in the AERS Database.

Table 18 (See Appendix I) lists all adverse events from the AERS Database (in MedDRA Primary Terms) associated with the outcome of death for IBU as a primary or secondary suspect drug for those ≥ 12 years of age and "age unknown." There were 100 deaths.

As **Table 18** demonstrates, the most common adverse events reported for IBU as a single drug from the AERS Database where the outcome was death were: completed suicide, non-accidental overdose and hemorrhage in the gastrointestinal tract.

In AERS there were 62 patients who overdosed, and a total of 56 serious overdose reports. There were 21 reports of death among these and 17 reports of completed suicide related to overdose.

Sixteen people experienced drug interactions (12 in the group at least 12 years of age). There was one associated death in which ibuprofen was the primary suspect drug. The patient appears to have had a gastrointestinal hemorrhage and renal failure. The specific drug interactions were not provided.

Among the 4 serious abuse reports were 2 reports of deaths. There were 2 reports of "alcoholism" and one of "medication error" among the 18 adverse events mentioned for these 4 reports. All abuse cases were in the group over 12 year of age.

Four women experienced serious pregnancy outcomes. Two had spontaneous abortions. A 3rd woman had a premature delivery associated with an infection. The 4th patient was described by the MedDRA Term "unevaluable reaction."

There were 828 serious and non-serious reports in the AERS Database for those at least 12 years of age who used IBU long-term (335 serious reports where IBU was the primary suspect drug and 144 where it was the secondary suspect drug). Among these reports were 79 deaths. For "age unknown" there were 358 total serious and non-serious reports in the database for those at least 12 years of age who used ibuprofen long-term (73 serious where IBU was the primary and 38 serious where it was the secondary suspect drug). Among these were 6 reports of deaths.

Comment: Among the long-term use reports for the different databases may be patients who took either prescription strength ibuprofen or OTC strength ibuprofen. OTC ibuprofen 200 mg is indicated for 3 days for fever and 10 days for pain unless directed by a doctor. It is unclear whether subjects in this data set were using the OTC product and if so, if they were using it under the direction of a doctor for an off label therapy.

PSE Single Ingredient Adverse Event Data

This section contains a review of AE data for PSE as a single agent from the SRS, WHR-GSSE, and AERS databases. The data was presented as tables of adverse events, tables enumerating the number of reports from each type of reporting source (health professional, non-health professional, and not specified), and tables listing numbers of subjects. These tables were not integrated so it was difficult, for example, to discern how many subjects were represented by the number of reports.

Table 19 lists the number of serious adverse events associated with overdose from the SRS and WHR databases for PSE as a single ingredient.

Table 19. Summary of SRS and WHR Data for PSE as a Single Ingredient.

	Total Spontaneously Reported Events	Serious AEs	Serious AEs OD**	Reports of Deaths	Reports of Hospitalizations
Age ≥ 12 years					
SRS*	968	409	75	25	95
WHR (8/1/1989 – 12/31/2000)	13	2	No Data Provided	0	1
Age Unknown					
SRS*	1005	140	45	7	37
WHR (8/1/1989 – 12/31/2000)	11	No Data Provided	No Data Provided	No Data Provided	No Data Provided

*Excludes WHR Supplied Reports. The number of serious AEs exceeds the number of reports.
** OD = overdose

There were 3 reporter categories (health professional, consumer, not specified). It is possible, therefore, for the same subject to be reported by more than one reporter.

There were no tables listing serious AEs, overdoses, deaths, or hospitalizations for the "age unknown" category for the WHR database. (It is unclear whether none were reported or whether this data was not submitted.)

SRS AE Data for PSE Single Ingredient

Table 20 (See Appendix II) is a tabulation of serious AEs in the SRS Database for those ≥12 years of age and of "unknown age."

Table 21 is a tabulation of the spontaneously reported fatal events in the FDA SRS Database for the ≥ 12-year-old age group and subjects of unknown age. As **Table 19** shows there were 25 reports of death in the ≥ 12-year-old group and 7 in the "age unknown" group (refer to **Table 19**).

Table 21. Fatal Events from the SRS Database Associated with PSE Use for the ≥ 12-Year-Old Age Group and Subjects of Unknown Age.

Body System Category	Fatal Event	Number Fatal AE	Fatal AE in Those ≥12
Body as a Whole	Death	4	2
	Drug Interaction	3	3
	Edema Face	1	1
	Headache	1	1
	Overdose Accidental	3	2
	Overdose, Intentional	1	1
	Pain, Abdominal	2	1
	Pain, Back	1	1
	Pain, Neck	1	1
	Reaction Aggravation	1	1
	Sepsis	1	1
	Sudden Death	3	3
Cardiovascular System	Angina Pectoris	1	0
	Arrhythmia	3	2
	Cardiomegaly	1	1
	Cardiovascular Disorder	1	1
	Fibrillation, Atrial	1	0
	Fibrillation, Ventricular	2	2
	Heart Arrest	6	6
	Hemorrhage	1	0
	Hemorrhage, Subarachnoid	1	1
	Hypertension	1	1
	Infarct, Myocardial	5	5
	Tachycardia	1	1
Digestive System	Hematemesis	1	1
	Hepatitis	1	0
	Liver, Fatty	3	0
Hemic and Lymphatic	Coagulation Disorder	1	1
	Cyanosis	1	1
Metabolic and Nutritional	Cyanosis	2	2
Nervous System	Aphasia	1	1
	Brain Syndrome, Chronic	1	1
	Coma, Convulsion	3	3
	Convulsion	2	2
	Drug Dependency	1	1
	Encephalopathy	1	1
	Hemorrhage, Subarachnoid	2	2
	Hypertension	2	2
	Stupor	1	1
Respiratory	Dyspnea	1	1
	Edema, Lung	2	2
	Hemorrhage, Lung	1	1
	Pneumonia	1	1
Skin and Appendages	Epidermal Necrolysis	1	1
	Stevens Johnson Syndrome	1	1
	Sweating	1	1
Urogenital System	Birth, Premature	1	0
	Stillbirth	1	0

