[

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Sponsor's proposed language:
Hepatitis, hepatic events:

[

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Reviewer's comments:
The wording should be more extensive, as follows:

Hepatitis, hepatic events: Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in the addict population receiving buprenorphine in both clinical trials and in post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver function test abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Measurement of liver functions tests prior to initiation of treatment is recommended to establish a baseline. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, the drug should be carefully discontinued to prevent withdrawal symptoms and a return to illicit drug use, monitoring of the patient should be initiated.

Allergic Reactions

The Sponsor has not includes a section on allergic reactions in the Warnings section. A suggested section is as follows:

Cases of acute and chronic hypersensitivity to Subutex have been reported in both clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine is a contraindication to Subutex or Suboxone use. A history of hypersensitivity to naloxone is a contraindication to Suboxone use.

8.3 Drug Interactions

Sponsor's proposed language:

Drug Interactions:

[

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Reviewer's comments:

The language should be stronger, and not limited to intravenous use of buprenorphine. The information on CYP3A4 will need to be reviewed by the clinical pharmacology staff. Proposed changes are as follows:

Drug Interactions:
There have been a number of reports in the post-marketing experience of coma and death associated with the concomitant ~~intravenous misuse~~ of buprenorphine and benzodiazepines by addicts. In many of these cases, buprenorphine was misused by self-injection of crushed Subutex tablets. Subutex and Suboxone should be prescribed with caution to patients on benzodiazepines or other drugs that act on the central nervous system, regardless of whether these drugs are taken on the advice of a physician or are taken as drugs of abuse. Patients should be warned of the potential danger of the intravenous self-administration of benzodiazepines while under treatment with SUBOXONE or SUBUTEX.

Buprenorphine is metabolized to norbuprenorphine by cytochrome CYP 3A4. Because CYP 3A4 inhibitors may increase plasma concentrations of buprenorphine, patients already on CYP 3A4 inhibitors

should have their dose of SUBUTEX or SUBOXONE

SKIP

Pregnancy
Pregnancy Category C:
Teratogenic effects:

SUBUTEX:

[redacted]

SUBOXONE:

[redacted]

SUBUTEX:

[redacted]

Neonatal Withdrawal:

[redacted]

Nursing Mothers:

[

]

Pediatric Use:

[

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Reviewer's comments:

The above section appears appropriate from a clinical point of view. The pharmacology/toxicology staff will need to review this section as well.

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ON ORIGINAL

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

/s/

Gerald DalPan
5/17/02 05:05:10 PM
MEDICAL OFFICER

You've already reviewed for entry into DFS.

Celia Winchell
6/4/02 10:01:13 AM
MEDICAL OFFICER

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REPORT RC000230

CUMULATIVE LISTINGS OF ADVERSE EVENTS FOLLOWING THE MARKETING OF SUBUTEX AND TEMGESIC.

The attached listings update:

- Adverse Event Information presented in the Original Suboxone application (Section 8.F.6.5.1, Volume 149) and
- Adverse Event Information presented in Attachment 6 of the Safety Update Report of October 8, 1999

PRODUCT = SUBUTEX: CUMULATIVE ADVERSE EVENTS REPORTED POST-MARKETING

EVENT	ORIGINAL	OCT 99		MAY 00	
		NEW	NEW	NEW	NEW
	TOTAL	EVENTS	TOTAL	EVENTS	TOTAL
	Jun-99	Oct-99	Oct-99	May-00	May-00
Application Site Disorders					
Injection Site Abscess	6		6	2	8
Injection Site Inflammation	5	2	7		7
Injection Site Necrosis	4		4		4
Injection Site Pain	2		2	1	3
Injection Site Reaction	3	2	5	1	6
Injection Site Reaction, Right Arm	1		1		1
Total For Application Site Disorders	**21**	**4**	**25**	**4**	**29**
Benign & Malignant Neoplasms					
Lymphoma Malignant	0	1	1		1
Total For Benign & Malignant Neoplasms	**0**	**1**	**1**		**1**
Body As A Whole					
Anorexia	2		2	2	4
Appetite Increased	1		1		1
Asthenia	3		3	2	5
Chest Pain	1		1		1
Crying Abnormal	2	2	4		4
Cyanosis					
Cyanosis Neonatal	2		2	1	3
Death	13	2	15		15
Disease Progression				1	1
Dizziness				1	1
Drug Interaction	0	1	1		1
Edema	4	1	5	4	9
Edema Peripheral	1		1	2	3
Facial Pain	1		1		1
Fatigue	0	1	1		1
Fever	9		9	4	13
Headache	9	0	9		9
Hyperpyrexia	1		1		1
Hypoxia	1		1		1
Malaise	8		8		8
No Adverse Reaction	2	1	3		3
Pain	2		2	1	3
Pallor	1		1		1
Rigors	1		1	2	3
Syncope	1		1		1
Withdrawal Syndrome	11	5	16	6	22
Total For Body As A Whole	**76**	**13**	**89**	**26**	**115**
Cardiovascular Disorders, General					
Circulatory Failure	1		1		1
ECG Abnormal	1		1		1
Hypertension	1		1		1
Hypotension	5		5		5
Myocardial Infarction	1		1		1
Myocardial Ischemia				1	1

