

IX. Use in Special Populations

Pregnant women and mothers who are nursing a baby should avoid using IBU/PSE.

It is recognized that accidental overdose has been a cause of serious adverse events in children under the age of 12. The safety of the combination product in children under 12 years of age will be reviewed separately (See **Introduction and Background**).

The elderly may be at increased risk of experiencing serious adverse events from IBU/PSE because they are at increased risk from taking single ingredient IBU and single ingredient PSE.

Because this product contains IBU, use should be avoided in people with a history of gastrointestinal bleeding and peptic ulcer disease, allergies to other nonsteroidal anti-inflammatory drugs, and a history of pre-existing renal disease, congestive heart failure, and hypertension. Use should also be avoided in people taking anticoagulant medication.

Because this product contains PSE, use should be avoided in those with hyperthyroidism, diabetes mellitus, cardiovascular disease, increased intraocular pressure, prostatic hypertrophy, and hypertension.

X. Conclusions and Recommendations

Conclusion:

The data submitted in this NDA does not suggest any new safety signals associated with the use of combination IBU/PSE. However, some of the information from the databases is incomplete. Compared with the data for IBU/PSE, the data suggests that deaths and serious adverse events are more common with IBU and with PSE as single ingredients, than with the combination product. The data does not suggest a significant problem with abuse of IBU/PSE. The data does not suggest that combination product IBU/PSE, when taken according to the directions, is unsafe for OTC availability.

The AE databases for IBU, include prescription strength as well as OTC strength IBU as a single ingredient. The data does not suggest new safety signals for IBU, but it is unclear which AE's are associated with which doses. Allergy, gastrointestinal (ulcer and bleeding) and renal signals (which have been associated with IBU and are detailed in the prescription labeling) were again prominent in this data. The PSE single ingredient data does not suggest new signals.

The pharmacokinetics data does not suggest differences in bioequivalence with the tablet formulation that would be of clinical significance. The PK Data indicates that in a fed state the IBU may not reach therapeutic levels as quickly from the Liqui-Gel formulation compared with the tablet formulation (therapeutic levels are reached in approximately 45 minutes with the Liqui-Gel compared to 30 minutes with the tablet). However, safety concerns about gastrointestinal toxicity are a compelling reason to eliminate the sponsor's suggested direction, ~~_____~~ from the product label.

The draft label for the NDA has deficiencies that can be addressed through the OTC drug monograph proposed rulemaking and/or FDA appointed advisory committee processes.

Recommendations:

The data suggest that, Advil® Cold & Sinus Liqui-Gels® should be safe for Over-the-Counter (OTC) availability if consumers use the product in accordance with the directions and warnings on the product label. Therefore the product could be approved for OTC use. However, 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." Taking non-steroidal anti-inflammatory drugs with milk may not prevent stomach pain. Further, if people experience stomach pain, it would be appropriate to stop taking the medication. It may be better to simply state _____

Because this product contains active ingredients that are regulated under both the OTC Monograph and NDA processes, consideration should be given to addressing the following labeling issues through the OTC drug monograph proposed rulemaking and/or FDA appointed advisory committee process. The need for a:

- More prominent gastrointestinal warning
- Renal warning
- Drug-drug interaction warning (e.g., anticoagulants)
- Glaucoma warning

XI. Appendices I – IV (See Below)

**APPEARS THIS WAY
ON ORIGINAL**

Appendix I – Ibuprofen Single Ingredient

Table 12. Serious AEs from SRS Database for IBU (Pages 57-66)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥12
Body as a Whole	Abdominal Enlargement	4	3
	Abdominal Syndrome, Acute	1	1
	Abscess	7	7
	Abscess Injection Site	1	1
	Allergic Reaction	45	38
	Anaphylaxis	76	64
	Anomaly congenital	25	3
	Anomaly congenital mult	1	0
	Ascites	3	3
	Asthenia	47	44
	Bacterial Resistance	1	1
	Cachexia	1	1
	Carcinoma	2	1
	Cellulitis	4	3
	Chills	6	6
	Chills Fever	13	11
	Collagen Disorder	2	2
	Cyst	2	2
	Death	15	10
	Digitalis Intoxication	9	9
	Drug Interaction	47	41
	Drug Level, Inc	21	20
	Edema, Face	27	26
	Edema, General	10	9
	Embolism, Leg	1	1
	Fetal Dis	1	0
	Fever	73	72
	Fibrosis, Retroperitoneal	1	1
	Flu Syndrome	2	2
	Granuloma	2	2
	Headache	32	29
	Hem Inject Site	1	0
	Hernia	11	10
	HIV Syndrome	1	1
	Hostility	10	6
	Hypothermia	2	2
	Immune System Disorder	1	1
	Increased Effect	1	1
	Infection	14	9
	Infection, Bacterial	3	3
	Infection, Super	1	1
	Infection, viral	1	1
	Injury, Accidental	11	9
	Injury, Intentional	1	1
	Laboratory Test Abnormality	3	2
	Laboratory Test, Interfer	2	1
	LE Syndrome	8	8
	Malaise	7	4
	Medication Error	1	1
	Neck, Rigid	10	10
	Neoplasia	3	3
	No Drug Effect	5	2
	Overdose	51	46
Overdose, Accidental	3	2	
Overdose, Intentional	102	94	

Table 12. Serious AEs from SRS Database for IBU (Pages 57-66)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥12
Body as a Whole (Continued)	Pain	9	7
	Pain, Abdominal	138	122
	Pain, Back	19	19
	Pain, Chest	24	22
	Pain Chest Substernal	2	2
	Pain, Flank	4	4
	Pain, Neck	1	1
	Pain, Pelvic	1	1
	Perinatal Dis	1	0
	Peritonitis	5	4
	Photosensitivity	1	1
	Reaction Aggravation	52	44
	Reaction Unevaluable	4	1
	Sepsis	29	27
	Serum Sickness	2	2
	Shock	50	42
Suicide Attempt	38	35	
Cardiovascular System	Adams Stokes Syndrome	1	1
	Angina Pectoris	3	3
	Anomaly Arterial	2	2
	Arrhythmia	8	8
	Arrhythmia, Ventricular	1	1
	Arteriosclerosis	1	1
	AV Block Comp	5	5
	AV Block FD	2	2
	Bradycardia	11	9
	Bradycardia Sinus	2	2
	Bundle Branch Block	2	2
	Cardiomyopathy	1	1
	Cardiovascular disorder	4	1
	Cerebrovascular Accident	14	14
	Cerebrovascular Disease	1	1
	Coronary Artery Disease	3	3
	Digitalis Intoxication	18	18
	ECG Abnormality	3	3
	Embolism	1	1
	Embolism Leg	2	2
	Embolism Pulmonary	5	5
	Extrasystoles Bigeminy	3	3
	Extrasystoles Ventricular	3	3
	Fibrillation, Atrial	14	13
	Fibrillation Ventricular	6	6
	Flutter, Atrial	1	1
	Heart Arrest	32	30
	Heart Block	1	1
	Heart Failure	6	4
	Heart Failure Right	17	15
	Hemopericard	1	0
	Hemorrhage	20	14
	Hemorrhage Cerebral	5	4
	Hemorrhage Intracranial	1	1
	Hypertension	23	20
	Hypotension	97	87
	Hypotension Postural	22	21
	Infarct Cerebral	1	1
	Infarct Myocardial	17	15
	Ischemia Cerebr	6	5
Ischemia Myocard	2	2	

Table 12. Serious AEs from SRS Database for IBU (Pages 57-66)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥12
Cardiovascular System (Continued)	Migraine	2	1
	Myocarditis, Allerg	1	1
	Nephrosclerosis	2	2
	Occlusion, Coronary	2	2
	Pallor	3	3
	Palpitation	4	3
	Phlebitis	2	1
	Purpura, Vascular	2	2
	QT Prolonged	1	1
	Shock	50	42
	Stenosis, Aortic	1	1
	Syncope	63	55
	Tachycardia	40	40
	Tachycardia, ventricular	7	7
	Thrombosis	1	1
	Thrombosis, Cerebral Artery	1	1
	Thrombophlebitis	2	2
	Thrombophlebitis, Deep	1	1
	Vascular Disorder	2	2
	Vasculitis,	18	17
	Vasculitis, Kidney	3	3
	Vasodilation	12	8
Vein Varicose	4	4	
Ventricular Septal Defect	3	3	
Digestive System	Anorexia	9	9
	Biliary Atresia	2	2
	Carcinoma, GI	6	4
	Carcinoma Liver	1	1
	Cholangitis	1	1
	Cholecystitis	4	4
	Cholelithiasis	2	2
	Cleft Palate	2	0
	Colitis	7	6
	Colitis, Hem	3	3
	Colitis, Pseudomembranous	1	1
	Coma, Hepatic	3	3
	Constipation	3	3
	Diarrhea	19	15
	Diarrhea, Bloody	6	6
	Dry Mouth	4	4
	Duodenitis	14	13
	Dyspepsia	15	11
	Dysphagia	36	28
	Edema, Tongue	18	15
	Eructation	1	1
	Esophagitis	29	26
	Flatulence	5	4
	Gangrene Ileum	1	0
	Gastritis	99	87
	Gastritis, Hemorrhagic	35	31
	Gastroenteritis	7	7
	GGTP Inc	3	1
	Gastrointestinal Disorder	20	16
	Gastrointestinal Perforation	2	2
	Glossitis	1	1
	Hemorrhage, Colonic	1	1
	Hemorrhage, Esophageal	21	21
Hemorrhage, Gastrointestinal	463	431	

Table 12. Serious AEs from SRS Database for IBU (Pages 57-66)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥12
Digestive System (Continued)	Hemorrhage, Gum	2	2
	Hemorrhage, Ileum	2	2
	Hemorrhage, Rectal	33	32
	Hematemesis	195	184
	Hepatitis	24	22
	Hepatorenal Syndrome	4	4
	Hepatosplenomegaly	3	3
	Ileitis	2	2
	Ileus	1	1
	Incontinence, Fecal	2	2
	Intestinal Large Perforation	3	3
	Intestinal Perforation	1	1
	Intestine Small Perforation	3	2
	Jaundice	9	6
	Jaundice Cholestatic	8	8
	Jaundice Neonat	1	0
	Liver Cirrhosis	4	4
	Liver Damage	4	3
	Liver Failure	6	6
	Liver Fatty	2	1
	Liver Function Abnormality	37	32
	Melena	227	211
	Monilia Oral	1	1
	Nausea	32	28
	Nausea Vomiting	60	55
	Nausea Vomiting Diarrhea	8	7
	Necrosis Liver	5	5
	Obstruction, Intestinal	3	3
	Pancreas Disorder	1	1
	Pancreatitis	20	18
	Pancreatitis Hemorrhagic	3	3
	Pancreatitis Necrotic	1	1
	Rectal Disorder	2	2
	Salivary Gland Enlargement	1	1
	Saliva Increased	1	1
	Stenosis, Esophageal	1	1
	Stenosis, Intestinal	1	1
	Stenosis, Intestinal Jejunum	1	1
	Stenosis Pyloris	2	2
	Stomatitis	2	1
	Ulcer Duodenal	60	53
	Ulcer Duodenal Hemorrhage	27	25
	Ulcer Duodenal Perforation	11	10
	Ulcer Duodenal Perhem	1	1
	Ulcer Esophageal	28	25
	Ulcer Intestinal	11	10
	Ulcer Intestinal Jejunum	1	1
	Ulcer Intestinal Perforation	2	2
	Ulcer Intestinal Perforation Ileum	1	1
	Ulcer Mouth	4	4
	Ulcer Peptic	15	13
	Ulcer Peptic Hemorrhage	13	11
	Ulcer Peptic Perforation	8	7
	Ulcer Peptic Perhem	1	1
	Ulcer Peptic React	1	0
	Ulcer Stomach	102	95
	Ulcer Stomach Hemorrhage	39	34
	Ulcer Stomach Perforation	10	9

Table 12. Serious AEs from SRS Database for IBU (Pages 57-66)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥12
	Ulcer Stomach Perhem Vomiting	3 42	2 38
Endocrine System	ADH Inapprop Adren Insuffic Aldosterone Inc Cushings Synd Diabetes Insipid Diabetes Mell Glucocort Inc Hyperthyr	5 2 1 1 2 3 1 1	4 2 1 1 1 3 1 1
Hemic and Lymphatic	Agranulocytosis ANA Anemia Anemia Aplastic Anemia Hemolytic Anemia Hemolytic DCN Anemia Hemolytic DCP Anemia Hemolitic ICP Anemia Hypochromic Anemia Iron Deficiency Anemia Microcytic Anticoagulation Increased Bleeding Time Increased Coagulation Disorder Coombs Dir Test Pos Cyanosis DIC Ecchymosis Eosinophilia ESR Inc Hepatosplenomegaly Hypervolemia Hypovolemia Jaundice Neonat Leukemia Acute Leukemia Acute Lympho Leukemia Acute Myelo Leukocytosis Leukopenia Lymphadeno Lymphangitis Lymphocytosis Lymphoma Like Reaction Marrow Depression Megakaryo Inc Myeloid Metaplasia Pancytopenia Petechia Prothromin Dec Purpura Purpura Thrombopen Purpura Thrombopen Th RBC Abnorm RE Hyperplasia Spleen Disorder Thrombocythem Thrombocytopenia Thromboplastin Dec	9 7 237 12 6 1 1 1 72 2 4 1 3 14 2 4 2 10 10 2 6 2 4 2 1 1 1 1 12 30 3 1 1 3 9 1 1 17 6 24 5 14 2 1 1 1 2 43 2	9 7 221 8 5 1 1 1 63 1 4 2 13 2 3 2 10 10 2 6 2 4 0 1 1 1 1 12 28 3 1 1 2 9 1 1 15 6 23 5 11 2 1 1 1 1 39 2