For the drug interaction category there were 3 reports of death. The drugs with which PSE may have had an adverse interaction are not provided. There were 18 reports in the ≥ 12 category of an overdose of PSE (See **Table 20**).

There were 3 subjects who abused PSE. Two were hospitalized (age unknown category) and one died (≥ 12 years category). The causes of death and hospitalization were not specifically provided for these 3 subjects and it is unclear whether they were listed among those who overdosed.

The sponsor provided a demographics table for reports associated with pregnancy in which they listed no patients. Yet, there was one premature birth and one stillbirth reported among the fatalities associated with PSE use.

The sponsor provided a table from the SRS database for long-term use of PSE that listed 17 reports of death in the ≥ 12-year-old age group. However, there were only 3 deaths listed for this age category in the sponsor's table of adverse events for long-term use.

WHR-GSSE Data for PSE Single Ingredient

The 2 serious adverse events in the WHR Database in the ≥ 12-year-old age group (refer to **Table 19)** were atrial fibrillation and tachycardia.

AERS AE Data for PSE

The FDA AERS Database for Single Agent PSE is summarized in **Table 22.**

Table 22. AERS Data for PSE (11/01/1997 – 9/30/2000)

	# Total Reports	# Serious Reports	# Serious Reports OD	Deaths	# Serious Abuse Reports	# Serious Reports with Pregnancy
Age ≥ 12 years						
AERS	236			8		
(PSE 1°Suspect Drug)	(191)	(33)	No Data Provided	(3)	No Data Provided	(1)
(PSE 2° Suspect Drug)	(45)	(25)	(4)	(5)	(1)	
Age Unknown						
AERS	180			3		
(PSE 1°Suspect Drug)	(167)	(6)	No Data Provided	(2)	No Data Provided	
(PSE 2° Suspect Drug	(13)	(7)	(1)	(1)	No Data Provided	(1)

Serious AEs in the AERS database for single ingredient PSE for ages ≥ 12 years and "age unknown" are displayed in **Table 23 (See Appendix II).** For subjects ≥ 12 years there were 58 serious reports of which 33 listed PSE as the primary suspect drug and 25 listed PSE as the secondary suspect drug. For those "age unknown" there were 6 reports. The most common serious events were headache, cardiac arrythmias (multiple types), drug interaction, convulsions, skin rashes (various types including 1 report of Stevens Johnson Syndrome), vomiting, and urinary retention.

Adverse Events in the AERS database associated with the outcome of death for single ingredient PSE for those ≥ 12 years of age and "age unknown" are listed in **Table 24.**

Table 24. Reports of Adverse Events Associated with the Outcome Death for PSE for Ages ≥ 12 Years and "Age Unknown" in AERS Database

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Cardiac Disorders	Cardiac Arrest	1	1
	Pulse Absent	1	1
Ear and Labyrinth Disorders	Earache	1	1
Eye Disorders	Eye Rolling	1	1
Gastrointestinal Disorders	Vomiting NOS	1	1
General Disorders and Administration	Condition Aggravated	1	1
	Difficulty in Walking	1	1
	Drug Interaction	2	1
	Hyperpyrexia	1	1
	Influenza-like Illness	1	1
	Pyrexia	1	0
	Sickness	1	0
Injury and Poisoning	Accidental Overdose (Therapeutic Agent)	1	1
	Alcohol Intoxication Acute	1	1
	Heat Stroke	1	0
	Medication Error	1	1
	Non-Accidental Overdose	1	0
	Vascular Injury NOS	1	1
Investigations	Drug Level NOS above Therapeutic	1	1
Metabolism and Nutrition Disorders	Hyponatremia	1	0
Musculoskeletal, connective tissue and bone disorders	Posture Abnormal	1	1
Nervous System Disorders	Cerebral Edema	2	1
	Cerebrovascular Accident NOS	1	1
	Coma	3	3
	Convulsions NOS	1	1
	Coordination Abnormal NOS	1	1
	Headache NOS	1	1
	Headache NOS Aggravated	1	2
	Hemiparesis	1	1
Psychiatric Disorders	Completed Suicide	1	1
Renal and Urinary Disorders	Urinary Incontinence	1	1
Respiratory, Thoracic and Mediastinal Disorders	Apnea	1	1
Vascular Disorders	Cerebral Arterial Aneurysm	1	1
	Cerebral Artery Thrombosis	1	1
	Cerebral Ischemia	1	1
	Collapse	3	3
	Peripheral Coldness	1	1
	Subarachnoid Hemorrhage NOS	1	1
	Thrombosis NOS	1	1
	Venous Stasis	1	1

There were a total of 11 fatalities (3 female, 8 male) to which the AEs in **Table 24** apply.