PRODUCT = SUBUTEX: CUMULATIVE ADVERSE EVENTS REPORTED POST-MARKETING

EVENT	ORIGINAL	OCT 99		MAY 00	
Pericarditis	2		2		2
Total For Cardiovascular Disorders, General	**11**	**0**	**11**	**1**	**12**
Central And Periph Nerv Syst Disorders					
Agitation Neonatal	3	1	4		4
Coma	29	2	31	1	32
Confusion	10		10		10
Convulsions	10		10	2	12
Convulsions Grand Mal	3		3		3
Convulsions Neonatal	2	1	3		3
Delirium	5	1	6		6
Dementia	1		1		1
Dyskinesia	1		1		1
Encephalopathy	1		1		1
Extrapyramidal Disorder	2		2		2
Hydrocephalus	1		1		1
Hyperesthesia	1		1		1
Hyperkinesia Neonatal	1		1		1
Hypertonia	5	1	6		6
Hypoesthesia	1		1		1
Hypotonia	1		1		1
Hypotonia Neonatal				1	1
Impaired Conciousness	1		1		1
Jerky Movement Nos	1		1		1
Loss of Consciousness	3		3		3
Meningitis	1		1		1
Mental Status, Altered	3		3		3
Myoclonus	4		4		4
Neuropathy Peripheral	1	1	2		2
Paralysis, Facial	1		1		1
Paresthesia	5		5	1	6
Somnolence	13	2	15	1	16
Somnolence Neonatal	2		2		2
Status Epilepticus	1		1		1
Tremor	1	1	2		2
Tremor Neonatal	8		8		8
Withdrawal Convulsions	1		1		1
Total For Central And Periph Nerv Syst Disorders	**123**	**10**	**133**	**6**	**139**
Disorders Of Blood And Lymphatic System					
Leukocytosis	1		1		1
Lymphadenopathy	4	1	5		5
Lymphangitis	4		4		4
Neutropenia	1		1		1
Polycythemia				1	1
Total For Disorders Of Blood And Lymphatic System	**10**	**1**	**11**	**1**	**12**
Disorders Of The Ear And Labyrinth					
Deafness				1	1
Tinnitus				1	1
Vertigo	2		2		2

PRODUCT = SUBUTEX: CUMULATIVE ADVERSE EVENTS REPORTED POST-MARKETING

EVENT	ORIGINAL	OCT 99		MAY 00	
Total For Disorders Of The Ear And Labyrinth	**2**	**0**	**2**	**2**	**4**
Disorders Of The Eye					
Choroiditis	1		1		1
Eye Pain	1		1		1
Miosis	23	2	25	2	27
Mydriasis	1		1	1	2
Papilledema	1		1		1
Photophobia	1		1		1
Retinal Disorder				1	1
Retinitis				1	1
Vision Abnormal	1		1		1
Visual Field Defect	1		1		1
Total For Disorders Of The Eye	**30**	**2**	**32**	**5**	**37**
Disorders Of The Immune System					
Allergic Reaction	1		1		1
Allergy	1	1	2		2
Angioedema	2	1	3		3
Scleroderma				1	1
Total For Disorders Of The Immune System	**4**	**2**	**6**	**1**	**7**
Disorders Of The Reproductive System					
Abortion	1		1		1
Abortion Threatened	1		1		1
Amenorrhea	1		1	1	2
Ejaculation Disorder	1		1		1
Ejaculation Failure	0	1	1		1
Ejaculation Premature	1		1		1
Gynecomastia	2	1	3	1	4
Hydramnios				1	1
Menstrual Disorder	1		1		1
Priapism				1	1
Sperm Disorder	1		1	1	2
Vaginal Disorder	1		1		1
Total For Disorders Of The Reproductive System And	**10**	**2**	**12**	**5**	**17**
Endocrine Disorders					
Adrenal Insuffciency				1	1
Growth Retarded	2		2		2
Hyperprolactinaemia		1	1		1
Hyperthyroidism		1	1	1	2
Lactation Nonpuerperal	3		3		3
TSH Decreased		1	1		1
Total For Endocrine Disorders	**5**	**3**	**8**	**2**	**10**
Foetal Disorders					
Brain Damage Congenital	1		1		1
Cleft Lip		1	1	1	2
Clubfoot		1	1		1
Death Fetal	4	2	6		6

PRODUCT = SUBUTEX: CUMULATIVE ADVERSE EVENTS REPORTED POST-MARKETING

	EVENT	ORIGINAL	OCT 99		MAY 00	
	Edwards Syndrome	1		1		1
	Face Malformation	1		1		1
	Fetal Distress	1		1		1
	Fetal Maturation Impaired		1	1		1
	Heart Malformation	1		1		1
	Hypospadias	1		1		1
	Malformation Foot	1		1		1
	Meningomyelocele		1	1		1
	Mongolism	1		1		1
	Stillbirth	1		1		1
	Urinary Tract Malformation		1	1		1
	Ventricular Septal Defect	1		1		1
	Total For Foetal Disorders	**14**	**7**	**21**	**1**	**22**
Gastro-Intestinal System Disorders						
	Abdominal Distension				1	1
	Abdominal Pain	6	2	8	2	10
	Diarrhea	5		5	1	6
	Dyspepsia				1	1
	Esophalgia	1		1		1
	Gastritis	2		2		2
	Gastro-Intestinal Disorder Nos	1		1		1
	Intestinal Obstruction	1		1	1	2
	Melena				1	1
	Mouth Dry	1		1		1
	Mouth Ulceration	1		1		1
	Nausea	5		5	3	8
	Pancreatitis	2		2		2
	Teething Pain	1		1		1
	Vomiting	6		6	5	11
	Vomiting Neonatal	1	2	3		3
	Total For Gastro-Intestinal System Disorders	**33**	**4**	**37**	**15**	**52**
Heart Rate And Rhythm Disorders						
	Bradycardia	1	1	2		2
	Bundle Branch Block	1		1		1
	Cardiac Arrest	0	1	1		1
	Heart Block	1		1		1
	Heart Rate Abnormal, Fetal	2		2		2
	Tachycardia	4		4	2	6
	Total For Heart Rate And Rhythm Disorders	**9**	**2**	**11**	**2**	**13**
Infection And Infestations						
	Abscess	1	1	2		2
	Infection	1		1		1
	Infection Bacterial	3		3		3
	Infection Fungal	1		1	1	2
	Pneumonia	1		1		1
	Pulmonary Infection	1		1		1
	Sepsis	3	1	4	1	5
	Shock, Septic	1		1		1
	Toxoplasmosis	1		1		1