Table 12. Serious AEs from SRS Database for IBU (Pages 57-66)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥12
Metabolic and Nutritional Disorders	Acidosis	30	27
	Acidosis Lactic	1	1
	Acidosis Resp	4	3
	Albuminuria	19	18
	Alcohol Intolerance	1	1
	Aldosterone Inc	2	2
	Amylase Inc	9	8
	Anemia Iron Defic	4	2
	Avitaminosis	1	1
	Bilirubinemia	16	14
	BUN Inc	83	78
	Cachexia	2	2
	Coma Hepatic	9	9
	Creatinine PK Inc	7	7
	Chreatinine Clear Dec	2	2
	Creatinine Inc	142	128
	Cyanosis	8	6
	Dehydration	14	12
	Diabetes Mellitus	8	6
	Edema	14	11
	Edema General	20	18
	Edema Peripheral	20	16
	Electrolyte Abnorm	2	1
	Electrolyte Deplet	1	1
	Enzyme Abnorm	4	4
	GGTP Inc	6	2
	Glucocort Inc	1	1
	Healing Abnorm	6	1
	Hypercalcemia	1	1
	Hyperglycemia	9	9
	Hyperkalemia	51	48
	Hyperlipemia	1	0
	Hypernatremia	4	4
	Hyperuricemia	2	2
	Hypervolemia	4	4
	Hypocalcemia	2	2
	Hypoglycemia	9	8
	Hypokalemia	12	11
	Hypomagnesemia	1	0
	Hyponatremia	10	10
	Hypoproteinemia	5	5
	Hypovolemia	8	8
	Hypoxia	7	6
Ketosis	4	4	
LDH Inc	6	6	
Lipase Inc	1	1	
Liver Fatty	4	2	
NPN Inc	6	6	
Phosphatase Alk Inc	5	5	
SGOT Inc	7	6	
SGPT Inc	5	4	
Uremia	13	10	
Water Intox	1	1	
Weight Dec	8	7	
Weight Inc	2	2	
Xanthoma	2	2	
Musculoskeletal System	Arthralgia	4	4
	Arthritis	4	3

Table 12. Serious AEs from SRS Database for IBU (Pages 57-66)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥12
Musculoskeletal System (Continued)	Arthritis Pyogen	2	2
	Atrophy Muscle	1	0
	Bone Disorder	1	1
	Bone Fract Spontan	1	1
	Cramps Leg	1	1
	Joint Disorder	3	1
	Myalgia	6	5
	Myasthenia	2	2
	Myopathy	7	7
	Necro Bone	1	1
	Osteoporosis Fract	1	1
	Pain Bone	1	1
	Rhabdo	8	8
Tenosynovitis	3	3	
Nervous System	Agitation	3	2
	Akathisia	1	1
	Amnesia	3	2
	Anxiety	3	2
	Aphasia	2	2
	Arachnoiditis	1	0
	Ataxia	7	6
	Atrophy Optic	1	1
	Brain Syndrome Acute	7	6
	Brain Syndrome Chronic	2	2
	Buccoglossal Syndrome	2	1
	Cerebrovascular Accident	28	28
	Cerebrovascular Disorder	2	2
	Choreoathetosis	2	1
	CNS Depression	2	2
	Coma	40	37
	Coma Hepatic	9	9
	Confusion	28	27
	Convulsion	24	24
	Convulsion Grand Mal	12	12
	Coordination Abnormality	5	5
	Cramps Leg	2	2
	CSF Abnorm	7	7
	Delirium	4	3
	Depression	7	6
	Depression Psychotic	2	1
	Diplopia	2	1
	Dizziness	71	69
	Dream Abnormality	1	1
	Drug Depend	2	2
	Drug Depend Addict	1	1
	Dry Mouth	8	8
	Dystonia	1	0
	Edema Brain	4	4
	EEG Abnorm	1	1
	Emotion Labil	4	3
	Encephalitis	7	7
	Encephalopathy	9	8
	Euphoria	1	1
	Extrapyr Synd	3	3
	Gait Abnorm	3	2
	Hallucin	14	12
	Hem Cerebral	10	8
Hem Intracranial	2	2	

Table 12. Serious AEs from SRS Database for IBU (Pages 57-66)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥12
Nervous System (Continued)	Hematoma Subdural	2	2
	Hemiplegia	3	3
	Hostility	20	12
	Hyperkinesia	1	0
	Hypertension	46	40
	Hypertonia	4	4
	Hysteria	1	0
	Ileus	2	2
	Infarct Cerebr	2	2
	Insomnia	4	3
	Intracran Hypertens	9	8
	Ischemia Cerebr	12	10
	Meningism	1	1
	Meningitis	61	57
	Miosis	1	1
	Movememt Dis	1	0
	Myelitis	1	1
	Neuritis	1	1
	Neuritis Optic	3	3
	Neuritis Periph	4	4
	Neuritis Retrobulbar	1	1
	Neuropathy	7	4
	Nystagmus	3	3
	Ophthalmoplegia	2	2
	Papilledema	2	2
	Paralysis	5	2
	Paralysis Facial	1	1
	Paralysis Spastic	1	1
	Paranoid React	1	1
	Paresthesia	15	12
	Person Dis	1	1
	Pleocytosis	6	6
	Psychosis	6	6
	Reflexes Dec	1	1
	Saliva Inc	2	2
	Screaming Syndrome	1	0
	Somnolence	20	19
	Speech Dis	6	4
	Stupor	11	10
	Thinking Abnorm	10	9
	Throm Cerebr Art	2	2
	Tremor	2	2
	Trismus	1	1
	Urin Retent	3	3
	Vasodilat	24	16
	Vertigo	4	4
	Withdraw Synd	5	5
Wrist Drop	1	1	
Respiratory System	Apnea	31	29
	Asthma	34	33
	Bronchitis	2	2
	Bronchosteno	2	2
	Carcinoma Lung	2	1
	Cough Inc	6	5
	Dyspnea	111	96
	Edema Larynx	13	12
	Edema Lung	15	14
Effusion Pleural	2	2	

Table 12. Serious AEs from SRS Database for IBU (Pages 57-66)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥12
Respiratory System (Continued)	Emb Pulm	10	10
	Epistaxis	4	3
	Fibro Lung	1	1
	Hem Lung	3	3
	Hemoptysis	3	2
	Hyperventil	10	10
	Hypoventil	4	4
	Hypoxia	14	12
	Laryngismus	6	5
	Laryngitis	2	1
	Lung Dis	8	6
	Neopl Larynx	1	1
	Pharyngitis	11	8
	Pleural Dis	1	1
	Pneumonia	18	17
	Pneumonia Interstit	3	2
	Pulm Mycosis	1	0
	Respirat Dis	14	13
	Respiratory Distress Syndrome	7	6
	Rhinitis	2	2
	Sputum Inc	1	1
	Stridor	3	3
Voice Alterat	2	2	
Skin and Appendages	Alopecia	2	1
	Angioedema	27	26
	Derm Exfol	5	4
	Epiderm Necro	10	9
	Erythema Mult	5	5
	Furunculosis	1	1
	Herpes Zoster	1	0
	Pruritus	35	33
	Psoriasis	1	1
	Rash	51	45
	Rash Mac Pap	11	10
	Rash Purpur	1	1
	Rash Vesic Bull	6	6
	Skin Discolor	1	2
	Stevens Johnson Synd	19	17
	Sweat	11	9
	Ulcer Skin	2	2
Urticaria	38	32	
Special Senses	Amblyopia	9	7
	Atrophy Optic	2	2
	Blind	5	4
	Cataract	4	3
	Cataract NOS	2	1
	Conjunctivitis	3	2
	Deaf	11	7
	Deaf Trans Part	1	1
	Diplopia	4	2
	Ear Dis	11	11
	Eye Dis	2	1
	Hem Eye	1	1
	Hem Retinal	1	1
	Keratitis	2	2
	Miosis	1	1
	Mydriasis	6	6
	Neuritis Optic	2	2

Table 12. Serious AEs from SRS Database for IBU (Pages 57-66)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥12
Special Senses (Continued)	Neuritis Retrobulbar	4	4
	Ophthalmoplegia	4	4
	Pain Eye	1	0
	Papilledema	4	4
	Photophobia	4	4
	Retinal Dis	1	1
	Tinnitus	19	16
	Ulcer Corneal Per	1	1
	Uveitis	1	0
	Vision Abnorm	10	9
	Visual Field Defect	4	3
Urogenital System	Abortion	10	4
	Abscess Kidney	1	1
	Albuminuria	38	36
	Anuria	5	5
	Birth Premat	2	1
	Carcinoma Breast	1	1
	Carcinoma Cervix	1	1
	Creatinine Clear Dec	2	2
	Cystitis	2	2
	Glomerulitis	9	8
	Gynecomastia	1	1
	Hem Pregn	1	0
	Hem Vaginal	2	2
	Hematuria	19	18
	Hepatorenal Synd	8	8
	Incontin Urin	1	1
	Infect Urin tract	8	8
	Kidney Calculus	2	2
	Kidney Failure	65	58
	Kidney Failure Acute	130	125
	Kidney Function Abnorm	35	30
	Kidney Tubul Dis	3	2
	Labor Abnorm	1	0
	Menorrhagia	1	1
	Necro Kidney Papill	4	4
	Necro Kidney Tubul	15	14
	Nephritis	36	34
	Nephropathy Toxic	2	2
	Nephrosclerosis	4	4
	Nephrosis	22	21
	Oliguria	11	10
	Pain Breast	1	1
	Pain Kidney	1	1
	Placenta Dis	1	1
	Preg Dis	4	3
	Preg Unintend	1	1
	Pyelonephritis	3	3
	Pyuria	2	2
	Sperm Arrest	1	1
	Stillbirth	6	2
	UG Dis	3	3
	Uremia	26	20
	Urin Abnorm	1	1
Urin Casts	2	2	
Urin Retent	6	6	
Urin Tract Dis	3	2	
Vasculitis Kidney	6	6	

Table 13. SRS Adverse Events Associated with Fatalities Age ≥ 12 Years and “Age Unknown” for Single Ingredient IBU (Pages 67-70)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥ 12
Body as a Whole	Abscess	2	2
	Allerg React	2	1
	Anaphyl	9	9
	Anomaly Congen	13	1
	Asthenia	3	3
	Carcinoma	1	0
	Cellulitis	1	0
	Chills Fever	1	0
	Collagen Dis	1	1
	Death	15	10
	Drug Interaction	6	3
	Drug Level Inc	4	3
	Fever	8	8
	HIV Synd	1	1
	Hostility	1	1
	Infect	4	0
	Infect Bact	1	1
	Overdose	10	8
	Overdose Intent	13	11
	Pain Abdo	6	6
	Pain Chest	2	1
	Peritonitis	2	1
	React Aggrav	5	5
	Reaction Uneval	1	0
	Sepsis	18	16
	Shock	13	11
	Suicide Attempt	14	14
	Cardiovascular System	Arrhythmia	1
Arteriosclerosis		1	1
AV Block Comp		1	1
Bradycardia		2	2
Cerebrovasc Acid		7	7
Cerebrovasc Dis		1	1
Emb Pulm		4	4
Fibrillat Atr		2	2
Fibrillat Vent		2	2
Heart Arrest		17	17
Heart Block		1	1
Heart Fail Right		6	5
Hem		2	1
Hem Cerebr		4	3
Hem Intracran		1	1
Hem Pericard		1	0
Hypertens		1	1
Hypotens		17	16
Infarct Myocard		6	5
Ischemia Cerebr		1	1
Occlus Coronary		1	1
Shock		13	11
Steno Aortic		1	1
Syncope		1	1
Tachycardia		4	4
Tachycardia Vent		1	1
Vasodilat		1	1
Vent Sept Def		2	2
Digestive System	Anorexia	1	1
	Carcinoma GI	2	2
	Coma Hepatic	2	2
	Constip	1	1
	Edema Tongue	2	2