In the AERS database, there were 7 subjects for which there were reports of drug interaction, one of which was serious where PSE was the primary suspect drug. That subject developed hypertension and a headache.

The sponsor stated that the total number of overdose cases associated with PSE in the AERS database was 7, but provided data for 5 reports. There was one overdose-associated fatality.

Adverse events associated with PSE and pregnancy were described in 2 patients. One patient had an abortion. The type of abortion was not specified. The AERS database MedDRA terms describing the adverse events associated with PSE (as a secondary suspect drug) in the other pregnant patient were a description of problems in the baby. They were: Cardiac murmur NOS, Ventricular Septal Defect NOS, Congenital Heart Disease NOS, Congenital Spleen Anomaly NOS, Multiple Congenital Abnormalities NOS, Situs Inversus, and Complications of Maternal Exposure to Therapeutic Drugs.

In the AERS database, 42 patients experienced serious side effects associated with long-term use of PSE. There were 7 deaths associated with long-term use in those ≥ 12 years and 2 deaths for those in the "age unknown" group.

C. Literature

The following papers pertaining were submitted by the sponsor from their literature search about safety information of IBU/PSE in the ≥ 12 years population.

1. Aselton P, Jick H, Milunsky A, et al: First-Trimester Drug Use and Congenital Disorders. Obstet Gynecol 1985;65:451-455.

This study determined the prevalence of certain congenital disorders (e.g., undescended testicle, congenital heart disease, chromosome disorders) among live-born infants of 6,509 mothers in a prepaid health plan that used a wide variety of drugs during the first trimester of pregnancy. Among these drugs was PSE. The study included all live born infants whose mothers had been members of the plan for at least 280 days before delivery. All infants with disorders that could, in principle, be drug induced that were diagnosed at or around the time of birth were identified from hospital discharge files.

Results:

Among the 6,509 women there were 105 (1.6%) who delivered an infant with one of the specified congenital disorders. Neither IBU nor PSE were associated with an increased prevalence of congenital disorders. Ongoing follow-up now encompasses 13,346 live births. There was no strong positive association with any of the drugs studied. The authors noted that the data on most of the drugs, although insufficient to rule out a modest association, do rule out a strong association with many commonly used drugs.

2. Dakovic-Svajcer K, Maksimovic D, Janosevic LJ: Ibuprofen-pseudoephedrine combination. Eur J Clin Pharmacol 1997;52(Suppl):A121.

This is a 2 paragraph long abstract describing two multicenter, randomized, double-blind, placebo-controlled clinical studies to evaluate efficacy and safety of IBU/PSE (Defrinol) in patients with acute or chronic nonbacterial nonallergic inflammations of the upper airways (Study 1) and bacterial inflammations of the upper airways (Study 2). Eighty of 140 outpatients were given 1 tablet of Defrinol or placebo every 6 hours for 5 days; sixty patients with sinusitis or otitis media received Defrinol plus an antibiotic or placebo plus an antibiotic every 8 hours for 10 days. Data about subjective symptoms and rhinomanometric evaluations was collected. The authors concluded that Defrinol was a safe and effective treatment of nonbacterial nonallergic inflammation of the upper airways. They also concluded that Defrinol plus an antibiotic was effective in the treatment of bacterial inflammation of the paranasal sinuses.

Comment: This submission cannot be critically evaluated because important information (study design details, types and number of side effects, patient population assessed, etc.) about each study is not provided.

3. Furey SA, Theoden WR, Greene JJ, et al. Side effect profile of ibuprofen with pseudoephedrine in upper respiratory tract infection. J Clin Pharmacol 1996;36(9):857.

This submission is an abstract summarizing a double-blind, multiple dose, randomized, actual-use trial in people with upper respiratory infections. The investigators evaluated the safety profile of the combination of ibuprofen 200 mg with pseudoephedrine 30 mg

(N = 294) compared with acetaminophen 500 mg plus pseudoephedrine 30 mg (N = 296) and placebo (N = 146). Participants were instructed to take 1-2 capsules every 4 – 6 hours, up to 6 capsules daily as needed, for up to 10 days. On each day of dosing, participants recorded the presence of "anything unusual," which they considered may have been related to the study medication. Overall, the frequency of adverse effects was described as being similar among groups (no statistically significant differences).

Comment: Specific adverse events were not mentioned in the abstract.

4. Neilson GL, Sorensen HT, Larsen H, Pedersen L: Risk of Adverse Birth Outcome and Miscarriage in Pregnant Users of Non-Steroidal Anti-Inflammatory Drugs: Population Based Observational Study and Case-Control Study. BMJ 2001, 322:266-270.

This is a population based cohort study and case-control study both based on data from a prescription registry, the Danish birth registry, and one county's hospital discharge registry.

Cohort Study: One thousand four hundred sixty-two pregnant women who, the authors state, had picked up prescriptions for non-steroidal anti-inflammatory drugs (NSAIDS) at the pharmacy in the period from 30 days before conception to birth and 17,259 pregnant women who were not prescribed any drugs during miscarriages.