PRODUCT = SUBUTEX: CUMULATIVE ADVERSE EVENTS REPORTED POST-MARKETING

EVENT	ORIGINAL	OCT 99		MAY 00	
Urinary Tract Infection	1		1		1
Total For Infection And Infestations	**14**	**2**	**16**	**2**	**18**
Injury And Poisoning					
Injury Accidental	3		3		3
Misuse	2		2		2
Total For Injury And Poisoning	**5**	**0**	**5**		**5**
Liver And Biliary System Disorders					
Bilirubinemia	1		1		1
Gamma-GT Increased	1		1		1
Hepatic Cirrhosis	1		1		1
Hepatic Cirrhosis Aggravated	1		1		1
Hepatic Disorder NOS		1	1	1	2
Hepatic Encephalopathy		1	1		1
Hepatic Enzymes Increased	13	1	14	1	15
Hepatic Failure	2		2		2
Hepatitis	5	5	10	2	12
Hepatitis Aggravated	1		1		1
Hepatitis Cholestatic	1	2	3		3
Hepatocellular Damage	1	1	2		2
Hepatorenal Syndrome	1		1		1
Jaundice	10		10	1	11
Jaundice, Neonatal	1		1		1
SGOT Increased	2		2		2
SGPT Increased	2		2		2
Total For Liver And Biliary System Disorders	**43**	**11**	**54**	**5**	**59**
Metabolic And Nutritional Disorders					
Acidosis	2		2		2
Acidosis Lactic	0	1	1		1
Amylase Increased	1		1		1
Calcinosis				1	1
Creatine Phosphokinase Increased	2		2		2
Dehydration				1	1
Hyperammonemia	1		1		1
Hyperosmolar Syndrome	3		3		3
Hypocalcemia	2		2		2
Hypoglycemia Neonatal	1		1		1
Hypokalemia				1	1
Weight Decrease	7	3	10	7	17
Weight Decrease Neonatal	1		1		1
Weight Increase				1	1
Total For Metabolic And Nutritional Disorders	**20**	**4**	**24**	**11**	**35**
Musculo-Skeletal System Disorders					
Arthralgia	2		2		2
Arthritis				1	1
Arthropathy				1	1
Back Pain	1		1		1
Bone Disorder	1		1		1
Joint Disorder				1	1

PRODUCT = SUBUTEX: CUMULATIVE ADVERSE EVENTS REPORTED POST-MARKETING

EVENT	ORIGINAL	OCT 99		MAY 00	
Muscle Disorder	1		1		1
Musculo-Skeletal Pain	1		1		1
Myalgia	3		3		3
Myositis	1		1		1
Rhabdomyolysis	2		2		2
Spondylitis				1	1
Tendon Disorder				4	4
Total For Musculo-Skeletal System Disorders	**12**	**0**	**12**	**8**	**20**
Neonatal and Infancy Disorders					
Maternal Drug Exposure	5	5	10	3	13
Small for Gestational Age	1		1		1
Withdrawal Syndrome Neonatal	50	16	66	15	81
Total For Neonatal And Infancy Disorders	**56**	**21**	**77**	**18**	**95**
Platelet, Bleeding And Clotting Disord					
Hematoma	1		1		1
Hemoperitoneum	1		1		1
Prothrombin Decreased	1		1		1
Purpura				1	1
Thrombocytopenia	3		3		3
Total For Platelet, Bleeding And Clotting Disord	**6**	**0**	**6**	**1**	**7**
Psychiatric Disorders					
Aggressive Reaction	6	1	7	1	8
Agitation	14	1	15	1	16
Anxiety	2	1	3		3
Apathy	1		1		1
Depression	3		3		3
Drug Abuse		1	1		1
Drug Dependence	3		3	3	6
Hallucination	9	2	11		11
Impotence		1	1	1	2
Insomnia	3		3	1	4
Libido Decreased	2		2		2
Manic Reaction	1	1	2		2
Nervousness	3		3		3
Paranoid Reaction	2	2	4		4
Personality Disorder	1	1	2		2
Psychiatric Disorder NOS		1	1		1
Suicide (Accomplished)	2		2		2
Suicide Attempt	6	1	7	1	8
Total For Psychiatric Disorders	**58**	**13**	**71**	**8**	**79**
Renal And Urinary System Disorders					
Blood Creatinine Increased				1	1
Dysuria	2		2		2
Nephritis	0	1	1		1
Nephrosis				1	1
Renal Failure Acute	2		2		2
Renal Insufficiency	1		1	1	2
Urinary Retention	1		1		1