Table 13. SRS Adverse Events Associated with Fatalities Age ≥ 12 Years and “Age Unknown” for Single Ingredient IBU (Pages 67-70)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥ 12	
	Esophagitis	1	1	
	Gangrene Ileum	1	0	
	Gastritis	1	1	
	Gastritis Hem	2	2	
	Gastroenteritis	1	1	
	GGTP Inc	1	1	
	Hem Esoph	2	2	
	Hem GI	31	24	
Digestive System Continued	Hem Ileum	2	2	
	Hem Rectal	3	3	
	Hematemesis	14	14	
	Hepatitis	7	6	
	Hepatorenal Synd	3	3	
	Intest Small Per	1	0	
	Jaundice	3	2	
	Liver Damage	2	1	
	Liver Failure	4	4	
	Liver Function Abnorm	3	3	
	Melena	7	7	
	Nausea	3	3	
	Nausea Vomit	3	3	
	Necro Liver	2	2	
	Pancreas Dis	1	1	
	Pancreatitis Hem	2	2	
	Pancreatitis Hecro	1	1	
	Ulcer Duoden	3	3	
	Ulcer Duoden Hem	5	4	
	Ulcer Duoden Per	6	5	
	Ulcer Duoden Perh	1	1	
	Ulcer Esoph	2	2	
	Ulcer Intest	1	0	
	Ulcer Peptic	1	0	
	Ulcer Peptic Hem	3	1	
	Ulcer Peptic Per	1	1	
	Ulcer Stomach Hem	2	2	
	Ulcer Stomach Per	3	2	
	Vomit	2	2	
	Endocrine System	Diabetes Mell	1	1
Hemic and Lymphatic	Agranulocytosis	2	2	
	ANA	1	1	
	Anemia	11	11	
	Anemia Aplast	6	4	
	Anemia Hemol	1	1	
	Anemia Hypochrom	4	4	
	Coagul Dis	8	7	
	Cyanosis	2	1	
	Eosinophilia	2	2	
	Hypovolem	2	2	
	Leukemia Acute	1	1	
	Leukocytosis	1	1	
	Leukopenia	4	3	
	Marrow Depress	1	1	
	Pancytopenia	4	4	
	Prothrombin Dec	1	1	
	Purpura	1	1	
	Purpura Thrombop	2	2	
	Re Hyperplasia	1	1	
	Thrombocytopenia	9	8	
	Metabolism and Nutrition Disorders	Acidosis	2	2
		Albuminuria	1	1
Bilirubinem		2	2	
BUN Inc		2	1	

Table 13. SRS Adverse Events Associated with Fatalities Age ≥ 12 Years and “Age Unknown” for Single Ingredient IBU (Pages 67-70)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥ 12	
	Coma Hepatic	6	6	
	Creatinine Inc	7	6	
	Cyanosis	4	2	
	Dehydrat	2	1	
	Diabetes Mell	2	2	
	Edema	2	1	
	Electrolyte Abnor	2	1	
	GGTP Inc	2	2	
	Hyperglycem	2	2	
	Hyperkalem	2	2	
Metabolism and Nutrition Disorders Continued	Hypovolem	4	4	
	Hypoxia	2	1	
	NPN Inc	2	2	
	SGOT Inc	1	1	
	Uremia	2	2	
Musculoskeletal System	Weight Dec	2	1	
Myasthenia	1	1		
Nervous System	Brain Synd Acute	4	4	
	Brain Synd Chron	2	2	
	Cerebrovasc Accid	14	14	
	Cerebrovasc Dis	2	2	
	Coma	11	9	
	Coma Hepatic	6	6	
	Convuls	4	4	
	Depression	1	1	
	Depression Psychotic	1	0	
	Edema Brain	3	3	
	Encephalitis	2	2	
	Encephalopathy	3	2	
	Extrapyr Synd	1	1	
	Hallucin	1	1	
	Hem Cerebr	8	6	
	Hem Intracran	2	2	
	Hostility	2	2	
	Hypertens	2	2	
	Ischemia Cerebr	2	2	
	Meningitis	3	3	
	Somnolence	2	2	
	Vasodilat	2	2	
	Respiratory System	Apnea	11	10
		Asthma	7	7
		Bronchitis	2	2
		Bronchosteno	2	2
		Carcinoma Lung	1	1
Dyspnea		12	11	
Edema Larynx		1	1	
Edema Lung		5	5	
Effus Pleural		1	1	
Emb Pulm		8	8	
Hem Lung		1	1	
Hyperventil		1	1	
Hypoxia		4	2	
Lung Dis		4	2	
Pneumonia		8	8	
Pneumonia Interstit		1	0	
Pulmonary Mycosis		1	0	
Respirat Dis		3	3	
Respirat Distress Synd		1	0	
Skin and Appendages		Derm Exfol	2	2
		Epiderm Necro	4	3
		Rash	1	1
	Rash Mac Pap	1	1	

Table 13. SRS Adverse Events Associated with Fatalities Age ≥ 12 Years and “Age Unknown” for Single Ingredient IBU (Pages 67-70)

Body System Category	Serious Event (COSTART Terms)	Number Serious AE	Serious AE in Those ≥ 12
	Rash Vesic Bull	1	1
	Stevens Johnson Synd	5	4
Urogenital	Abortion	6	0
	Albuminura	2	2
	Anuria	3	3
	Birth Premature	1	0
	Hematuria	1	1
	Hepatorenal Synd	6	6
	Infect Urin Tract	1	1
	Kidney Fail	10	9
	Kidney Fail Acute	17	16
	Kidney Funct Abnorm	6	4
	Necro Kidney Tubul	1	1
	Nephritis	1	1
	Nephrosis	2	2
	Preg Dis	1	0
	Stillbirth	5	1
	Uremia	4	4

**APPEARS THIS WAY
ON ORIGINAL**

Table 14. Tabulation of Serious AEs for IBU in the WHR-GSSE Database for Subjects ≥ 12 Years of Age and "Age Unknown." (Pages 71-75)

Body System Category	Serious Event	Number Serious AE	Serious AE in Subjects ≥ 12
Body as a Whole	Allergic Reaction	12	10
	Anaphylaxis	21	19
	Asthenia	8	7
	Cachexia	1	1
	Carcinoma	1	1
	Chills	3	3
	Death	3	3
	Digitalis Intoxication	1	1
	Edema Face	12	10
	Edema General	1	1
	Fever	9	8
	Headache	1	1
	Hernia	2	2
	Infection	3	3
	Injury, Accidental	1	1
	Laboratory Test Abnormal	1	1
	LE Syndrome	1	1
	Malaise	2	2
	Mucous Membrane Disorder	1	1
	Neoplasm	1	1
	No Drug Effect	1	1
	Overdose	8	6
	Overdose Accidental	1	1
	Overdose Intentional	9	9
	Pain	1	1
	Pain, Abdominal	13	12
	Pain, Back	1	1
	Pain, Chest	3	3
	Pain, Pelvic	1	0
	Peritonitis	1	1
	Reaction Aggravation	2	2
Reaction Unevaluable	2	1	
Sepsis	2	2	
Suicide Attempt	2	2	

APPEARS THIS WAY
ON ORIGINAL

Table 14. Tabulation of Serious AEs for IBU in the WHR-GSSE Database for Subjects ≥12 Years of Age and "Age Unknown." (Pages 71-75)

Body System Category	Serious Event	# Serious AEs	Serious AE in Subjects ≥ 12
Cardiovascular System	Angina Pectoris	2	2
	Arrhythmia	1	1
	Arteriospasm	1	1
	Cerebrovascular Accident	1	1
	Digitalis, Intoxication	2	2
	ECG Abnormal	1	1
	Hemorrhage	1	1
	Hemorrhage, Intracranial	1	1
	Hypertension	2	1
	Hypotension	8	7
	Oculus Mesenter	1	1
	Palpitation	1	1
	Purpura, Vascular	1	1
	Syncope	7	6
	Tachycardia	4	4
	Thrombophlebitis	1	1
	Vasculitis	1	1
Vasodilatation	1	1	
Digestive System	Colitis	2	2
	Colitis, Hemorrhagic	1	1
	Colitis, Pseudomembranous	1	1
	Constipation, Diarrhea	1	1
	Diarrhea	6	6
	Duodenitis	1	1
	Dyspepsia	4	4
	Dysphagia	6	4
	Edema Tongue	3	3
	Esophagitis	4	4
	Gastritis	7	7
	Gastritis, Hemorrhagic	1	1
	Gastroenteritis	1	1
	GGTP, Inc	1	1
	Gastrointestinal Disorder	1	1
	Hemorrhage, Gastrointestinal	25	20
	Hemorrhage, Gum	1	1
	Hemorrhage, Rectal	6	6
	Hematemesis	10	10
	Hepatitis	10	10
	Hepatitis, Nonspecific	2	2
	Jaundice	3	3
	Jaundice, Cholestatic	1	1
	Liver Damage	4	4
	Liver Failure	3	3
	Liver function Abnormalities	3	2
	Melena	11	11
	Nausea	9	9
	Nausea, Vomiting	2	2
	Pancreatitis	3	3
	Stomatitis	1	1
	Ulcer, Duodenal	1	1
	Ulcer, Duodenal Hemorrhage	1	1
	Ulcer, Duodenal perforation	3	2
	Ulcer, Esophageal	1	1
	Ulcer, Mouth	1	1
	Ulcer, Peptic	1	1
	Ulcer, Stomach	10	8
	Ulcer Stomach Hemorrhage	8	6
	Ulcer, Stomach Perforation	2	1
Vomiting	14	11	

Table 14. Tabulation of Serious AEs for IBU in the WHR-GSSE Database for Subjects ≥12 Years of Age and "Age Unknown." (Pages 71-75)

Body System Category	Serious Event	# Serious AEs	Serious AE in Subjects ≥ 12
Hemic and Lymphatic System	Agranulocytosis	2	2
	Anemia	7	7
	Anemia, Aplastic	8	6
	Anemia, Iron Deficiency	1	1
	Coagulation Disorder	1	1
	Ecchymosis	1	1
	Hemolysis	1	1
	Leukemia, Chronic Myelogenous	1	1
	Leukocytosis	1	1
	Leukopenia	8	7
	Lymphocytosis	1	1
	Marrow Depression	1	1
	Pancytopenia	4	4
	Petechia	1	1
	Purpura	6	6
	Purpura, Thrombocytopenic	6	6
Thrombin, Decreased	2	2	
Thrombocytopenia	16	15	
Metabolic and Nutritional	Acidosis	2	2
	Anemia, Iron Deficiency	2	2
	Bilirubinemia	1	1
	Cachexia	2	2
	Creatinine, Increased	1	1
	Dehydration	4	4
	Edema	6	3
	Edema, General	2	2
	Edema, Peripheral	4	3
	GGTP, Inc	2	2
	Hyperkalemia	2	2
	Hypokalemia	1	1
	Hypomagnesemia	1	1
	Hyponatremia	1	1
	NPN Increased	1	1
	Phosphatase, Alkaline Increased	1	1
	SGOT, Increased	3	3
	SGPT, Increased	3	3
	Uremia	2	2
	Musculoskeletal System	Arthralgia	3
Myalgia		1	1

**APPEARS THIS WAY
ON ORIGINAL**

Table 14. Tabulation of Serious AEs for IBU in the WHR-GSSE Database for Subjects ≥12 Years of Age and “Age Unknown.” (Pages 71-75)

Body System Category	Serious Event	# Serious AEs	Serious AE in Subjects ≥ 12
Nervous System	Anomaly, Congenital CNS	1	1
	Anxiety	1	1
	Aphasia	1	1
	Arteriospasm	2	2
	Cerebrovascular Accident	2	2
	CNS Depression	1	1
	Coma	3	3
	Convulsion	4	1
	Convulsion, Grand Mal	1	1
	Diplopia	3	3
	Dizziness	3	3
	Dysarthria	1	1
	EEG Abnormality	1	0
	Encephalitis	1	1
	Encephalopathy	1	0
	Hemorrhage, Intracranial	2	2
	Hyperkinesia	1	1
	Hypertension	4	2
	Intracranial Hypertension	2	2
	Meningism	1	1
	Meningitis	5	4
	Nervousness	1	1
	Neuritis, Optic	1	1
	Papilledema	2	2
Somnolence	5	5	
Urinary Retention	1	1	
Vasodilatation	2	2	
Vertigo	4	4	
Respiratory	Apnea	2	1
	Asthma	4	4
	Bronchitis	2	2
	Cough, Increased	2	2
	Dyspnea	20	18
	Epistaxis	5	5
	Hemorrhage, Lung	1	1
	Hyperventilation	1	1
	Laryngismus	1	1
	Respiratory Disorder	1	1
	Rhinitis	1	1
	Stridor	1	1
Skin and Appendages	Angioedema	10	10
	Epidermal Necrolysis	2	2
	Erythema Multiforme	4	4
	Necrotic Skin	1	1
	Pruritus	10	8
	Psoriasis	1	1
	Rash	15	15
	Rash Maculopapular	4	4
	Rash, Vesicular Bullous	1	1
	Stevens Johnson Syndrome	6	5
	Sweat	2	2
	Ulcer Skin	1	1
	Urticaria	16	15

Table 14. Tabulation of Serious AEs for IBU in the WHR-GSSE Database for Subjects ≥12 Years of Age and "Age Unknown." (Pages 71-75)

Body System Category	Serious Event	# Serious AEs	Serious AE in Subjects ≥ 12
Special Senses	Amblyopia	1	1
	Diplopia	6	6
	Neuritis Optic	2	2
	Papilledema	4	4
	Tinnitus	1	1
Urogenital System	Abortion	1	1
	Fibrosis, Kidney	1	1
	Hematuria	2	2
	Incontinence, Urinary	1	1
	Infection Urinary Tract	1	1
	Kidney Failure	6	4
	Kidney Failure, Acute	11	11
	Kidney Function Abnormality	7	7
	Necrosis Kidney Tubular	1	1
	Nephritis	6	6
	Nephrosis	2	1
	Oliguria	1	1
	Penis Disorder	1	1
	Stillbirth	1	0
	Uremia	4	4
	Urinary Abnormalities	1	1
	Urinary Frequency	1	1
	Urinary Retention	2	2