Case-Control Study: Four thousand two hundred sixty-eight women who had miscarriages, of whom 63 had taken NSAIDS, and 29,750 primiparous controls who had live births.

The main outcome measures: Incidence of congenital abnormality, low birth weight, preterm birth, and miscarriage.

Results: Ibuprofen was one of several NSAIDS prescribed to or used by the women. There was no significant association between "take-up" of prescriptions for NSAIDS during pregnancy and risk of congenital abnormality, low birth weight or preterm birth. There was, however, a significant association with miscarriage.

Comment: There was no specific information about compliance with the different NSAID prescriptions, only that they were "taken up" and paid for in part by the patients. The article does not specify whether ibuprofen itself caused miscarriage. The reasons for prescribing NSAIDS were not provided.

5. Oliver SD, Rees TP, Daniel RJE: Pharmacokinetics and Clinical Activity of a Soluble Combination of Ibuprofen and Pseudoephedrine. Eu J Clin Res 1996;8:269-280.

This article reports 3 studies (a bioavailability study , an efficacy study and a tolerability study) of a new soluble formulation of 60 mg pseudoephedrine and 400 mg ibuprofen in volunteers and in patients with symptoms of severe common cold or influenza-like illness. The tolerability study is reviewed here.

The objective of the tolerability study was to assess the tolerability of the soluble formulation in patients with severe common cold and influenza-like symptoms. The medication as taken 3 X /day for 2 days, followed by an early morning dose on the third day. Patients were instructed not to take any other cough/cold preparations or pain-killers during the study.

Study Design:
Ninety-one patients aged 18-70 years old were recruited to this open label, single treatment, multicenter study. Each was given a diary on Visit 1 (the initial assessment) in which to record the time at which the medication was taken and the incidence of any adverse events. The investigator evaluated the diary at Visit 2 (3rd day of treatment). Adverse events were summarized by body system, severity, and relationship to the formulation.

Results:
No serious events were reported. However, 8 (9%) patients failed to complete the 3-day study due to personal reasons or unwanted effects (nausea). Fifty-three patients (63%) reported no adverse events during the study period. The remaining 34 patients (37%) reported adverse events (66 reports). Of these, 14 patients reported 20 events "probably" related to the soluble formulation and 17 reported 26 events "possibly" related to the medication.

The most common adverse events included nausea (8%), dizziness (7%), and dry mouth (7%). Other events reported were hyperkinesia, anorexia, somnolence, insomnia, diarrhea, dyspepsia, eructation, flatulence, vomiting, fatigue, rhinitis, rash, pruritus, sweating, taste perversion and eye abnormality. Two patients experienced 3 "severe" adverse events (dizziness, mouth ulcer, insomnia), 14 patients experienced 18 events of moderate intensity, and 16 patients experienced 25 events of mild intensity, which were all "probably" or "possibly" related to the soluble formulation.

Comment: Since this study was not blinded or placebo controlled, it is difficult to interpret the results, except to say that there were no serious adverse events or deaths that occurred. The precise numbers of the different adverse events were not provided.

6. Sperber SJ, Sorrentino JV, Riker DK, et al: Evaluaton of an Alpha Agonist Alone and in Combination with a Nonsteroidal Anti-inflammatory Agent in the Treatment of Experimental Rhinovirus Colds. Bull NY Acad Med 1989,65:145-160.
This is a report of a randomized, double-blind, placebo-controlled study using pseudoephedrine alone and in combination with IBU in treating experimental rhinovirus colds. Fifty-eight healthy adults with a serum neutralizing antibody titer of ≤ 1:2 to the challenge rhinovirus were eligible for participation. Subjects were excluded if they had upper respiratory symptoms or fever within 1 week prior to initiation of the study, active or chronic sinusitis, asthma, or recent hay fever. They were also excluded if they required use of antihistamines, systemic or topical nasal decongestants, aspirin, or other NSAIDS, monoamine oxidase inhibitors, or phenothiazines, had a history of hypersensitivity to aspirin or other NSAIDS, pseudoephedrine, or other

sympathomimetics, were pregnant or lactating or would be smoking during the study period.

Intranasal rhinovirus was administered in 2 inocula over a 15-minute period by a calibrated pipette (50 µl/nostril). The subjects were isolated in motel rooms for 5 days beginning 24 hours after the rhinovirus challenge. Based on pretreatment nasal airway flow rates, they were randomly assigned to receive 2 identically appearing capsules containing PSE 60 mg and IBU 200mg, PSE 60 mg plus placebo, or 2 placebo capsules. Treatment was initiated 30 hours after virus inoculation. Two doses were given the first evening after virus challenge and four time/day on the subsequent 4 days for a total of 18 doses. Subjects were discharged from the motel on the 6th day after inoculation and seen in follow-up 2 weeks later at which time sera were obtained to measure antibody response to the challenge.

Results:
Infections (seroconversion or positive nasal washings) occurred at similar rates in all 3 treatment groups. Illness severity was reduced by both pseudoephedrine alone and in combination with ibuprofen. Both PSE and IBU/PSE were well tolerated. No subjects withdrew from the study due to adverse events. Possible adverse events with IBU/PSE were light-headedness and insomnia, dry mouth, "feeling hyper," "feeling more awake," "flushed face and increased heart rate." Possible adverse events with PSE were light headedness lethargy, and indigestion. None of these side effects were significant when compared with placebo.