PRODUCT = SUBUTEX: CUMULATIVE ADVERSE EVENTS REPORTED POST-MARKETING

EVENT	ORIGINAL	OCT 99		MAY 00	
Total For Renal And Urinary System Disorders	**6**	**1**	**7**	**3**	**10**
Respiratory System Disorders					
Acute Respiratory Distress	2		2	1	3
Acute Respiratory Distress Syndrome	1		1		1
Apnea				1	1
Asphyxia	22		22		22
Aspiration		1	1		1
Asthma Aggravated	1		1		1
Bradypnea	1		1	1	2
Bronchiolitis	1		1		1
Bronchospasm	0		0		0
Coughing	1		1		1
Dyspnea	8		8	3	11
Emphysema				1	1
Hypercapnia	1		1		1
Hypertension Pulmonary	1	1	2		2
Hypoventilation	12		12		12
Nasal Disorder (NOS)	1		1		1
Pleural Effusion	2		2		2
Pulmonary Edema	1	3	4	1	5
Pulmonary Fibrosis	0	1	1		1
Pulmonary Granuloma	1		1		1
Rales	1		1		1
Respiratory Arrest		2	2		2
Respiratory Depression	2	2	4	2	6
Respiratory Depression NE		1	1		1
Respiratory Disorder	1		1		1
Respiratory Insufficiency	3	1	4		4
Sleep Apnea Syndrome				1	1
Tachypnea	3		3		3
Total For Respiratory System Disorders	**66**	**12**	**78**	**11**	**89**
Skin And Subcutaneous Tissue Disorders					
Eczema	3		3		3
Erythema	6	2	8	1	9
Erythema Nodosum	1		1		1
Fixed Eruption	2		2		2
Photosensitivity Reaction	3	1	4		4
Plaque Skin		1	1		1
Pruritus	4	2	6	1	7
Skin Disorder	2		2		2
Skin Necrosis	2		2	1	3
Skin Nodule				1	1
Sweating Increased	5		5	3	8
Urticaria	3		3		3
Total For Skin And Subcutaneous Tissue Disorders	**31**	**6**	**37**	**7**	**44**
Special Senses Other, Disorders					
Taste Persersion	1		1		1
Total For Special Senses Other, Disorders	**1**	**0**	**1**		**1**

PRODUCT = SUBUTEX: CUMULATIVE ADVERSE EVENTS REPORTED POST-MARKETING

EVENT	ORIGINAL	OCT 99		MAY 00	
Surgical And Medical Procedures					
Amputation	3		3		3
Procedure	1		1	1	2
Total For Surgical And Medical Procedures	**4**	**0**	**4**	**1**	**5**
Vascular (Extracardiac) Disorders					
Embolism Pulmonary		2	2		2
Gangrene	1		1		1
Livedo Reticularis	1		1		1
Necrosis Ischemic	2		2		2
Peripheral Ischemia	1		1		1
Raynaud's Disease				1	1
Thrombophlebitis	2		2		2
Thrombophlebitis Arm	1		1		1
Thrombosis	1		1		1
Thrombosis Retinal Artery	1		1		1
Vascular Disorder				1	1
Vasculitis	1		2		2
Vein Disorder	1		1		1
Total For Vascular (Extracardiac) Disorders	**12**	**3**	**15**	**2**	**17**
TOTAL OF EVENTS	**682**	**124**	**806**	**148**	**954**
NUMBER OF SUBJECTS	**322**	**80**	**402**	**79**	**481**

APPEARS THIS WAY
ON ORIGINAL

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Adverse Reaction:	Count
APPLICATION SITE DISORDERS	
INJECTION SITE ABSCESS	2
INJECTION SITE PAIN	1
INJECTION SITE REACTION	1
Total Adverse Reaction Count for APPLICATION SITE DISORDERS	4
Total Patient Count for APPLICATION SITE DISORDERS	4
BODY AS A WHOLE - GENERAL DISORDERS	
ANOREXIA	2
ASTHENIA	2
CYANOSIS NEONATAL	1
DISEASE PROGRESSION	1
DIZZINESS	1
EDEMA	4
EDEMA PERIPHERAL	2
FEVER	4
PAIN	1
RIGORS	2
WITHDRAWAL SYNDROME	6
Total Adverse Reaction Count for BODY AS A WHOLE - GENERAL DISORDERS	26
Total Patient Count for BODY AS A WHOLE - GENERAL DISORDERS	21
CARDIOVASCULAR DISORDERS, GENERAL	
MYOCARDIAL ISCHEMIA	1
Total Adverse Reaction Count for CARDIOVASCULAR DISORDERS, GENERAL	1
Total Patient Count for CARDIOVASCULAR DISORDERS, GENERAL	1

Drug(s):	Dosage form(s):	Start Date: 01/08/1999
SUBUTEX (BUPRENORPHINE HCL)	ALL DOSES	Cutoff Date: 31/01/2000

Adverse Reaction:	Count
CENTR AND PERIPH NERV SYST DISORDERS	
COMA	1
CONVULSIONS	2
HYPOTONIA NEONATAL	1
PARESTHESIA	1
SOMNOLENCE	1
Total Adverse Reaction Count for CENTR AND PERIPH NERV SYST DISORDERS	6
Total Patient Count for CENTR AND PERIPH NERV SYST DISORDERS	6
DISORDERS OF BLOOD AND LYMPHATIC SYSTEM	
POLYCYTHEMIA	1
Total Adverse Reaction Count for DISORDERS OF BLOOD AND LYMPHATIC SYSTEM	1
Total Patient Count for DISORDERS OF BLOOD AND LYMPHATIC SYSTEM	1
DISORDERS OF THE EAR & LABYRINTH	
DEAFNESS	1
TINNITUS	1
Total Adverse Reaction Count for DISORDERS OF THE EAR & LABYRINTH	2
Total Patient Count for DISORDERS OF THE EAR & LABYRINTH	2
DISORDERS OF THE EYE	
MIOSIS	2
MYDRIASIS	1
RETINAL DISORDER	1
RETINITIS	1
Total Adverse Reaction Count for DISORDERS OF THE EYE	5
Total Patient Count for DISORDERS OF THE EYE	5