**APPEARS THIS WAY
ON ORIGINAL**

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Blood and Lymphatic System	Anemia NOS	30	26
	Bone Marrow Depression	1	1
	Coagulation Disorder	3	3
	Eosinophilia (Exc Pulmonary)	5	5
	Hemolytic Anemia NOS	4	4
	Idiopathic Thrombocytopenic Purpura	2	1
	Iron Deficiency Anemia	2	2
	Leukocytosis NOS	8	8
	Leukopenia NOS	5	5
	Lymphadenopathy	1	0
	Megakaryocytes Increased	1	1
	Microcytic Anemia	2	2
	Monocytosis	1	0
	Neutropenia	3	2
	Pancytopenia	4	4
	Platelet Abnormalities NOS	1	1
	Splenomegaly	3	3
	Sulphemoglobinemia	1	1
	Thrombocythemia	1	1
	Thrombocytopenia	16	16
Thrombotic Thrombocytopenic Purpura	2	2	
Von Willebrand's Disease	1	1	
Cardiac Disorders	Angina Unstable	2	2
	Atrial Fibrillation	1	1
	Atrioventricular Block First Degree	3	3
	Atrioventricular Block NOS	1	1
	Bradycardia NOS	5	5
	Bundle Branch Block Left	1	1
	Cardiac Arrest	5	4
	Cardiac Failure Aggravated	1	0
	Cardiac Failure NOS	3	2
	Cardio-Respiratory Arrest	5	5
	Cardiomegaly	1	1
	Cardiovascular Disorder NOS	2	2
	Coronary Artery Occlusion	1	1
	Cyanosis NOS	1	1
	Myocardial Infarction	3	3
	Myocardial Ischemia	1	0
	Myocarditis NOS	1	1
	Nodal Arrhythmia	1	1
	Edema, Lower Limb	10	8
	Edema NOS	12	10
	Edema Peripheral	3	3
	Edema Upper Limb	4	2
	Palpitations	1	1
	Pericardial Effusion	1	1
	Pericarditis	1	1
	Pulmonary Edema NOS	6	5
	Pulse Absent	1	1
	Pulsus Bigeminus	1	1
	Sinus Bradycardia	1	1
	Sinus Tachycardia	3	3
	Tachycardia, NOS	21	19
	Valvular Heart Disease NOS	1	1
	Ventricular Extrasystoles	2	2
	Ventricular Fibrillation	3	3
Ventricular Flutter	1	1	

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Cardiac Disorders (Continued)	Ventricular Tachycardia	2	2
Congenital and Familial/Genetic Disorders	Epidermolysis Bullosa	1	1
	Gastrointestinal Arterio-Venous Malformation	1	1
	Polycystic Kidney	1	1
	Venous Malformation	1	0
Ear and Labyrinth Disorders	Deafness NOS	2	2
	Ear Disorder NOS	1	0
	Meniere's Disease	1	1
	Tinnitus	1	1
	Vertigo NEC	1	1
Endocrine disorders	Hypothyroidism	2	2
Eye Disorders	Amblyopia NOS	3	3
	Binocular Eye Movement Disorder NOS	1	1
	Blindness NEC	3	3
	Blindness Unilateral	1	1
	Conjunctival Disorder NOS	1	1
	Conjunctivitis NEC	2	2
	Diplopia	2	2
	Disorder of Globe or Orbit	1	1
	Eye Disorder NOS	1	0
	Lacrimation Increased	1	1
	Maculopathy	1	1
	Miosis	1	1
	Mydriasis	1	1
	Optic Ischemic Neuropathy	1	1
	Optic Neuritis NEC	1	1
	Optic Neuritis Retrobulbar	1	1
	Papilledema	3	2
	Photophobia	1	1
	Photopsia	1	1
	Uveitis NOS	1	1
Vision Abnormal NEC	3	3	
Vision Blurred	3	2	
Gastrointestinal Disorders	Abdominal Distension	8	8
	Abdominal Pain Lower	1	1
	Abdominal Pain NOS	58	53
	Abdominal Pain Upper	29	21
	Abdominal Tenderness	3	3
	Acute Abdomen	1	1
	Anal Disorder NOS	1	1
	Anastamotic Ulcer	1	1
	Appendix Disorder NOS	1	1
	Ascites	3	3
	Bezoar	1	1
	Bowel Sounds Abnormal	3	3
	Change in Bowel Habits NOS	1	1
	Colitis Hemorrhagic	2	2
	Colitis Ischemic	1	1
	Colitis NOS	6	5
	Colonic Hemorrhage	1	1
	Colonic Obstruction	1	1
	Colonic Perforation	1	1
	Colonic Stenosis	1	1
	Constipation	7	5
	Diarrhea Hemorrhagic	5	5
	Diarrhea NOS	20	19

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Gastrointestinal Disorders (Continued)	Diverticulitis NOS	2	2
	Diverticulum Intestinal	1	1
	Diverticulum Intestinal Hemorrhagic	1	1
	Diverticulum NOS	1	1
	Dry Mouth	4	3
	Duodenal Erosions	1	1
	Duodenal Ulcer	28	25
	Duodenal Ulcer Hemorrhage	10	9
	Duodenal Ulcer Perforation	4	4
	Duodenitis	7	7
	Dyspepsia	3	2
	Dysphagia	7	6
	Enteritis	1	1
	Eructation	1	1
	Fecal Abnormality NOS	1	1
	Feces Discolored	32	21
	Feces Hard	1	1
	Feces Pale	1	1
	Flatulence	1	1
	Food Poisoning NOS	1	1
	Frequent Bowel Movements	2	1
	Gastric Erosions	7	7
	Gastric Function Disorder NOS	2	2
	Gastric Hemorrhage	2	1
	Gastric Irritation	3	3
	Gastric Perforation	1	1
	Gastric Polyps	1	1
	Gastric Ulcer	31	29
	Gastric Ulcer Hemorrhage	14	12
	Gastric Ulcer Perforation	3	3
	Gastritis Hemorrhagic	1	1
	Gastritis NOS	26	23
	Gastro-Esophageal Reflux Disease	2	1
	Gastrointestinal Disorder NOS	13	11
	Gastrointestinal Disorder NOS Post-Op	1	1
	Gastrointestinal Hemorrhage NOS	137	114
	Gastrointestinal Irritation	3	3
	Gastrointestinal Ulcer NOS	8	0
	Gastrointestinal Upset	2	2
	Hematemesis	95	78
	Hemorrhoids	1	1
	Hiatus Hernia	3	3
	Ileus Paralytic	1	1
	Intestinal Ischemia	1	1
	Intestinal Ulcer	3	2
	Irritable Bowel Syndrome	2	2
	Loose Stools	1	1
	Mallory-Weis Syndrome	2	2
	Melena	85	69
	Mouth Hemorrhage	1	1
	Nausea	60	52
	Esophageal Disorder	2	1
	Esophageal Hemorrhage	1	1
	Esophageal Reflux	1	1
	Esophageal Stenosis	1	1
	Esophageal Ulcer	5	3
	Esophageal Varices NOS	5	4

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Gastrointestinal Disorders (Continued)	Esophagitis NOS	6	5
	Oral Mucosal Blistering	1	1
	Oral Mucosal Eruption	2	2
	Pancreatic Disorder	1	0
	Pancreatitis Acute	1	1
	Pancreatitis NOS	5	4
	Peptic Ulcer	11	11
	Peptic Ulcer Perforation	1	1
	Peptic Ulcer Reactivated	1	1
	Peritonitis	3	3
	Pyloric Stenosis NOS	3	3
	Pyloric Ulcer	3	3
	Rectal Bleeding	17	14
	Sore Throat NOS	3	2
	Stomatitis	2	2
	Throat Irritation	2	2
	Upper Gastrointestinal Hemorrhage	20	18
Vomiting NOS	68	63	
General Disorders and Administration	Alcohol Interaction	3	3
	Asthenia	10	9
	Chest Pain NEC	17	15
	Condition Aggravated	35	29
	Death NOS	3	3
	Difficulty in Walking	1	1
	Discomfort NOS	3	1
	Drug Effect Increased	1	1
	Drug Ineffective	6	4
	Drug Interaction NOS	16	12
	Fall	7	7
	Fatigue	30	24
	Feeling Abnormal	2	1
	Feeling Drunk	1	1
	Fistula NOS	2	2
	Hemorrhage NOS	19	10
	Impaired Healing	1	0
	Inflammation NOS	4	4
	Influenza-Like Illness	2	2
	Lethargy	4	3
	Malaise	12	12
	Mucosal Erosion NOS	2	2
	Mucous Membrane Disorder NOS	2	2
	Multi-Organ Failure	6	4
	Neck Edema	1	1
	No Adverse Effect	1	1
	Pain Exacerbated	3	2
	Pain NOS	17	14
	Pyrexia	36	35
	Rigors	7	7
	Shivering	1	1
	Sickness	1	1
	Sluggishness	2	1
	Swelling NOS	3	3
	Tenderness NOS	1	1
	Thirst	1	1
	Ulcer Hemorrhage NOS	2	1
Ulcer NOS	7	3	
Unevaluable Reaction	3	2	

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
General Disorders and Administration (Continued)	Weakness	36	30
Hepato-Biliary Disorders	Autoimmune Hepatitis	2	2
	Bile Duct Stricture	1	0
	Biliary Colic	2	2
	Biliary Tract Disorder NOS	1	1
	Budd Chiari Syndrome	1	1
	Cholangitis NOS	1	0
	Cholecystitis NOS	2	1
	Cholelithiasis	4	4
	Cholestasis	1	1
	Gall Bladder Disease NOS	2	1
	Gall Bladder Disorder NOS	1	1
	Hepatic Atrophy	1	1
	Hepatic Cirrhosis NOS	4	4
	Hepatic Congestion	1	1
	Hepatic Disorder	2	2
	Hepatic Failure	10	9
	Hepatic Fibrosis	2	2
	Hepatic Function Abnormal NOS	3	3
	Hepatic Necrosis	6	6
	Hepatic Vein Thrombosis	1	1
	Hepatitis Cholestatic	3	3
	Hepatitis NOS	14	14
	Hepato-Lenticular Degeneration	1	1
	Hepatocellular Damage	6	6
	Hepatomegaly	6	6
	Hepatorenal Syndrome	1	1
	Hepatotoxicity NOS	1	1
	Hyperbilirubinemia	2	2
	Jaundice Cholestatic	2	1
	Jaundice Extrahepatic Obstructive NOS	1	0
	Jaundice NOS	13	12
	Liver Fatty	2	2
	Portal Hypertension	1	1
Immune System Disorders	Anaphylactic Reaction	4	2
	Anaphylactic Shock	3	3
	Anaphylactoid Reaction	6	6
	Drug Hypersensitivity	4	3
	Hypersensitivity NOS	12	11
Infections and Infestations	Bronchitis NOS	1	1
	Candida NOS	1	1
	Cellulitis	1	1
	Cellulitis, Streptococcal	1	0
	Chickenpox	1	1
	Cystitis Escherichia	1	1
	Echo Virus Infection NOS	1	1
	Enterococcal Bacteremia	1	1
	Escherichia Infection NOS	2	2
	Fibromyalgia Syndrome	1	1
	Gastroenteritis Helicobacter	5	5
	Gastroenteritis NOS	5	5
	Gastroenteritis Viral NOS	1	0
	Hepatitis B	2	2
	Herpes Simplex	2	2
	Herpes Zoster	1	1
	Infection NOS	3	2

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Infections and Infestations (Continued)	Influenza	2	1
	Keratoconjunctivitis	1	1
	Kidney Infection NOS	1	1
	Meningitis Bacterial NOS	1	1
	Meningitis Herpes	1	1
	Meningitis NOS	4	4
	Meningitis Viral Nec	1	1
	Necrotising Fasciitis NOS	5	4
	Oral Candidiasis	1	1
	Pericarditis Viral NOS	1	1
	Peritonitis Bacterial NOS	1	1
	Pneumonia NOS	14	14
	Post-Viral Fatigue Syndrome	1	1
	Pseudomonas Aeruginosa Infection NOS	2	2
	Pseudomonas Infection NOS	2	2
	Purulence	1	1
	Pyelonephritis NOS	3	3
	Sepsis NOS	10	9
	Sepsis Secondary	1	1
	Septicemia Escherichial	1	1
	Septicemia Pseudomonal	1	1
	Superinfection	1	1
	Toxic Shock Syndrome	1	0
	Urinary Tract Infection	11	10
Viral Infection NOS	1	1	
Injury and Poisoning	Accidental Overdose (Therapeutic Agent)	2	2
	Animal Bite	1	1
	Back Injury NOS	1	1
	Blister	2	2
	Digoxin Toxicity	4	2
	Drug Toxicity NOS	8	7
	Ear Drum Perforation	1	1
	Foot Fracture	1	1
	Hypothermia	4	4
	Injury NOS	1	0
	Joint Dislocation NEC	1	0
	Laceration	1	1
	Limb Injury NOS	1	1
	Medication Error	13	12
	Nephropathy Toxic	1	1
	Non-Accidental Overdose	39	36
	Overdose NOS	22	20
	Pneumothorax Traumatic	1	1
	Rib Fracture	1	0
	Road Traffic Accident	2	1
Therapeutic Agent Poisoning	2	2	
Investigations	Alanine Aminotransferase Increased	5	5
	Albuminuria Present	2	2
	Ammonia Increased	1	1
	Analgesic Drug Level NOS Above Therapeutic	1	1
	Anion Gap Abnormal	1	1
	Antibody NOS Positive	2	2
	Antinuclear Factor Positive	3	3
	Aspartate Aminotransferase Increased	4	4
	Bacteruria NOS Present	1	1
	Biopsy Liver Abnormal	2	2