Comment: There were no serious adverse events or deaths reported in this trial.

D. Marketing History Outside of the United States

Combination products containing IBU 200 mg plus PSE 30 mg have been marketed in 27 nations outside the United States (See **Appendix III, Table 25**).

The combination product has not been removed anywhere by a regulatory authority for safety reasons. In August, 2000, the United Kingdom discontinued it for commercial reasons but the license is still active. Italy suspended the combination product on July 24, 2000 because it was never marketed but the product license is still active.
The Czech Republic switched PSE from OTC to prescription status in 2000. This was intended to stop diversion of OTC PSE to illicit manufacture of methamphetamine, and was not directly related to safety concerns with PSE itself.

The McNeil Consumer Healthcare IBU/PSE oral suspension formulation (approved in the United States on August 1, 2000) is the only pediatric OTC or prescription IBU/PSE combination currently marketed worldwide. Whitehall-Robins Healthcare has pending NDA 21-373 (submitted 2001) for an IBU/PSE suspension product.

E. Reports Of Overdose and Abuse

This section examines the reports of overdose and abuse potential with IBU, PSE and the combination, given concomitantly or in the same product. Several databases, including

FDA's AERS, SRS, sponsor files, American Association of Poison Control Centers (AAPCC), Drug Abuse Warning Network (DAWN), and the medical literature were reviewed.

Overdose

The AAPCC data looked at 7 categories of drug exposure for all age categories:

- PSE without concomitants, PSE all exposures
- IBU without concomitants
- IBU all exposures
- IBU/PSE without concomitants
- IBU/PSE all exposures
- Concomitant use of IBU and PSE (not formulated together) all exposures

Table 26 displays AAPCC data on exposure and outcome for the years 1994-2000 in subjects at least 12 years of age for the following categories: all IBU/PSE exposures, IBU/PSE products without concomitants, and concomitant use of IBU and PSE not formulated together. For this table, the sponsor states that the AAPCC considers "Unintentional Ingestion" to be general, therapeutic error, unintentional misuse, environmental, bite/sting, misuse, and food poisoning. It is unclear what the terms "general" and "bite/sting" mean in this context. "Intentional Ingestion" is considered to be intentional misuse, abuse, and suicide attempt. "Major Outcomes" are signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability.

Table 26. Exposure and Outcome Data from the 1994 – 2000 AAPCC Reports Selected for IBU/PSE Preparations for Patients Aged ≥ 12 Years

Substance	Year	# Exposures	# Unintentional Exposures	# Intentional Exposures	Major Outcomes	Deaths
IBU/PSE: All Exposures	1994	210	82	105	0	0
	1995	241	102	113	1	0
	1996	231	100	112	0	0
	1997	226	127	78	0	0
	1998	224	114	89	1	0
	1999	222	116	77	0	0
	2000	280	137	101	1	0
Totals: IBU/PSE All Exposures		**1634**	**778**	**675**	**3**	**0**
***IBU/PSE:* Products Without Concomitants**	1994	107	48	44	0	0
	1995	117	48	53	1	0
	1996	99	41	46	0	0
	1997	95	52	33	0	0
	1998	103	52	40	0	0
	1999	88	41	28	0	0
	2000	127	61	36	0	0
Totals: IBU/PSE Products Without Concomitants		**736**	**343**	**280**	**1**	**0**
Concomitant use of IBU and PSE (not formulated together) All Exposures	1994	40	5	33	0	0
	1995	43	7	33	1	0
	1996	52	10	37	0	0
	1997	42	10	27	0	0
	1998	32	7	23	0	0
	1999	38	9	28	0	0
	2000	108	13	90	2	0
Totals: Concomitant Use of IBU and PSE (Not formulated together) All Exposures		**355**	**61**	**271**	**3**	**0**

From the AAPCC data (refer to **Table 26**) all IBU/PSE and concomitant IBU and PSE exposures totaled 2725. During the years reviewed, 1182 of 2725 (43%) poison exposures were associated with the "unintentional ingestion." One thousand two hundred twenty-six (45%) were "intentional ingestions." The nature of the remaining exposures was not provided.

There were no fatal outcomes and 7 major outcomes reported for exposures. There were 3 major outcomes for the ibuprofen/pseudoephedrine all exposures category, 1 for the ibuprofen/pseudoephedrine without concomitants category, and 3 for the concomitant use of ibuprofen and pseudoephedrine (not formulated together) all exposures. The sponsor did not provide details about the major outcomes.

Table 27 contains AAPCC single ingredient data for PSE and for IBU for subjects ages 12 years and older. There were no deaths for PSE as a single agent but there were 23 for IBU in this age category since 1994.

Table 27. Selected Exposure and Outcome Data from the AAPCC reports for Ibuprofen and Pseudoephedrine Hydrochloride in Subjects ≥12 Years of Age.