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Adverse Reaction:	Count
DISORDERS OF THE IMMUNE SYSTEM	
SCLERODERMA	1
Total Adverse Reaction Count for DISORDERS OF THE IMMUNE SYSTEM	1
Total Patient Count for DISORDERS OF THE IMMUNE SYSTEM	1
DISORDERS OF THE REPRODUCTIVE SYSTEM AND	
AMENORRHEA	1
GYNECOMASTIA	1
HYDRAMNIOS	1
PRIAPISM	1
SPERM DISORDER	1
Total Adverse Reaction Count for DISORDERS OF THE REPRODUCTIVE SYSTEM AND	5
Total Patient Count for DISORDERS OF THE REPRODUCTIVE SYSTEM AND	5
ENDOCRINE DISORDERS	
ADRENAL INSUFFICIENCY	1
HYPERTHYROIDISM	1
Total Adverse Reaction Count for ENDOCRINE DISORDERS	2
Total Patient Count for ENDOCRINE DISORDERS	2
FOETAL DISORDERS	
CLEFT LIP	1
Total Adverse Reaction Count for FOETAL DISORDERS	1
Total Patient Count for FOETAL DISORDERS	1
GASTROINTESTINAL SYSTEM DISORDERS	
ABDOMINAL DISTENSION	1
ABDOMINAL PAIN	2

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Adverse Reaction:	Count
DIARRHEA	1
DYSPEPSIA	1
INTESTINAL OBSTRUCTION	1
MELENA	1
NAUSEA	3
VOMITING	5
Total Adverse Reaction Count for GASTRO-INTESTINAL SYSTEM DISORDERS	**15**
Total Patient Count for GASTRO-INTESTINAL SYSTEM DISORDERS	**9**
HEART RATE AND RHYTHM DISORDERS	
TACHYCARDIA	2
Total Adverse Reaction Count for HEART RATE AND RHYTHM DISORDERS	**2**
Total Patient Count for HEART RATE AND RHYTHM DISORDERS	**2**
INFECTION AND INFESTATIONS	
INFECTION FUNGAL	1
SEPSIS	1
Total Adverse Reaction Count for INFECTION AND INFESTATIONS	**2**
Total Patient Count for INFECTION AND INFESTATIONS	**2**
LIVER AND BILIARY SYSTEM DISORDERS	
HEPATIC DISORDER NOS	1
HEPATIC ENZYMES INCREASED	1
HEPATITIS	2
JAUNDICE	1
Total Adverse Reaction Count for LIVER AND BILIARY SYSTEM DISORDERS	**5**
Total Patient Count for LIVER AND BILIARY SYSTEM DISORDERS	**3**

Drug(s):	Dosage form(s):	Start Date: 01/08/1999
SUBUTEX (BUPRENORPHINE HCL)	ALL DOSES	Cutoff Date: 31/01/2000

Adverse Reaction:	Count
METABOLIC AND NUTRITIONAL DISORDERS	
CALCINOSIS	1
DEHYDRATION	1
HYPOKALEMIA	1
WEIGHT DECREASE	7
WEIGHT INCREASE	1
Total Adverse Reaction Count for METABOLIC AND NUTRITIONAL DISORDERS	11
Total Patient Count for METABOLIC AND NUTRITIONAL DISORDERS	10
MUSCULO-SKELETAL SYSTEM DISORDERS	
ARTHRITIS	1
ARTHROPATHY	1
JOINT DISORDER	1
SPONDYLITIS	1
TENDON DISORDER	4
Total Adverse Reaction Count for MUSCULO-SKELETAL SYSTEM DISORDERS	8
Total Patient Count for MUSCULO-SKELETAL SYSTEM DISORDERS	8
NEONATAL AND INFANCY DISORDERS	
MATERNAL DRUG EXPOSURE	3
WITHDRAWAL SYNDROME NEO	15
Total Adverse Reaction Count for NEONATAL AND INFANCY DISORDERS	18
Total Patient Count for NEONATAL AND INFANCY DISORDERS	17
PLATELET, BLEEDING AND CLOTTING DISORD	
PURPURA	1

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Adverse Reaction:	Count
Total Adverse Reaction Count for PLATELET, BLEEDING AND CLOTTING DISORD	1
Total Patient Count for PLATELET, BLEEDING AND CLOTTING DISORD	1
PSYCHIATRIC DISORDERS	
AGGRESSIVE REACTION	1
AGITATION	1
DRUG DEPENDENCE	3
IMPOTENCE	1
INSOMNIA	1
SUICIDE ATTEMPT	1
Total Adverse Reaction Count for PSYCHIATRIC DISORDERS	8
Total Patient Count for PSYCHIATRIC DISORDERS	8
RENAL & URINARY SYSTEM DISORDERS	
BLOOD CREATININE INCREASED	1
NEPHROSIS	1
RENAL INSUFFICIENCY	1
Total Adverse Reaction Count for RENAL & URINARY SYSTEM DISORDERS	3
Total Patient Count for RENAL & URINARY SYSTEM DISORDERS	3
RESPIRATORY SYSTEM DISORDERS	
ACUTE RESPIRATORY DISTRES	1
APNEA	1
BRADYPNEA	1
DYSPNEA	3
EMPHYSEMA	1
PULMONARY EDEMA	1