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Investigations (Continued)	Bleeding Time Prolonged	3	3
	Blood Albumin Decreased	1	1
	Blood Albumin Increased	1	1
	Blood Alkaline Phosphatase NOS Increased	1	1
	Blood Amylase Decreased	1	0
	Blood Amylase Increased	3	3
	Blood Bicarbonate Abnormal	1	1
	Blood Bicarbonate Decreased	1	1
	Blood Bilirubin Increased	7	7
	Blood Calcium	1	1
	Blood Calcium Decreased	1	0
	Blood Carbon Dioxide Decreased	2	1
	Blood Chloride Decreased	1	1
	Blood Chloride Increased	2	2
	Blood Creatine Increased	4	4
	Blood Creatine Phosphokinase Increased	5	5
	Blood Creatine Phosphokinase MB Incr	1	1
	Blood Creatinine Abnormal	2	2
	Blood Creatinine Increased	49	40
	Blood Culture Positive	2	2
	Blood Fibrinogen Increased	1	1
	Blood Glucose Increased	4	4
	Blood Immunoglobulin G Increased	1	1
	Blood in Stool	22	19
	Blood Lactate Dehydrogenase Increased	1	1
	Blood Magnesium Increased	1	0
	Blood pH Decreased	4	4
	Blood pH Increased	1	0
	Blood Potassium Decreased	2	2
	Blood Potassium Increased	2	1
	Blood Pressure Decreased	4	3
	Blood Pressure Systolic Decreased	1	1
	Blood Pressure Increased	1	1
	Blood Sodium	1	1
	Blood Sodium Decreased	1	1
	Blood Thyroid Stim Hormone Increased	3	3
	Blood Triglycerides Increased	1	1
	Blood Urea Abnormal	2	2
	Blood Urea Increased	22	15
	Body Temperature Decreased	3	3
	Body Temperature Increased	1	1
	C-Reactive Protein increased	5	5
	Coagulation Time NOS Prolonged	1	0
	Complement Factor C3 Increased	1	1
	Computerized Tomogram Abnormal	1	1
	Creatinine Renal Clearance Normal	1	1
	CSF Lymphocyte Count Increased	1	1
	CSF Pressure Increased	1	2
	CSF Protein Increased	1	1
	Culture NOS Positive	1	1
	Culture Urine Positive	1	1
	Differential White Blood Cell Count Abnormal	1	1
	DNA Antibody NOS Positive	1	1
	Drug Level NOS Above Therapeutic	14	12
	Electrocardiogram Abnormal NOS	8	8

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Investigations (Continued)	Electrocardiogram QRS Complex Prolonged	2	2
	Electrocardiogram QT Shortened	1	1
	Electrocardiogram ST Segment Abnormal	1	1
	Electrocardiogram ST Segment Depression	2	2
	Enzyme Abnormality NOS	1	1
	Eosinophil Count Increased	1	1
	Erythrocyte Sedimentation Rate Increased	1	1
	Fecal Occult Blood	2	2
	Fecal Occult Blood Positive	12	9
	Gamma-Glutamyltransferase Increased	19	19
	Glycosuria Present	1	1
	Hematocrit Decreased	9	1
	Hematuria Present	10	10
	Hemoglobin Decreased	19	20
	Heart Rate Increased	10	9
	Hepatitis A Antibody Positive	1	1
	Hepatic C antibody Positive	1	0
	International Normalized Ratio Decreased	1	1
	International Normalized Ratio Increased	5	2
	Leukocyte Count Decreased	7	7
	Leukocyte Count Increased	10	10
	Lipase Increased	3	3
	Lipids NOS Increased	1	1
	Liver Function Tests NOS Abnormal	17	14
	Neutrophil Count Increased	1	1
	Nuclear Magnetic Resonance Imaging Abnormal	1	1
	Oxygen Saturation Decreased	16	16
	Pancreatic Enzymes NOS Increased	1	1
	Paracetamol Increased	1	1
	PH Urine Increased	1	1
	Platelet Count Decreased	7	5
	PO2 Increased	3	2
	Protein C Decreased	1	1
	Proteinuria Present	3	3
	Prothrombin Level Increased	4	4
	Prothrombin Time Abnormal NOS	1	1
	Prothrombin Time Prolonged	5	5
	Pulse Abnormal NOS	1	1
	Pulse Pressure Decreased	1	1
	Pyelogram Intravenous Abnormal	1	1
	Red Blood Cell Count Decreased	1	1
	Respiratory Rate Decreased	4	4
	Respiratory Rate Increased	2	2
	Rheumatoid Factor	1	1
	Rheumatoid Factor Positive	1	1
	Salicylate Increased	1	1
	Scan NOS Abdomen Abnormal	2	2
	Toxicology NOS Abnormal	3	3
	Transaminase NOS Increased	6	5
	Ultrasound Bladder Abnormal	1	1
	Urine Analysis Abnormal NOS	1	1
	Urine Sodium Increased	1	1
	Weight Decreased	8	6
	Weight Increased	3	3
	White Blood Cells Urine Positive	4	4

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Investigations (Continued)	X-Ray NOS Abnormal	1	1
	X-Ray NOS Chest Abnormal	3	3
	X-Ray NOS Upper Gastrointestinal Tract Abnormal	1	1
Metabolism and Nutrition Disorders	Acidosis NOS	6	6
	Alkalosis	1	1
	Anorexia	5	5
	Appetite Decreased NOS	8	5
	Calcinosis	1	1
	Cow's Milk Intolerance	1	1
	Dehydration	13	13
	Diabetes Mellitus Insulin-Dependent	1	1
	Diabetes Mellitus Non Insulin Dependent	1	1
	Eating Disorder NEC	1	1
	Food Intolerance NOS	3	3
	Glucose Tolerance Impaired	1	1
	Gout	1	1
	Hyperglycemia NOS	2	2
	Hyperkalemia	10	9
	Hyperlipidemia NOS	2	2
	Hypernatremia	2	2
	Hypertriglyceridemia	3	3
	Hypoglycemia	1	1
	Hypokalemia	3	3
	Hyponatremia	3	3
	Hypovolemia	1	1
	Lactic Acidosis	4	4
Metabolic Acidosis NOS	9	9	
Polydipsia	3	2	
Renal Tubular Acidosis	1	1	
Musculoskeletal, Connective Tissue	Arthralgia	6	6
	Arthralgia Aggravated	1	1
	Arthritis NOS	1	1
	Arthritis NOS Aggravated	1	1
	Articular Disc Disorder	1	1
	Back Pain	13	13
	Bone Pain	1	1
	Intervertebral Disc Disorder	1	1
	Joint Swelling	1	0
	Lumbar Disc Lesion	1	1
	Muscle Cramps	1	1
	Muscle Weakness NOS	1	1
	Musculoskeletal Pain	2	1
	Myalgia	7	6
	Neck Stiffness	1	1
	Neck Pain	1	1
	Pain in Jaw	1	1
	Pain in Limb	3	2
	Rhabdomyolysis	3	3
	Sjogren's Syndrome	1	0
Systemic Lupus Erythematosus	3	3	
Neoplasms Benign and Malignant	Adenocarcinoma NOS	1	0
	Breast Cancer Female NOS	1	1
	Breast Cancer In Situ	1	0
	Colon Cancer NOS	1	1
	Colon Neoplasm NOS	2	2
	Fibroma NOS	1	1

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Neoplasms Benign and Malignant (Continued)	Gastric Cancer NOS	1	1
	Granuloma NOS	1	1
	Lipoma NOS	1	1
	Metastases to Lymph Nodes	1	1
	Nonhodgkin's Lymphoma	1	1
	Rectal Neoplasm NOS	1	1
Nervous System Disorders	Amnesia NEC	2	2
	Aphasia	1	1
	Ataxia	1	1
	Balance Impaired NOS	1	1
	Brain Herniation	1	1
	Burning Sensation NOS	4	3
	Central Nervous System Depression NOS	2	2
	Cerebral Edema	3	3
	Chorea NOS	1	1
	Coma NEC	23	22
	Convulsions NOS	6	6
	Convulsions NOS Aggravated	1	1
	Corneal Reflex Decreased	2	2
	Dementia	1	1
	Depressed Level of Consciousness	8	8
	Dizziness (Exc Vertigo)	54	42
	Dizziness Postural	1	1
	Drooling	1	1
	Dysarthria	4	4
	Dystonia	1	1
	Encephalitis NOS	2	2
	Encephalopathy NOS	1	1
	Epilepsy Aggravated	2	1
	Gait Abnormal NOS	2	2
	Grand Mal Convulsion	2	2
	Hemorrhagic Stroke	1	1
	Headache NOS	14	14
	Headache NOS Aggravated	3	3
	Hepatic Encephalopathy	3	2
	Hypoesthesia	4	3
	Hyporeflexia	1	1
	Insomnia NEC	5	4
	Loss of Consciousness	9	8
	Memory Impairment	3	3
	Meningitis Aseptic	5	5
	Mental Impairment NOS	2	2
	Metabolic Encephalopathy NOS	1	1
	Migraine Aggravated	1	1
	Motor Dysfunction NOS	1	1
	Myasthenic Syndrome	1	1
	Myoclonic Jerks	1	1
	Neurological Disorder NOS	1	0
	Parkinson's Disease NOS	2	2
	Paresthesia NEC	4	3
	Paralysis NOS	2	1
	Pupil Fixed	1	1
	Pupillary Disorder NOS	1	1
	Pupillary Reflex Impaired	1	1
	Reflexes Abnormal NEC	1	1
	Sciatic Nerve Lesion NOS	1	1
Sedation	12	11	

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Nervous System Disorders (Continued)	Sleep Phase Rhythm Disturbance	1	1
	Speech Disorder NEC	8	6
	Spinal Stenosis NOS	1	0
	Status Epilepticus	1	0
	Stupor	1	1
	Syncope	20	14
	Tardive Dyskinesia	2	2
	Transient Global Amnesia	1	1
	Tremor NEC	6	5
	Trismus	1	1
	Vasovagal Attack	1	1
Visual Field Defect NOS	1	1	
Pregnancy, Puerperium and Perinatal Conditions	Abortion Spontaneous NOS	2	2
	Complications of Maternal Exposure to Therapeutic Drugs	2	0
	Premature Baby	1	0
	Premature Rupture of Membranes	1	0
Psychiatric Disorders	Abnormal Behavior NOS	1	1
	Abuse NOS	1	1
	Agitation	7	5
	Alcoholism	3	3
	Anxiety NEC	4	4
	Apathy	1	1
	Circadian Rhythm Sleep Disorder	1	1
	Cognitive Deterioration	1	1
	Completed Suicide	15	14
	Confusion	7	7
	Delusion NOS	2	2
	Depressed Mood	1	1
	Depression NEC	6	6
	Distress	2	1
	Drug Dependence	1	1
	Emotional Disturbance NOS	3	2
	Fear, Focus NEC	1	1
	Grandiosity	2	2
	Hallucinations Aggravated	1	1
	Hallucinations, Mixed	1	1
	Hostility	1	1
	Hypomania	2	2
	Impulsive Behavior NOS	2	2
	Irritability	1	1
	Listless	2	2
	Major Depressive Disorder NOS	1	1
	Mania	1	1
	Markedly Reduced Food Intake	6	5
	Mood Alteration NOS	1	1
	Mood Disorder	1	1
Paranoia	1	1	
Personality Disorder NOS	1	1	
Psychotic Disorder NOS	1	1	
Schizophrenia NOS	1	1	
Suicide Attempt	11	10	
Thinking Abnormal NEC	2	2	
Renal and Urinary Disorders	Acute Pre-Renal Failure	1	0
	Anuria	3	3
	Chronic Renal Impairment	1	1
	Diabetic Nephropathy NOS	1	1