Year	Substance	# Exposures	Ingestion		Major Outcome	Death
			Unintentional	Intentional		
2000**	PSE Alone	795	563	176	1	0
	PSE Alone, in age ≥ 12	1574	870	600	8	0
	IBU Alone	11275	3873	6969	27	1
	IBU Alone, in age ≥ 12	20988	5648	14538	204	5
1999	PSE Alone	981	725	193	2	0
	PSE Alone, in age ≥ 12	1642	1031	496	8	0
	IBU Alone	10786	4124	6284	27	0
	IBU Alone, in age ≥ 12	17512	5748	11065	101	3
1998	PSE Alone	901	617	220	2	0
	PSE Alone, in age ≥ 12	1619	961	539	9	0
	IBU Alone	10892	3991	6546	16	0
	IBU Alone, in age ≥ 12	17718	5480	11576	95	3
1997	PSE Alone	930	578	288	0	0
	PSE Alone, in age ≥ 12	1984	1128	689	2	0
	IBU Alone	9834	3209	6260	18	0
	IBU Alone, in age ≥ 12	17964	5427	11737	84	4
1996	PSE Alone	974	622	277	2	0
	PSE Alone, in age ≥ 12	1773	958	667	5	0
	IBU Alone	9963	3047	6525	18	0
	IBU Alone, in age ≥ 12	16574	4186	11680	73	3

Table 27 (Continued). Selected Exposure and Outcome Data from the AAPCC Reports for Ibuprofen and Pseudoephedrine Hydrochloride in Subjects ≥12 Years of Age.

Year	Substance	# Exposures	Ingestion		Major Outcome	Death
			Unintentional	Intentional		
1995	PSE Alone	954	589	286	5	0
	PSE Alone, in age ≥ 12	1682	863	674	9	0
	IBU Alone	9364	2593	6403	17	0
	IBU Alone, in age ≥ 12	15798	3620	11546	70	4
1994	PSE Alone	766	425	286	0	0
	PSE Alone, in age ≥ 12	1390	642	650	3	0
	IBU Alone	8618	2361	5959	12	0
	IBU Alone, in age ≥ 12	14207	3191	10515	62	1

Table 28 provides exposure and outcome data from the 1994-2000 AAPCC reports for single ingredients ibuprofen, acetaminophen and aspirin in a population of all ages (children and adults).

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Table 28. Exposure and Outcome Data From the 1994-2000 AAPCC Reports for Ibuprofen, Acetaminophen and Aspirin in a Population of All Ages (Children and Adults).

Year	Substance	# Exposures	Ingestion*		Major Outcome	Death
			Unintentional	Intentional		
2000**	Ibuprofen	57,876	41,216	15,539	225	5
	Acetaminophen	56,371	36,259	19,443	856	99
	Aspirin	16,649	6,942	9,270	297	52
1999	Ibuprofen	54,643	41,986	11,678	105	3
	Acetaminophen	61,092	43,293	17,122	740	85
	Aspirin	13,854	6,236	7,226	251	45
1998	Ibuprofen	52,751	39,397	12,425	97	4
	Acetaminophen	66,885	47,544	18,671	723	70
	Aspirin	14,263	6,062	7,822	222	33
1997	Ibuprofen	51,738	37,434	13,203	95	6
	Acetaminophen	72,580	51,665	20,063	566	65
	Aspirin	15,648	7,072	8,158	162	44
1996	Ibuprofen	43,777	29,453	13,375	88	3
	Acetaminophen	72,947	51,037	21,065	533	53
	Aspirin	15,516	6,373	8,675	146	46
1995	Ibuprofen	39,361	24,815	13,639	80	6
	Acetaminophen	72,889	51,450	20,730	501	55
	Aspirin	15,548	6,220	8,924	164	48
1994	Ibuprofen	35,703	22,285	12,723	76	3
	Acetaminophen	68,496	48,604	19,281	483	59
	Aspirin	15,890	6,264	9,237	143	40

*There were cases where the "ingestion" category was neither "unintentional" or "intentional."

** The year 2000 data does not specifically state that the ibuprofen, acetaminophen and aspirin were single ingredient products; the data for the other years is for single ingredient ibuprofen, acetaminophen, and aspirin.

The AAPCC data from **Table 28** demonstrates that from 1994 – 1999 there was a total of 277,973 poison exposures associated with ibuprofen-containing single ingredient products for all age groups. By comparison, there were 414,889 exposures associated with single ingredient acetaminophen formulations and 90,719 exposures for aspirin. Approximately 70% of the ibuprofen (195,370) and 71% of acetaminophen (293,593) exposures were associated with "unintentional ingestion," whereas 38,227 approximately 42% of the aspirin exposures were associated with this category. There were 25 deaths associated with ibuprofen, compared with 387 associated with acetaminophen, and 256 with aspirin.

There were 541 cases of "major outcome" associated with ibuprofen, 3,546 cases with acetaminophen, and 1,088 with aspirin.

Comment: It is unclear from the way the year 2000 data is presented whether the ibuprofen, acetaminophen and aspirin were single ingredient products. Thus, data from 2000 was not included in the above calculations.

Abuse

The assessment of drug abuse potential for the proposed combination product containing IBU and PSE is based on examination of the abuse potential for each active ingredient and the combination products containing both IBU and PSE. There are 2 sources of information use in the analysis:

- Summaries issued by the DAWN
- Spontaneous adverse drug experience reports obtained from the FDA

In addition, the scientific literature was reviewed to determine drug abuse potential.