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Adverse Reaction:	Count
RESPIRATORY DEPRESSION	2
SLEEP APNEA SYNDROME	1
Total Adverse Reaction Count for RESPIRATORY SYSTEM DISORDERS	11
Total Patient Count for RESPIRATORY SYSTEM DISORDERS	9
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
ERYTHEMA	1
PRURITUS	1
SKIN NECROSIS	1
SKIN NODULE	1
SWEATING INCREASED	3
Total Adverse Reaction Count for SKIN AND SUBCUTANEOUS TISSUE DISORDERS	7
Total Patient Count for SKIN AND SUBCUTANEOUS TISSUE DISORDERS	6
SURGICAL AND MEDICAL PROCEDURES	
PROCEDURE	1
Total Adverse Reaction Count for SURGICAL AND MEDICAL PROCEDURES	1
Total Patient Count for SURGICAL AND MEDICAL PROCEDURES	1
VASCULAR (EXTRACARDIAC) DISORDERS	
RAYNAUD'S DISEASE	1
VASCULAR DISORDER	1
Total Adverse Reaction Count for VASCULAR (EXTRACARDIAC) DISORDERS	2
Total Patient Count for VASCULAR (EXTRACARDIAC) DISORDERS	2
Total # Adverse Reactions in this Report	148
Total # of Patients in this Report	79

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
APPLICATION SITE DISORDERS							
1999-09-0247	FRANCE	20 Y	F		INJECTION SITE ABSCESS		Not Yet Recovered Hospitalized, Required Intervention, Drug Abuse/Misuse

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form :	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication :				
DRUG DEPENDENCE	12MG QD	UNKNOWN		

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT WITH HISTORY OF DRUG ABUSE WAS UNDER SUBSTITUTION THERAPY WITH SUBUTEX (BUPRENORPHINE) 12MG QD. PATIENT WAS HOSPITALIZED DUE TO A VOLUMINOUS ABSCESS OF LEFT WRIST WITH COLLECTION AND A LESS IMPORTANT ABSCESS OF BEND OF ELBOW THAT REQUIRED A SURGERY. PATIENT WAS IN FACT MISUSING PARTIALLY THE TABLETS OF SUBUTEX BY INJECTING THEM BY IV ROUTE WITH USED SYRINGES. REPORTER CONSIDERED ABSCESS AT INJECTION SITE AND DRUG MISUSE UNLIKELY RELATED WITH SUBUTEX.

1999-09-0830	FRANCE	26 Y	F		INJECTION SITE PAIN WEIGHT DECREASE		Not Yet Recovered Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form :	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication :				
DRUG DEPENDENCE	UNKNOWN	CONTINUING		

Other Suspect Drug(s)/Dosage Form/ Dose(s):

COCAINE	UNKNOWN	INTRAVENOUS

Comment: A PATIENT WITH HISTORY OF DRUG DEPENDANCE TO MORPHINE-LIKE AND COCAINE-LIKE DRUGS AND HISTORY OF HEPATITIS, WAS ADRESSED FOR CHECK-UP OF HER GENERAL STATE AND WEIGHT LOSS OF 15 KG. IT WAS REPORTED THAT IT WAS IMOSSIBLE TO PRECISE THE START DATE OF DRUG DEPENDANCE TO SUBUTEX IV. AT THE PRESENT TIME, SHE WAS INJECTING IV SUBUTEX AND COCAIN. AT HER ADMISSION TO THE DEPARTMENT OF INTERNAL MEDICINE (DATE NOT PROVIDED), SHE PRESENTED WITH PAIN IN THE RIGHT LOWER LIMB, AFTER THE INJECTION IN THE FEMORAL VEIN. IT WAS REPORTED THAT AS OF THE DATE OF THIS REPORT PATIENT HAD NOT YET RECOVER. REPORTER CONSIDERED AE DOUBTFULLY RELATED TO SUBUTEX.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
APPLICATION SITE DISORDERS							
1999-10-0447	FRANCE	25 Y	M		INJECTION SITE ABSCESS	—	Not Yet Recovered Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication : DRUG DEPENDENCE	8MG QD	UNKNOWN		

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT HOSPITALIZED FOR WEANING FROM SUBUTEX (BUPRENORPHINE). PATIENT WAS INJECTING HIMSELF SUBUTEX 8 MG QD BY IV ROUTE SINCE 2 TO 3 MONTHS ACCORDING TO HIM (BUT PROBABLY SINCE 1 YEAR). AN ABSCESS ON LEFT FOREARM WAS NOTED AND REQUIRED A DRAINAGE. REPORTER STATED THAT ABSCESS WAS STARTING AND PATIENT WAS STILL CONTINUING TO INJECT HIMSELF SUBUTEX IN THE SAME AREA. REPORTER CONSIDERED ABSCESS AT INJECTION SITE POSSIBLY RELATED TO SUBUTEX.

1999-10-1144	FRANCE	33 Y	F		INJECTION SITE REACTION	—	Not Yet Recovered Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication : DRUG DEPENDENCE	UNKNOWN	UNKNOWN		

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT WITH HISTORY OF HIV INFECTION TREATED WITH TRITHERAPY INITIATED DRUG SUBSTITUTION THERAPY WITH SUBUTEX (BUPRENORPHINE) AT AN UNKNOWN DATE AND UNKNOWN DOSE. IMPORTANT INFLAMMATORY REACTION ON ARM AND HAND ASSOCIATED WITH LYMPHANGITIS AND IMPORTANT PAIN WAS NOTED AND WAS DUE TO INJECTION OF SUBUTEX. PATIENT WAS HOSPITALIZED. REPORTER STATED THAT THE TRITHERAPY HAD BEEN MAYBE DISCONTINUED 1 WEEK BEFORE.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
BODY AS A WHOLE - GENERAL DISORDERS							
1999-09-0559	FRANCE	25 Y	M		EDEMA	17/09/1999	Not Yet Recovered
					ERYTHEMA		Non Serious
					PARESTHESIA	17/09/1999	

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	0.8 MG QD	CONTINUING		

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: A PATIENT WITH HISTORY OF DRUG ABUSE, INITIATED (DATE NOT PROVIDED) SUBUTEX (BUPRENORPHINE HCL) FOR DRUG SUBSTITUTION THERAPY. AT THE PRESENT TIME HE WAS TAKING 2 TABLETS OF 0.4MG QD IN THE SAME ADMINISTRATION. HE REPORTED FORMICATION IN HIS HANDS TO THE PHARMACIST, WHO NOTED THAT THERE WAS AN EDEMA AT THE BACK OF THE BOTH HANDS AND OF THE FINGERS, ACCOMPAGNIED WITH LOCAL SIGNS OF INFLAMMATION WITH REDNESS. THE PHARMACIST REPORTED ANOTHER THREE CASES OF PATIENTS, TREATED WITH SUBUTEX FOR DRUG SUBSTITUTION THERAPY, AT VARIOUS DOSES, WHO PRESENTED WITH EDEMA OF THE HANDS.