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Renal and Urinary Disorders (Continued)	Difficulty in Micturition	4	4
	Dysuria	1	1
	Fluid Retention	2	2
	Glomerulonephritis Membranous	1	1
	Glomerulonephritis Minimal Lesion	1	1
	Glomerulonephritis NOS	1	1
	Glomerulonephritis Proliferative	1	1
	Hydronephrosis	3	3
	Loin Pain	6	6
	Nephritis Interstitial	17	15
	Nephritis NOS	7	7
	Nephrosclerosis	1	1
	Nephrotic Syndrome	3	1
	Oliguria	11	11
	Polyuria	2	1
	Pyuria	1	1
	Renal Cyst NOS	2	2
	Renal Disorder	1	1
	Renal Failure Acute	49	46
	Renal Failure Acute on Chronic	1	0
	Renal Failure Aggravated	3	1
	Renal Failure Chronic	2	1
	Renal Failure NOS	27	21
	Renal Impairment NOS	22	19
	Renal Interstitial Fibrosis	5	5
	Renal Papillary Necrosis	1	1
	Renal Tubular Atrophy	1	1
Renal Tubular Necrosis	8	5	
Urinary Frequency	1	1	
Urinary Incontinence	1	1	
Urine Discoloration	8	7	
Reproductive System and Breast Disorders	Amenorrhea NOS	1	1
	Benign Prostatic Hyperplasia	1	1
	Breast Pain	1	1
	Genital Disorder Female NOS	2	2
	Genital Ulceration NOS	1	1
	Pelvic Pain NOS	1	1
	Vaginal Discharge	1	1
	Vaginal Hemorrhage	1	1
Respiratory, Thoracic and Mediastinal Disorders	Adult Respiratory Distress Syndrome	3	2
	Airway Obstruction NOS	1	1
	Apnea	4	4
	Asthma Aggravated	2	2
	Asthma NOS	2	2
	Atelectasis	1	1
	Brain Hypoxia	1	1
	Breath Sounds Decreased	2	2
	Bronchospasm NOS	7	6
	Chest Tightness	5	5
	Cough	4	4
	Creptitations	1	1
	Cystic Fibrosis Lung	1	1
	Dyspnea Exacerbated	3	2
	Dyspnea Exertional	4	4
	Dyspnea NOS	39	37
	Epistaxis	8	5
	Hemoptysis	5	4

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Respiratory, Thoracic and Mediastinal Disorders (Continued)	Hypercapnia	1	1
	Hyperventilation	1	1
	Hypoventilation	2	2
	Hypoxia	1	1
	Laryngeal Edema	1	1
	Laryngospasm	1	1
	Lung Disorder NOS	4	4
	Nasal Edema	1	1
	Non-Cardiogenic Pulmonary Edema	1	1
	Pleural Effusion	4	3
	Pleural Fibrosis	1	1
	Pleuritic Pain	1	1
	Pneumonia Aspiration	2	2
	Pneumothorax NOS	1	1
	Pulmonary Alveolar Hemorrhage	3	3
	Respiratory Arrest (Exc Neonatal)	5	5
	Respiratory Depression	2	1
	Respiratory Disorder NOS	3	3
	Respiratory Distress	4	4
	Respiratory Failure (Exc Neonatal)	4	4
	Rhinitis NOS	1	1
	Rhinorrhea	1	1
	Sinus Congestion	1	1
	Sneezing	2	2
Tachypnea	7	7	
Throat Edema	4	3	
Throat Tightness	3	2	
Skin and Subcutaneous Tissue Disorders	Angioneurotic Edema	16	14
	Clamminess	4	4
	Dermatitis Allergic	2	1
	Dermatitis Bullous	5	4
	Dermatitis Exfoliative	2	1
	Dermatitis NOS	22	17
	Eccymosis	7	7
	Eczema NOS	1	1
	Epidermal Necrolysis	7	6
	Erythema Multiforme	2	2
	Erythema NEC	2	2
	Eyelid Edema	5	5
	Face Edema	18	16
	Hemorrhage Subcutaneous	1	1
	Leukocytoclastic Vasculitis	2	2
	Localized Skin Reaction	1	1
	Edema Mouth	1	1
	Petechiae	6	6
	Photosensitivity Reaction NOS	1	1
	Pigmentation Disorder NOS	1	1
	Pruritis NOS	16	13
	Purpura NOS	6	6
	Rash Erythematous	11	10
	Rash Generalized	3	2
	Rash Macular	1	1
	Rash Maculo-Papular	5	5
	Rash Morbilliform	2	2
	Rash Papular	3	2
	Rash Pruritic	2	2
	Rash Vesicular	1	1

Table 17. Serious AEs for IBU as Single Drug in AERS (Primary and Secondary Suspect Drug Combined) (Pages 76-89)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Skin and Subcutaneous Tissue Disorders (Continued)	Skin Discoloration	1	1
	Skin Disorder NOS	1	1
	Skin Lesion NOS	1	1
	Skin Necrosis	1	1
	Skin Ulcer	3	3
	Skin Warm	1	1
	Sloughing of Skin	1	1
	Stevens Johnson Syndrome	8	8
	Sweating Increased	7	5
	Systemic Lupus Erythematosus Rash	1	1
	Tongue Edema	10	7
	Toxicoderma	4	4
	Urticaria NOS	13	12
Vitiligo	1	1	
Social circumstances	Drug Abuse	4	4
	Immobile	1	1
	Occupational Exposure to Toxic Agents NOS	1	1
	Tobacco Abuse	1	1
Surgical and Medical Procedures	Blood Product Transfusion	1	1
	Cholecystectomy	1	1
	Dialysis NOS	5	5
	Hemodialysis	6	6
	Knee Arthroplasty	1	1
	Liver Transplant	2	2
	Nerve Block	1	1
	Operation NOS	1	1
	Post-Operative Complications	1	1
	Post-Operative Hemorrhage	1	1
	Post-Operative Wound Infection	1	1
	Stitch Abscess	1	1
	Whole Blood Transfusion	2	1
Vascular Disorders	Acute Circulatory Failure	2	1
	Collapse	4	4
	Flushing	3	1
	Hematoma	3	3
	Hemodialysis	1	1
	Henoch-Schonlein Purpura	1	1
	Hot Flushes	2	2
	Hypertension Aggravated	2	2
	Hypertension NOS	5	5
	Hypotension NOS	37	33
	Intracranial Hemorrhage NOS	2	1
	Pallor	3	3
	Postural Hypotension	9	7
	Pulmonary Embolism	3	2
	Subarachnoid Hemorrhage NOS	1	1
	Thromboembolism NOS	3	3
	Thrombophlebitis Deep	1	1
	Varicose Veins NOS	2	0
	Vascular Disorder NOS	1	1
	Vasculitis NOS	1	1
	Vasodilatation	2	2
	Vein Disorder NOS	1	1
	Venous Thrombosis Deep Limb	2	2
Venous Ulcer NOS	1	1	

Table 18. Adverse Events Associated with the Outcome of Death with Single Agent IBU from FDA AERS Database for Those ≥ 12 Years of Age and “Age Unknown.” (Pages 90-95)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Subjects ≥ 12
Blood and Lymphatic System Disorders	Anemia NOS	2	2
	Coagulation Disorder NOS	1	1
	Leucocytosis NOS	1	1
	Pancytopenia	2	2
	Splenomegaly	2	2
	Thrombocytopenia	2	2
Cardiac Disorders	Atrial Fibrillation	1	1
	Bradycardia NOS	3	3
	Bundle Branch Block Left	1	1
	Cardial Arrest	5	4
	Cardio-Respiratory Arrest	5	2
	Cardiovascular Disorder NOS	1	1
	Coronary Artery Occlusion	1	1
	Edema Upper Limb	1	0
	Edema Lower Limb	2	2
	Edema NOS	1	1
	Edema Peripheral	3	3
	Myocardial Infarction	1	1
	Myocardial Ischemia	1	0
	Myocarditis NOS	1	1
	Pulmonary Edema NOS	1	1
	Pulse Absent	1	1
	Sinus Tachycardia	1	1
	Tachycardia NOS	6	5
	Valvular Heart Disease NOS	1	1
Ventricular Flutter	1	1	
Ventricular Tachycardia	1	1	
Congenital and Familial/Genetic	Epidermolysis bullosa	1	1
	Venous Malformation	1	1
Eye Disorders	Binocular Eye Movement Disorder NOS	1	1
	Conjunctivitis NEC	2	2
	Maculopathy	1	1

**APPEARS THIS WAY
ON ORIGINAL**

Table 18. Adverse Events Associated with the Outcome of Death with Single Agent IBU from FDA AERS Database for those ≥ 12 Years of Age and Age Unknown (Pages 90-95).

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Subjects ≥ 12
Gastrointestinal Disorders	Abdominal Distension	1	1
	Abdominal Pain NOS	5	5
	Abdominal Pain Upper	2	2
	Acute Abdomen	1	1
	Ascites	1	1
	Bezoar	1	1
	Bowel Sounds Abnormal	1	1
	Colitis NOS	2	2
	Colonic Perforation	1	1
	Constipation	1	1
	Diarrhea Hemorrhagic	1	1
	Diarrhea NOS	4	4
	Duodenal Ulcer	6	6
	Duodenal Ulcer Hemorrhage	3	3
	Duodenal Ulcer Perforation	3	3
	Esophagitis NOS	1	1
	Food Poisoning NOS	1	1
	Gastric Erosions	1	1
	Gastric Ulcer	1	1
	Gastric Perforation	1	1
	Gastric Ulcer Hemorrhage	3	1
	Gastric Ulcer Perforation	1	1
	Gastritis NOS	3	3
	Gastrointestinal Disorder NOS	2	2
	Gastrointestinal Hemorrhage NOS	18	17
	Hematemesis	11	11
	Hiatus Hernia	2	2
	Intestinal Ischemia	1	1
	Intestinal Ulcer	1	0
	Loose Stools	1	1
	Melena	11	9
	Nausea	6	6
	Oral Mucosal Blistering	1	1
	Oral Mucosal Eruption	1	1
Pancreatitis NOS	2	2	
Peptic Ulcer	2	1	
Peptic Ulcer Perforation	1	2	
Peritonitis	2	2	
Pyloric Stenosis NOS	1	1	
Rectal Bleeding	2	2	
Sore Throat NOS	1	1	
Vomiting NOS	9	9	
General Disorders and Administration Site Conditions	Alcohol Interaction	2	2
	Condition Aggravated	8	7
	Death NOS	3	3
	Drug Ineffective	1	0
	Drug Interaction NOS	1	1
	Fall	1	1
	Hemorrhage NOS	6	4
	Impaired Healing	1	0
	Malaise	1	1
	Multi-Organ Failure	5	3
	Pain Exacerbated	1	0
	Pain NOS	1	1
	Pyrexia	4	4
	Sluggishness	1	1
	Swelling NOS	1	1
	Sickness	1	1
Weakness	4	2	

Table 18. Adverse Events Associated with the Outcome of Death with Single Agent IBU from FDA AERS Database for Those ≥ 12 Years of Age and Age Unknown (Pages 90-95).

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Subjects ≥ 12
Hepatobiliary Disorders	Hepatic Cirrhosis NOS	1	1
	Hepatic Congestion	1	1
	Hepatic Failure	5	4
	Hepatic Function Abnormal NOS	1	1
	Hepatic Necrosis	1	1
	Hepatocellular Damage	1	1
	Hepatomegaly	2	2
	Jaundice NOS	1	1
Immune System Disorders	Drug Hypersensitivity	1	1
	Hypersensitivity NOS	1	1
Infections and Infestations	Cellulitis Streptococcal	1	0
	Echo Virus Infection NOS	1	1
	Enterococcal Bacteremia	1	1
	Escherichia Infection NOS	2	2
	Gastroenteritis NOS	2	2
	Infection NOS	1	0
	Influenza	1	1
	Necrotizing Fasciitis NOS	2	1
	Pneumonia NOS	9	9
	Pseudomonas Infection NOS	1	1
	Sepsis NOS	7	6
	Sepsis Secondary	1	1
	Septicemia Escherichial	1	1
	Septicemia Pseudomonal	1	1
	Toxic Shock Syndrome	1	0
	Urinary Tract Infection NOS	3	3
Injury and Poisoning	Accidental Overdose (Therapeutic Agent)	2	2
	Durg Toxicity NOS	3	3
	Hypothermia	2	2
	Medication Error	5	2
	Non-Accidental Overdose	21	20
	Overdose NOS	4	4
	Pneumothorax Traumatic	1	1

**APPEARS THIS WAY
ON ORIGINAL**

Table 18. Adverse Events Associated with the Outcome of Death with Single Agent IBU from FDA AERS Database for Those ≥ 12 Years of Age and Age Unknown (Pages 90-95).

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Subjects ≥ 12
Investigations	Alanine Aminotransferase Increased	2	2
	Albuminuria Present	1	1
	Ammonia Increased	1	1
	Analgesic Drug Levels NOS Above Therapeutic	1	1
	Antinuclear Factor Positive	1	1
	Aspartate Aminotransferase Increased	1	1
	Blood Alkaline Phosphatase NOS Increased	1	1
	Blood Bilirubin Increased	2	2
	Blood Carbon Dioxide Decreased	1	0
	Blood Chloride Increased	1	1
	Blood Creatine Increased	1	1
	Blood Creatinine Increased	6	6
	Blood Culture Positive	1	1
	Blood in Stool	2	2
	Blood pH Increased	1	0
	Blood Potassium Increased	1	1
	Blood Pressure Decreased	1	1
	Blood Pressure Systolic Decreased	1	1
	Blood Thyroid Stimulating Hormone Increased	1	1
	Blood Urea Increased	3	2
	Body Temperature Decreased	2	2
	C-Reactive Protein Increased	1	1
	Drug Level NOS Above Therapeutic	10	10
	Gamma-Glutamyl Transferase Increased	1	1
	Hematocrit Decreased	1	1
	Hemoglobin Decreased	2	1
	International Normalized Ratio Increased	1	1
	Leukocyte count Decreased	2	2
	Leukocyte Count Increased	1	2
	Liver Function Tests NOS Abnormal	3	1
	Oxygen Saturation Decreased	1	1
	Paracetamol Increased	1	1
	Platelet Count Decreased	3	3
	PO ₂ Increased	1	0
	Prothrombin Time Prolonged	2	2
	Respiratory Rate Decreased	2	2
	Respiratory Rate Increased	1	1
	Salicylate Increased	1	1
	Scan NOS Abdomen Abnormal	1	1
	Toxicology NOS Abnormal	2	2
	Transaminase NOS Increased	1	1
	X-Ray NOS Chest Abnormal	3	3
	X-Ray NOS Upper Gastrointestinal Tract Abnormal	1	1
Metabolism and Nutrition Disorders	Acidosis NOS	4	4
	Alkalosis NOS	1	1
	Calcinosis	1	1
	Dehydration	3	3
	Hyperkalemia	1	1
	Hypernatremia	1	1
	Hypokalemia	2	2
Musculoskeletal, Connective tissue and bone disorders	Arthralgia	2	2
	Back Pain	2	2
	Joint Swelling	1	0
	Musculoskeletal Pain	1	1
	Myalgia	2	1
Neoplasms benign and malignant	Colon Cancer NOS	1	1

Table 18. Adverse Events Associated with the Outcome of Death with Single Agent IBU from FDA AERS Database for Those ≥ 12 Years of Age and age Unknown (Pages 90-95).