DAWN Medical Examiner Data

The Annual Medical Examiner (ME) reporting system defines a drug abuse death as being either drug-induced or drug-related. A drug-induced death is any death in which the ME concluded that the fatality was caused directly by the drug. For this classification, the ME has found or strongly suspected a toxic level of drug in the victim; typically fatalities resulting from an overdose are classified as drug-induced. The sponsor notes that typically, fatalities resulting from an overdose are classified as drug-induced. On the other hand, a drug-related death is a fatality in which the ME concluded that drug use contributed to the death but was not its sole cause. Examples of drug-related deaths may include the use of a:

- Prescription drug in a manner inconsistent with accepted medical practice
- Nonprescription (OTC) product contrary to approved labeling
- Substance for either psychic effect or dependence

The term "drug mention" refers to a substance or drug that is reported in a drug abuse death report submitted to DAWN. The raw data in the DAWN represent only those facilities that reported to DAWN during all or at least 10 months of a given reporting year. Thus, the DAWN Annual Reports do not represent the nation as a whole or even the total of ME drug abuse cases for a given reporting area. In order to examine trends of drug abuse over time, a subset of the total ME facilities reporting drug abuse deaths for at least10 months of a contiguous series of years is used. This subset of reporting MEs

constitutes the Consistent Panel data. Data from the Consistent Panel permits detection of either new substances or new combinations of substances that result in drug abuse fatalities. For a given Annual Report, only 4 years of data are presented in the Consistent Panel data – the current year plus a 3-year retrospective. The limited time series is because, from one year to the next, a different set of reporting MEs contribute to the Consistent Panel.

The sponsor states that "drug mentions" shown in **Table 29** were extracted from the six most recently published Annual Medical Examiner Data Reports (1994-1999). (The sponsor states that the Medical Examiner section of Dawn for the year 2000 was not published in time to be included in this submission.) The upper part of the Table displays values for "raw" drug mentions associated with drug abuse fatalities for the indicated year. The lower part of the table displays the Consistent Panel data for drug abuse fatalities over a 4-year period.

Table 29. Drug Mentions by Medical Examiners

	Mention Frequency by Reporting Year					
Substance	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**
Raw Data						
Acetaminophen	309	367	353	403	401	427
Aspirin	80	105	107	92	101	104
Ibuprofen	36	26	32	40	31	35
Pseudoephedrine	28	38	43	37	41	67
Total # of Drug Abuse Cases	8426	9216	9484	9743	10123	11651
Consistent Panel Data						
Acetaminophen	---	---	342	392	395	425
Aspirin	---	---	103	87	98	104
Ibuprofen	---	---	NM*	NM	NM	NM
Pseudoephedrine	---	---	NM	NM	NM	NM
Total # of Drug Abuse Cases	---	---	9242	9501	10056	11570

*NM signifies zero mentions

During this time period, the number of drug abuse deaths attributed to IBU was lower than for two other OTC analgesics, acetaminophen and aspirin. The only decongestant product mentioned for the 6-year period was PSE. The number of drug mentions for this ingredient was also lower than for either acetaminophen or aspirin. The Consistent Panel Data for the 4-year period showed no drug abuse deaths recorded for IBU/PSE-containing, single ingredient products.

Two data displays ("Mentions of Top 15 Drugs Reported in Combination" and "Two-Way Drug Combinations Mentioned Most Frequently in Drug Abuse Deaths) in the 6 DAWN Annual Medical Examiner Data reports revealed no mentions of fatalities attributed to the combination of IBU and PSE. There were a total of 6 mentions in both reports.

DAWN Emergency Department Visit Data

The Annual, Detailed DAWN Emergency Department (ED) Tables present estimates of ED drug abuse episodes seen in Emergency Rooms for a given year throughout the coterminous states of the United States including 21 metropolitan areas. Case visits are obtained from a statistical sample of hospitals and these visits are weighted to be representative of all such episodes that occurred in 24-hour, short-stay, non-Federal hospitals. In addition to the number of drug abuse visits, the report also contains estimates for mentions of specific drugs associated with these ED visits. Similar to the DAWN ME data, an ED drug abuse episode (or ED episode), refers to any ED admission that was induced by or related to drug abuse. Unlike the ME reports, drug abuse for the ED reports is defined as non-medical use of a substance for any of the following reasons: psychic effect, dependence, or suicide attempt/gesture. Non-medical use for purposes of the ED report series is meant as the use of:

- Prescription drugs in a manner inconsistent with accepted medical practice
- OTC drugs contrary to approved labeling
- Any substance for psychic effect, dependence or suicide

The terms "ED drug mention" or "D mention" refer to a substance that was mentioned in a drug abuse episode. Up to 4 substances can be reported for each ED episode.

Table 30 lists the number of ED drug mentions for 1994-1999.