1999-09-0639	FRANCE				EDEMA		Unknown
							Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	UNKNOWN	UNKNOWN		

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: EDEMA OF THE HANDS WAS REPORTED.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome

BODY AS A WHOLE - GENERAL DISORDERS

1999-09-0640 FRANCE — EDEMA — Unknown, Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				

Indication : DRUG DEPENDENCE — UNKNOWN — UNKNOWN

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: EDEMA OF THE HANDS WAS REPORTED.

1999-09-0641 FRANCE — EDEMA — Unknown, Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				

Indication : DRUG DEPENDENCE — UNKNOWN — UNKNOWN

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: EDEMA OF THE HANDS WAS REPORTED.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
BODY AS A WHOLE - GENERAL DISORDERS							
1999-09-0816	FRANCE	35 Y	M		EDEMA PERIPHERAL		Unchanged Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	UNKNOWN IV			00/00/1999
Indication : DRUG DEPENDENCE	6 MG/D SL	CONTINUING	00/00/1999	

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT INJECTED SUBUTEX BY IV ROUTE AND EDEMA OF LOWER LIMBS APPEARED.HE STOPPED 6 MONTHS AGO TO INJECT SUBUTEX AND TOOK HIS TREATMENT BY SL ROUTE.HE WAS HOSPITALIZED FOR EXPLORATION OF THE EDEMA WHICH ARE STILL PRESENT.

1999-10-0499	FRANCE	25 Y	F		WITHDRAWAL SYNDROME MATERNAL DRUG EXPOSURE	—	Improved Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	UNKNOWN	CONTINUING	00/00/1999	
Indication : DRUG DEPENDENCE				

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: FEMALE PATIENT BECAME PREGNANT WHILE ON SUBUTEX (SHE WAS SNIFFING IT). AFTER DELIVERY, SHE EXPERIENCED WITHDRAWAL SYNDROME. SUBUTEX WAS REINITIATED AND THE PATIENT WAS DOING BETTER.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
BODY AS A WHOLE - GENERAL DISORDERS							
1999-10-1085	FRANCE		F		FEVER DRUG DEPENDENCE		Not Yet Recovered Hospitalized

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication : DRUG DEPENDENCE	4 MG	UNKNOWN	00/00/1998	

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT WHO USED SUBUTEX BY IV ROUTE WAS PRESCRIBED SUBUTEX BY ORAL ROUTE BUT CONTINUED TO INJECT THE PRODUCT BY IV.SHE WAS HOSPITALIZED FOR FEVER AT 40.5 DEGREES CELSIUS.

1999-11-1060	FRANCE	35 Y	M		WITHDRAWAL SYNDROME		Recovered without sequelae Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication : DRUG DEPENDENCE	6MG QD	12 MONTH(S)	~	

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT WITH HISTORY OF HEROIN ADDICTION WAS UNDER DRUG SUBSTITUTION THERAPY WITH SUBUTEX (BUPRENORPHINE). PATIENT WAS TAKING SUBUTEX 6MG QD BY SUBLINGUAL ROUTE OR IV ROUTE. PATIENT WAS HOSPITALIZED FOR WEANING. SUBUTEX WAS DISCONTINUED 2 DAYS BEFORE HOSPITALIZATION. DRUG WITHDRAWAL SYNDROME OCCURRED WITH SWEATING, MIDRIASIS, ANXIETY AND ABDOMINAL CRAMPS (DATE NOT PROVIDED). REPORTER CONSIDERED DRUG ABUSE POSSIBLY RELATED WITH SUBUTEX.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
BODY AS A WHOLE - GENERAL DISORDERS							
1999-11-1061	FRANCE	39 Y	M		WITHDRAWAL SYNDROME		Recovered without sequelae Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	8-6 MG QD	3 YEAR(S)	—	

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT STARTED DRUG SUBSTITUTION THERAPY WITH SUBUTEX (BUPRENORPHINE) AT THE INITIAL DOSE OF 8MG QD AND THEN 6MG QD. REPORTER STATED PATIENT WAS TAKING SUBUTEX BY IV ROUTE PERMANENTLY. PATIENT WAS HOSPITALIZED FOR A WEANING. DRUG WITHDRAWAL SYNDROME OCCURRED (DATE NOT PROVIDED) WITH ANXIETY, PAIN, AGITATION AND SWEATING WHEN URINE BUPRENORPHINE LEVEL WAS AT 4NG/ML AND CREATININE WAS AT 1.3NG/ML. REPORTER CONSIDERED DRUG ABUSE POSSIBLY RELATED WITH SUBUTEX.