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Subjects ≥ 12
Nervous System Disorders	Brain Herniation	1	1
	Cerebral Edema	2	2
	Coma NEC	12	11
	Convulsions NOS	2	2
	Corneal Reflex Decreased	1	1
	Dementia NOS	1	1
	Depressed Level of Consciousness	5	6
	Drooling	1	1
	Encephalitis NOS	1	1
	Headache NOS Aggravated	1	1
	Hemorrhagic Stroke	1	1
	Hepatic Encephalopathy	1	0
	Hyporeflexia	1	1
	Loss of Consciousness NEC	2	1
	Meningitis Aseptic	1	1
	Mental Impairment NOS	1	1
	Parkinson's Disease NOS	2	2
	Pupillary Reflex Impaired	1	1
	Sedation	1	1
	Stupor	1	1
Syncope	1	1	
Tardive Dyskinesia	1	2	
Tremor NEC	2	2	
Pregnancy, puerperium and perinatal conditions	Complications of Maternal Exposure to Therapeutic Drugs	1	0
	Premature Baby	1	0
	Premature Rupture of Membranes	1	0
Psychiatric Disorders	Abuse NOS	1	1
	Alcoholism	1	1
	Completed Suicide	29	28
	Depression NEC	2	2
	Hallucinations Aggravated	1	1
	Hallucinations, Mixed	1	1
	Paranoia	1	1
	Schizophrenia NOS	1	1
Thinking Abnormal NEC	1	1	
Renal and Urinary Disorders	Glomerulonephritis Minimal Lesion	1	1
	Nephritis Interstitial	1	1
	Nephritis NOS	2	2
	Oliguria	4	4
	Renal Failure Acute	5	5
	Renal Failure Acute on Chronic	1	0
	Renal Failure NOS	4	4
	Renal Impairment NOS	3	3
Urinary Incontinence	1	1	
Reproductive System and Breast Disorders	Vaginal hemorrhage	1	1
Respiratory, Thoracic and Mediastinal Disorders	Adult Respiratory Distress Syndrome	3	2
	Apnea	1	1
	Brain Hypoxia	1	1
	Breath Sounds Decreased	1	1
	Creptitations	1	1
	Cystic Fibrosis Lung	1	1
	Hypercapnia	1	1
	Hypoventilation	1	1
	Lung Disorder NOS	3	3
	Pneumonia Aspiration	2	2
	Pneumothorax NOS	1	1
	Pulmonary Alveolar Hemorrhage	3	3
	Respiratory Arrest (Exc Neonatal)	3	3
	Respiratory Depression	1	1
	Respiratory Distress	1	1
	Respiratory Disorder NOS	1	1
Respiratory Failure (Exc Neonatal)	4	4	
Tachypnea	2	2	

Table 18. Adverse Events Associated with the Outcome of Death with Single Agent IBU from FDA AERS Database for Those ≥ 12 Years of Age and Age Unknown (Pages 90-95).

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Subjects ≥ 12
Skin & Subcutaneous Tissue Disorders	Clamminess	1	1
	Dermatitis Exfoliative NOS	1	1
	Dermatitis NOS	2	1
	Ecchymosis	2	2
	Epidermal necrolysis	2	2
	Erythema NEC	1	1
	Hemorrhage Subcutaneous	1	1
	Petechiae	1	1
	Purpura NOS	1	1
Social Circumstances	Drug Abuse	3	3
Surgical and Medical	Dialysis NOS	1	1
	Post-Operative Hemorrhage	1	1
	While Blood Transfusion	1	1
Vascular Disorders	Acute Circulatory Failure	1	0
	Collapse	2	2
	Hypotension NOS	14	13
	Pallor	1	1
	Pulmonary Embolism	1	1
	Subarachnoid Hemorrhage NOS	1	1
	Thromboembolism NOS	3	3
	Vein Disorder NOS	1	1

**APPEARS THIS WAY
ON ORIGINAL**

Appendix II – Pseudoephedrine Hydrochloride as a Single Ingredient

Table 20. Serious AEs Associated with PSE in SRS Database for Subjects ≥12 Years of Age and Age Unknown. (Pages 96-99)

Body System Category	Serious Event	Number Serious AE	Serious AE in Those ≥12
Body as a Whole	Abdominal, Enlarged	1	0
	Allergic Reaction	2	1
	Anaphylaxis	5	4
	Anomaly, Congenital	2	0
	Asthenia	6	4
	Chills	1	0
	Death	4	2
	Drug Interaction	7	6
	Edema Face	3	3
	Edema General	1	1
	Fever	6	4
	Headache	4	4
	Infection	2	1
	Infection, Super	2	2
	Malaise	1	0
	Mucous Membrane Disorder	1	1
	No Drug Effect	1	1
	Overdose	5	5
	Overdose Accidental	5	3
	Overdose, Intentional	12	10
	Pain, Abdominal	7	1
	Pain, Back	1	1
	Pain, Chest	9	8
	Pain, Neck	1	1
	Reaction Aggravation	2	2
	Reaction Uneval	3	1
	Sepsis	3	3
Shock	1	1	
Sudden Death	3	3	
Suicide Attempt	4	4	
Cardiovascular System	Angina Pectoris	3	2
	Arrythmia	5	4
	Arteritis	1	1
	Cardiomegaly	1	1
	Cardiomyopathy	2	2
	Cardiovascular Disorder	2	1
	Cerebrovascular Accident	3	2
	Fibrillation, Atrial	8	7
	Fibrillation, Ventricular	2	2
	Heart Arrest	8	8
	Heart Failure	1	1
	Heart Failure, Right	3	3
	Hemorrhage	3	1
	Hemorrhage, Cerebral	1	0
	Hemorrhage, Intracranial	3	2
	Hemorrhage, Subarachnoid	1	1
	Hypertension	12	9
	Hypotension	10	8
	Hypotension, Postural	1	1
	Infarct, Cerebral	1	0
Infarct, Myocardial	8	7	

Table 20. Serious AEs Associated with PSE in SRS Database for Subjects ≥12 Years of Age and Age Unknown. (Pages 96-99)

Body System Category	Serious Event	Number Serious AE	Serious AE in Those ≥12
Cardiovascular System (Continued)	Ischemia, Cerebral	1	0
	Migraine	2	1
	Palpitations	1	1
	QT Prolonged	1	1
	Shock	1	1
	ST Elevated	1	1
	Syncope	9	7
	Tachycardia	16	13
	Tachycardia, Supraventricular	2	2
	Tachycardia, Ventricular	2	1
	Thrombosis, Arterial	1	1
Digestive System	Anorexia	1	1
	Diarrhea	1	0
	Dysphagia	4	4
	Hemorrhage, Rectal	2	2
	Hematemesis	2	2
	Hepatitis	2	1
	Liver, Damage	1	0
	Liver, Fatty	1	0
	Nausea	1	0
	Nausea, Vomiting	6	4
	Rectal Disorder	1	0
	Stomatitis	1	1
	Vomiting	2	1
Endocrine System	Diabetes Insipidus	1	1
	Hyperthyroidism	1	1
Hemic and Lymphatic System	Anemia	1	0
	Bleeding Time, Inc	1	1
	Coagulation Disorder	2	2
	Cyanosis	1	1
	Leukocytosis	1	1
	Leukopenia	1	1
	Marrow Depression	2	2
	Pancytopenia	1	1
Purpura	1	1	
Metabolic and Nutritional	Creatine PK Inc	1	1
	Cyanosis	2	2
	Dehydration	2	1
	Edema, General	3	2
	Hyperkalemia	1	1
	Hypokalemia	1	1
	Hypoxia	2	2
Musculoskeletal System	Anomaly, Congenital	2	0
	Arthrosis	1	1
	Cramps Leg	1	1
	Twitching	1	1
Nervous System	Agitation	5	3
	Amnesia	2	1
	Anxiety	3	3
	Aphasia	1	1
	Brain Stem Disorder	1	1
	Brain Syndrome, Chronic	1	1
	Cerebrovascular Accident	6	4
	CNS Depression	1	1

Table 20. Serious AEs Associated with PSE in SRS Database for Subjects ≥ 12 Years of Age and Age Unknown. (Pages 96-99)

Body System Category	Serious Event	Number Serious AE	Serious AE in Those ≥ 12
Nervous System (Continued)	Coma	12	9
	Confusion	3	2
	Convulsion	10	9
	Coordination Abnormality	1	1
	Cramps, Leg	2	2
	Delirium	4	1
	Delusions	1	1
	Depersonalization	1	1
	Depression	3	2
	Diplopia	1	1
	Dizziness	4	2
	Dream Abnormality	1	1
	Drug Dependency	3	1
	Dystonia	1	1
	Emotional Lability	1	1
	Encephalopathy	3	3
	Encephalopathy, Hypertensive	2	0
	Euphoria	1	0
	Gait Abnormality	1	0
	Hallucination	5	4
	Hemorrhage, Cerebral	2	0
	Hemorrhage, Intracranial	2	4
	Hemorrhage, Subarachnoid	2	2
	Hematoma, Subdural	1	1
	Hemiplegia	1	1
	Hypertension	24	18
	Hypertonia	1	1
	Hypesthesia	2	1
	Infarct, Cerebral	2	0
	Insomnia	3	1
	Intracranial Hypertension	1	0
	Ischemia, Cerebral	2	0
	Manic Depressive Reaction	1	1
	Nervousness	5	5
	Neuritis, Optic	1	1
	Paralysis	2	1
	Paranoid Reaction	3	1
	Paresthesia	3	3
	Psychosis	3	1
	Somnolence	2	1
	Speech Disorder	2	2
	Stupor	2	2
	Thinking Abnormality	3	2
Tremor	8	7	
Twitching	2	2	
Urinary Retention	2	2	
Vertigo	1	1	
Vestibular Disorder	1	1	
Respiratory System	Apnea	1	1
	Dyspnea	19	14
	Edema, Lung	3	2
	Hemorrhage, Lung	1	1
	Hyperventilation	1	1
	Hypoxia	4	4

Table 20. Serious AEs Associated with PSE in SRS Database for Subjects ≥12 Years of Age and Age Unknown. (Pages 96-99)

Body System Category	Serious Event	Number Serious AE	Serious AE in Those ≥12
Respiratory System (Continued)	Laryngismus	1	1
	Lung, Disorder	1	0
	Pneumonia	3	2
	Respiratory Disorder	3	3
	Rhinitis	2	2
Skin and Appendages	Angioedema	3	3
	Dermatitis, Exfoliative	2	2
	Epidermal Necrolysis	2	2
	Erythema, Multiforme	1	1
	Erythema Nod	1	1
	Hair Discolor	1	1
	Pruritis	3	3
	Rash	4	3
	Rash, Macular Papular	1	1
	Rash, Vesicular-Bullous	2	2
	Stevens Johnson Syndrome	2	2
	Sweating	3	3
	Urticaria	5	4
Special Senses	Amblyopia	2	2
	Blind	1	0
	Conjunctivitis	1	1
	Diplopia	2	2
	Glaucoma	1	0
	Neuritis, Optic	2	2
	Tinnitus	1	1
	Vestibular Disorder	2	2
	Visual Field Defects	1	1
Urogenital System	Abortion	1	0
	Anomaly, Congenital UG	2	0
	Anuria	1	1
	Birth, Premature	1	0
	Dysuria	1	1
	Incontinence, Urinary	1	1
	Kidney Calculus	2	1
	Kidney, Failure	1	0
	Labor Abnormality	2	0
	Pain, Kidney	1	1
	Stenosis, Bladder	1	1
	Stillbirth	2	0
	Urinary Retention	4	4