Table 30. ED Drug Mentions (1994-1999)

	Mention Frequency by Reporting Year						
Substance	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**
Acetaminophen (% of Total)	38,674 (7.46%)	36,563 (7.12%)	38,265 (7.44%)	35,448 (6.73%)	32,257 (5.95%)	28,258 (5.09%)	33,613 (5.59%)
Aspirin (% of Total)	19,358 (3.74%)	16,729 (3.26%)	15,854 (3.08%)	14,623 (2.77%)	15,457 (2.85%)	12,815 (2.31%)	15,657 (2.60%)
Ibuprofen (% of Total)	9,031 (1.75%)	21,250 (4.14%)	16,979 (3.30%)	17,070 (3.24%)	17,146 (3.16%)	14,400 (2.59%)	17,923 (2.98%)
Pseudoephedrine (% of Total)	2,377 (0.46%)	1,956 (0.38%)	1,362 (0.26%)	1,793 (0.34%)	1,355 (0.25%)	598 (0.11%)	948 (0.16%)
IBU/PSE	NM	NM	NM	NM	NM	NM	NM
Total estimated drug abuse episodes in hospitals (all drugs)	518,521	513,633	514,347	527,058	542,544	554,932	601,776

The sponsor states that unlike the ME data previously discussed, information related to a Consistent Panel of reporting EDs was omitted because in the 1999 report there were insufficient numbers of either IBU- or PSE-drug mentions associated with ED visits, for inclusion in that report's 4-year trend table. **Table 30** shows that overall the number of ED visits associated with ibuprofen abuse was less than the numbers of ED visits associated with acetaminophen abuse, but greater than the number of visits associated with aspirin abuse. The number of ED visits associated with pseudoephedrine

hydrochloride over the 7 years were fewer than for any of the analgesics. There were no mentions of ED visits attributable to combination ibuprofen/pseudoephedrine products.

Spontaneous Adverse Drug Experience Reporting

The SRS and AERS databases were searched by the sponsor for potential signals indication that pseudoephedrine hydrochloride, ibuprofen, or ibuprofen/pseudoephedrine hydrochloride may be substances of abuse. The databases were searched with the following terms:

- For SRS: Drug Depend and Drug Depend Addict
- For AERS: Abuse NOS, Drug Abuse, and Drug Dependence

The results of this search are in **Table 31.**

Table 31. Drug Abuse Reports Contained in the Freedom of Information (FOI) Data Extracts for the SRS and AERS Databases.

	SRS Database		AERS Database	
Substance Names	# of Reports	% Abuse Reports	# of Reports	% Abuse Reports*
Acetaminophen – Unspecified	3	0.04	1	0.06
Acetaminophen – Tylenol	5	0.06	2	0.12
Aspirin	5	0.06	0	0
Ibuprofen – Advil	3	0.04	0	0
Ibuprofen – Motrin	7	0.09	0	0
Ibuprofen – Unspecified	1	0.01	0	0
Pseudoephedrine	2	0.03	0	0
Pseudoephedrine-Sudafed	5	0.06	0	0
IBU/PSE	0	0	0	0
Alprazolam	742	9.60	12	0.76
Tramadol HCl	296	3.81	92	5.85
Total Records in Database	1,486,926		498,733	

*Only reports noted as "initial" are included.

For the abuse cases associated with either single ingredient IBU or single ingredient PSE products, the reported patient age was outside of the specified range (0 to <12 years of age) or else no age information was contained in the report. There were no abuse reports for IBU/PSE combination products.

Medical/Scientific Literature

A review of the literature performed by the sponsor on overdose/abuse for ibuprofen, pseudoephedrine HCl, and the combination in subjects at least 12 years of age revealed:

- Pseudoephedrine HCl – No articles for overdose and one report of abuse in an 18-year-old (see below).
- Ibuprofen –No articles for overdose or abuse.
- Ibuprofen/Pseudoephedrine HCl combination – No articles for overdose or abuse.

Sullivan G: Acute psychosis following intravenous abuse of pseudoephedrine hydrochloride: a case report. J Psychopharmacol 1996;10(4):324-325.
An 18-year-old male, with a history of occasional intravenous abuse of temazepam presented to the emergency room (ER) with somatic hallucinations, a general increase in psychomotor activity, and threatening suicide. He also exhibited a general increase in psychomotor activity. He was administered Clopixol Acuphase 50 mg. Three days post-admission he stated that prior to admission he had prepared an injectable form of Sudafed 60 mg, crushing the tablet, dissolving it in water and self-injected it intravenously. He recovered within 24 hours.

VIII. Dosing, Regimen, and Administration Issues

- The sponsor has submitted a proposed label (**See Appendix IV**), with the regimen of one capsule every 4 – 6 hr while symptoms persist. The proposed labeling states that if symptoms do not respond to 1 capsule, 2 capsules may be used, not to exceed 6 capsules in any 24-hr period unless directed by a doctor. The tablets are not to be taken for colds for more than 7 days or for fever for more than 3 days unless directed by a physician. The following are comments about and suggested revisions to the draft label:
- The label states, "relieves sinus — nasal congestion, and fever." —————
- The label states "take with food or milk if stomach upset occurs." ——
- ——

The draft Drug Facts label submitted by the sponsor reflects approved labeling of other OTC products containing ibuprofen and pseudoephedrine hydrochloride. Consideration should be given to adding the following warnings to products that contain ibuprofen and pseudoephedrine hydrochloride:

- ——
- ——
- ——
- ——

Because this product contains active ingredients that are regulated under both the OTC drug monograph and NDA processes, these labeling issues can be addressed through the OTC drug monograph proposed rulemaking and/or through a FDA Advisory Committee meeting.