Table 23. Serious AEs (AERS Database) for Single Ingredient PSE for Ages ≥ 12 Years and “Age Unknown.” (Pages 100-103)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Blood and Lymphatic System	Anemia NOS	1	1
	Leukocytosis NOS	1	1
Cardiac Disorders	Arrythmia NOS	2	2
	Atrial Fibrillation	2	1
	Atrial Flutter	2	2
	Bradycardia NOS	1	1
	Cardiac Arrest	1	1
	Cardiomegaly NOS	1	1
	Myocardial Infarction	2	2
	Edema, Lower Limb	2	1
	Edema Upper Limb	1	1
	Pulse Absent	1	1
	Sinus Tachycardia	1	1
	Supraventricular Tachycardia	2	1
	Tachycardia, NOS	5	4
Ear and Labyrinth Disorders	Earache	1	1
	Hearing Impaired	1	1
Eye Disorders	Amblyopia NOS	1	1
	Eye Pain	1	1
	Eye Rolling	1	1
	Mydriasis	1	1
	Vision Blurred	1	1
Gastrointestinal Disorders	Abdominal Pain NOS	1	1
	Diarrhea NOS	1	1
	Mouth Ulceration	1	1
	Nausea	3	3
	Vomiting NOS	5	5
General Disorders and Administration	Chest Pain NEC	3	3
	Condition Aggravated	2	2
	Difficulty in Walking	1	1
	Drug Ineffective	1	1
	Drug Interaction NOS	6	6
	Fall	1	1
	Fatigue	2	2
	Feeling Abnormal	1	1
	Feeling Drunk	1	1
	Feeling Hot	1	1
	Hemorrhage NOS	1	1
	Hyperpyrexia	1	1
	Influenza Like Illness	1	1
	Jet Lag	1	1
	Lethargy	1	1
	Malaise	3	3
	Mucous Membrane Disorder	1	1
	Pain NOS	1	1
Pyrexia	3	2	
Rigors	1	1	
Weakness	2	2	
Immune System Disorders	Drug Hypersensitivity	1	1
	Hypersensitivity NOS	3	1
Infections and Infestations	Croup Infections	1	1
	Pneumonia NOS	1	1
	Sinusitis NOS	2	1
	Upper Respiratory Tract Infection	1	1
	Urinary Tract Infection	1	1
	Viral Infection NOS	1	1

Table 23. Serious AEs (AERS Database) for Single Ingredient PSE for Ages ≥ 12 Years and “Age Unknown.” (Pages 100-103)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Injury and Poisoning	Abrasion NOS	1	1
	Accidental Overdose (Therapeutic Agent)	1	1
	Alcohol Intoxication Acute	2	2
	Head Injury	1	1
	Heat Stroke	2	1
	Medication Error	3	3
	Non-Accidental Overdose	3	2
	Overdose NOS	2	2
	Scratch	1	2
	Vascular Injury NOS	1	2
VIIth Nerve Injury	1	1	
Investigations	Audiogram Abnormal	1	1
	Blood Calcium Decreased	1	1
	Blood Creatinine Phosphokinase Increased	2	2
	Blood pH Decreased	1	1
	Blood Potassium Increased	1	1
	Blood Pressure Decreased	1	1
	Blood Pressure Increased	2	2
	Blood Pressure Systolic Increased	1	1
	Drug Level NOS Above Therapeutic	3	3
	Electrocardiogram Abnormal NOS	1	1
	Electrocardiogram QT Prolonged	1	1
	Electrocardiogram ST Segment Depression	2	2
	Electrocardiogram ST Segment Elevation	1	1
	Electrocardiogram T-Wave Inversion	1	1
	Heart Rate Increased	1	1
	Myoglobinuria Present	1	1
	Respiratory Rate	1	1
Respiratory Rate Increased	1	1	
Scan NOS Renal Abnormal	1	1	
Metabolism and Nutrition Disorders	Acidosis NOS	1	1
	Anorexia	1	1
	Hyperkalemia	1	1
	Hypocalcemia	1	1
	Hyponatremia	1	0
Musculoskeletal, Connective Tissue	Joint Swelling	1	1
	Muscle Cramps	1	1
	Pain in Limb	1	1
	Posture Abnormal	1	1
	Rhabdomyolysis	1	1
Nervous System Disorders	Amnesia NEC	1	1
	Balance Impaired NOS	1	1
	Cerebral Edema	3	2
	Cerebrovascular Accident NOS	2	2
	Coma NEC	3	3
	Convulsions NOS	5	5
	Coordination Abnormal NOS	1	1
	Disturbance in Attention NEC	1	1
	Dizziness (Esc Vertigo)	1	1
	Grand Mal Convulsion	2	2
	Headache NOS	8	8
	Headache NOS Aggravated	1	1
	Hemiparesis	2	2
	Hemorrhagic Stroke	1	1
	Hypoesthesia	3	3
	Insomnia NEC	3	3
	Myoclonic Jerks	1	1

Table 23. Serious AEs (AERS Database) for Single Ingredient PSE for Ages ≥ 12 Years and “Age Unknown.” (Pages 100-103)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Nervous System Disorders (Continued)	Neurological Disorder NOS	1	1
	Paresthesia NEC	1	1
	Sedation	1	1
	Serotonin Syndrome	1	1
	Simple Partial Seizures	1	1
	Syncope	1	1
	Tremor NEC	1	1
	Visual Field Defect NOS	1	1
Pregnancy, Puerperium and Perinatal Disorders	Abortion NOS	1	1
Psychiatric Disorders	Abnormal Behavior NOS	2	2
	Aggression	1	1
	Agitation	2	2
	Agitation Aggravated	1	1
	Anxiety NEC	1	1
	Belligerence	1	1
	Catatonia	1	1
	Completed Suicide	1	1
	Depressed Mood	1	1
	Drug Dependence	1	1
	Exacerbation of Anxiety	1	1
	Intentional Self-Injury	1	1
	Mania	1	1
	Nervousness	2	2
	Panic Disorder NEC	1	1
	Paranoia	1	1
	Psychotic Disorder NOS	1	1
Stress Symptoms	3	3	
Suicide Attempt	1	1	
Suicidal Ideation	1	1	
Renal and Urinary Disorders	Difficulty in Micturition	1	1
	Dysuria	1	1
	Oliguria	2	2
	Polyuria	1	1
	Renal Impairment NOS	2	1
	Urinary Incontinence	1	1
	Urinary Retention	4	4
Urinary Tract Disorder NOS	1	1	
Reproductive System and Breast Disorders	Intermenstrual Bleeding	1	1
	Ovarian Cyst	1	1
Respiratory, Thoracic and Mediastinal Disorders	Apnea	1	1
	Bronchospasm NOS	1	1
	Dyspnea NOS	2	2
	Hypoventilation	1	1
	Nasal Passage Irritation	1	1
	Respiratory disorder NOS	1	1
	Sinus Congestion	1	1
Sputum Abnormal	1	1	
Skin and Subcutaneous Tissue Disorders	Angioneurotic Edema	1	0
	Dermatitis Bullous	1	1
	Dermatitis NOS	4	4
	Dry Skin	1	1
	Dyshidrosis	1	1
	Ecchymosis	1	1
	Epidermal Necrolysis	2	2
	Eyelid Edema	2	2

Table 23. Serious AEs (AERS Database) for Single Ingredient PSE for Ages ≥ 12 Years and “Age Unknown.” (Pages 100-103)

MedDRA System Organ Class	MedDRA Primary Term	Report Frequency	AE in Those ≥ 12
Skin and Subcutaneous Tissue Disorders (Continued)	Face edema	2	2
	Pruritis NOS	3	3
	Rash Erythematous	4	3
	Rash Generalized	2	2
	Rash Morbilliform	1	0
	Stevens Johnson Syndrome	1	1
	Sweat Gland Disorder NOS	1	1
	Sweating Decreased	1	1
	Urticaria NOS	7	5
Social Circumstances	Drug Abuse	1	1
Surgical and Medical Procedures	Cardioversion	1	1
Vascular Disorders	Arterial Occlusion NOS	1	1
	Blood Pressure Fluctuation	1	1
	Cerebral Arterial Aneurysm	1	1
	Cerebral Artery Occlusion	1	1
	Cerebral Artery Thrombosis	1	1
	Cerebral Infarction	1	1
	Cerebral Ischemia	1	1
	Collapse	4	4
	Flushing	2	2
	Hematoma NOS	1	1
	Hypertension NOS	3	3
	Hypotension NOS	3	3
	Peripheral Coldness	1	1
	Subarachnoid Hemorrhage NOS	1	1
	Thrombosis NOS	1	1
	Transient Ischemic Attack	2	2
	Vasculitis NOS	2	2
	Venous Stasis	1	1

**APPEARS THIS WAY
ON ORIGINAL**

Appendix III

Table 25. Marketing History of IBU/PSE Combination (pages 104-105)

Country/Region: Product	Rx or OTC	Dose (mg)	Dosing Schedule	Age Range (years)	Registration Date	Withdrawal Date
Austria: Advil Cold Tablets	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	2 Jan 2001	N/A
Bulgaria: Advil Cold *	Rx	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	June 2000	N/A
Czech Republic: Advil Cold*	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	20 Sept 2000	N/A
Hungary: Advil Cold*	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	27 July 2000	N/A
Slovak Republic: Advil Cold*	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	12 Dec 2000	N/A
Poland: Advil Cold*	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	16 July 1999	N/A
United Kingdom: Advil Cold & Sinus*	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	2 Feb 1996	Aug 2000
Italy: CoAdvil*	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	1 July 1992	24 July 2000
France: Rhinadvil*	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	19 July 1991	N/A
Ireland: Advil Cold & Flu*	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	8 Sept 1994	N/A
Aruba: Advil Cold & Sinus Caplets	OTC	IBU 200 PSE 30	1 or 2 caplets. Maximum 6 in 24 hrs	≥ 12	May 1991	N/A
Aruba: Advil Cold & Sinus Tablets	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	Sept 1994	N/A
Curacao: Advil Cold & Sinus Caplets	OTC	IBU 200 PSE 30	1 or 2 caplets. Maximum 6 in 24 hrs	≥ 12	May 1991	N/A
Curacao: Advil Cold & Sinus Tablets	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	Sept 1994	N/A
Jamaica: Advil Cold & Sinus Caplets	OTC	IBU 200 PSE 30	1 or 2 caplets. Maximum 6 in 24 hrs	≥ 12	June 1999	N/A
Jamaica: Advil Cold & Sinus Tablets	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	June 2000	N/A
Trinidad: Advil Cold & Sinus Caplets	OTC	IBU 200 PSE 30	1 or 2 caplets. Maximum 6 in 24 hrs	≥ 12	June 1991	N/A
Trinidad: Advil Cold & Sinus Tablets	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	In process	N/A
Guyana: Advil Cold & Sinus Caplets	OTC	IBU 200 PSE 30	1 or 2 caplets. Maximum 6 in 24 hrs	≥ 12	Not registered	**
Guyana: Advil Cold & Sinus Tablets	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	Oct 1999	N/A
Canada: Dristan Sinus Tablets	OTC	IBU 200 PSE 30	1 or 2 tablets. Maximum 6 in 24 hrs	≥ 12	1993	N/A
Argentina: Ibudristan*	Rx	IBU 200 PSE 30	1 capsule every 4-6 hrs. Maximum 6 in 24 hrs	≥ 12	30 Jul 1992	N/A
Colombia: Dristan Sinus Tablets	OTC	IBU 200 PSE 30	1 tablet every 4-6 hrs. Maximum 6 in 24 hrs	≥ 12	8 May 1995 (Made locally) 20 Jan 2000 (Imported)	N/A
Bahrain: Advil Cold & Sinus Caplets	Rx	IBU 200 PSE 30	1 or 2 caplets per 4 hrs. Maximum 6 in 24 hrs.	≥ 12	**	N/A

* Formulation not specifically provided by sponsor although directions refer to tablets

N/A = Not Applicable

** Information not provided by sponsor

Table 25. Marketing History of IBU/PSE Combination (pages 104-105)

Country/Region: Product	Rx or OTC	Dose (mg)	Dosing Schedule	Age Range (years)	Registration Date	Withdrawal Date
Ghana: Advil Cold & Sinus Caplets	Rx	IBU 200 PSE 30	1 or 2 caplets per 4 hrs. Maximum 6 in 24 hrs.	≥ 12	**	N/A
Kuwait: Advil Cold & Sinus Caplets	Rx	IBU 200 PSE 30	1 or 2 caplets per 4 hrs. Maximum 6 in 24 hrs.	≥ 12	**	N/A
Lebanon: Advil Cold & Sinus Caplets	Rx	IBU 200 PSE 30	1 or 2 caplets per 4 hrs. Maximum 6 in 24 hrs.	≥ 12	**	N/A
Oman: Advil Cold & Sinus Caplets	Rx	IBU 200 PSE 30	1 or 2 caplets per 4 hrs. Maximum 6 in 24 hrs.	≥ 12	**	N/A
Palestine: Advil Cold & Sinus Caplets	Rx	IBU 200 PSE 30	1 or 2 caplets per 4 hrs. Maximum 6 in 24 hrs.	≥ 12	**	N/A
Qatar: Advil Cold & Sinus Caplets	Rx	IBU 200 PSE 30	1 or 2 caplets per 4 hrs. Maximum 6 in 24 hrs.	≥ 12	**	N/A
United Arab Emirate Advil Cold & Sinus Caplets	Rx	IBU 200 PSE 30	1 or 2 caplets per 4 hrs. Maximum 6 in 24 hrs.	≥ 12	**	N/A

* Formulation not specifically provided by sponsor although directions refer to tablets

N/A = Not Applicable

** Information not provided by sponsor

**APPEARS THIS WAY
ON ORIGINAL**

WITHHOLD 1 PAGE (S)

DRAFT Labeling

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

/s/

Andrea Segal
4/16/02 07:19:58 AM
MEDICAL OFFICER

Linda Katz
4/19/02 09:46:38 AM
MEDICAL OFFICER