1999-12-1093	FRANCE	30 Y	M		WITHDRAWAL SYNDROME ABDOMINAL PAIN AGITATION	/	Recovered without sequelae Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS		1 DAY(S)	—	

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT INCLUDED IN A METHADONE PROGRAM AT DOSE 65 MG QD FOR ONE MONTH. ON — 1999 HE TOOK HIS USUAL DOSE OF METHADONE AND 0.5 G OF COCAINE LATER IN THE DAY. HE THEN TOOK A PIECE OF A TABLET OF SUBUTEX (BUPRENORPHINE) PER OS DOSED AT 8 MG. LATER HE TOOK SOME LAROXYL (AMITRIPTYLINE), IVADAL (ZOLPIDEM), LEXOMIL (BROMAZEPAM) AND TERCIAN (CYAMEMAZINE), FOLLOWED BY THE REST OF THE SUBUTEX TABLET IN IV. AT 11 PM ON THE SAME DAY, HIS FAMILLY CALLED THE LOCAL POISON UNIT BECAUSE HE WAS AGGITATED AND PRESENTED AN EXCESSIVE SWEATING WITH INSOMNIA. HE WAS THEN ADMITTED TO THE EMERGENCY ROOM WITH A SUSPICION OF WITHDRAWAL SYNDROME TO OPIATE WITH ABDOMINAL PAIN AND SOME AGITATION. HE WAS GIVEN SOME MORPHINE IV AT DOSE 1 MG, 2 TABLETS OF VISCERALGINE FORTE (METAMIZOLE TIEMONIUM) AND 50MG OF LOXAPAC IM (LOXAPINE) ORALLY. FOLLOWING THE FIFTH DOSE OF MORPHINE IV (TOTAL OF 5 MG), A SEDATIVE EFFECT WAS SEEN AT 0:20 AM. THE PATIENT WOKE-UP IN THE MORNING IN A GOOD HEALTH.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)
Dosage form(s): ALL DOSES
Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
BODY AS A WHOLE - GENERAL DISORDERS							
2000-01-0002	FRANCE	35 Y	M		EDEMA PERIPHERAL		Unchanged Hospitalized

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	8 MG BID	UNKNOWN		

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT WAS TAKING SUBUTEX FOR SEVERAL YEARS FOR SUBSTITUTION THERAPY AT THE DOSE OF 8 MG BID. HE WAS ALSO TREATED AT THE TIME OF THE EVENT WITH TRANXENE 10 MG BID, ZOLOFT 2 DAILY, TOPALGIC 6 DAILY. BY — 1999, PATIENT HAD A VERY PAINFUL EDEMA OF THE RIGHT LOWER LIMB.PATIENT WAS HOSPITALIZED ON — 99.A DEEP PHLEBITIS WAS RULED OUT.

2000-01-1149	FRANCE	32 Y	M		WITHDRAWAL SYNDROME FEVER TACHYCARDIA		Recovered without sequelae Hospitalized

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	UNKNOWN	UNKNOWN		

Indication : UNKNOWN
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT, DRUG ADDICTED, TOOK SUBUTEX 2MG (BUPRENORPHINE) UNTIL 27MAY1999. ON — HYPERTHERMIA AT 39.5°C AND TACHYCARDIA (EKG) OCCURRED. PATIENT WAS HOSPITALIZED. INFECTIOUS CHECK-UP: WBC = 12000, PLATELETS = 141000 AND CRP = 37. PATIENT DISCHARGED AGAINST MEDICAL OPINION. DISCHARGE PRESCRIPTION WAS EFFERALGAN (PARACETAMOL) AND MUCOMYST (ACETYLCYSTEINE). REPORTER CONSIDERED THE EVENTS DOUBTFULLY RELATED TO SUBUTEX.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
CARDIOVASCULAR DISORDERS, GENERAL							
1999-09-0013	FRANCE		M		MYOCARDIAL ISCHEMIA	—	Unknown Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	UNKNOWN	UNKNOWN		

Indication : UNKNOWN
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT WAS MISUSING SUBUTEX (BUPRENORPHINE) BY SNIFFING IT AT AN UNKNOWN DATE. ABOUT 2 YEARS AGO, MYOCARDIAL ISCHEMIA OCCURRED AND PATIENT WAS HOSPITALIZED.

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
DISORDERS OF BLOOD AND LYMPHATIC SYSTEM							
1999-11-0031	FRANCE		M		POLYCYTHEMIA ASTHENIA IMPOTENCE	/	Unchanged Hospitalized

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	UNKNOWN		00/00/1997	—

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT WAS HOSPITALIZED FOR ASTHENIA AND IMPOTENCE. POLYCYTHEMIA WAS DIAGNOSED.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
DISORDERS OF THE EAR & LABYRINTH							
2000-01-0415	FRANCE	26 Y	M		DEAFNESS	—	Recovered without sequelae Medically Significant

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	UNKNOWN	CONTINUING		

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: A 26 YEAR OLD MALE PATIENT WITH THE HISTORY OF DRUG DEPENDANCE TO HEROIN WAS STARTED WITH SUBUTEX (BUPRENOPRHINE) . IN — 1999, A FEW WEEKS AFTER INITIATING SUBUTEX, HE DEVELOPED A DECREASE OF THE AUDITION. AN AUDIOMETRY CHECK-UP SHOWED A SLIGHT BILATERAL PERCEPTIVE DEAFNESS (-25 DB). SUBUTEX DOSE WAS DECREASED (NOS). ON — 2000 A CONTROL AUDIOMETRY CHECK-UP WAS NORMAL. THE PRECOCIOUS CEREBRAL TRUNK AUDITIVE EVOKED POTENTIAL WAS NORMAL. THE PATIENT RECOVERED WITHOUT SEQUELAE. THE REPORTER EVOKED THE POSSIBILITY OF AN OVERDOSE TO SUBUTEX OR THE USE OF HEROIN BY THE PATIENT AS CAUSALITY ASSESSMENT FOR THE EVENT.

DISORDERS OF THE EYE							
1999-12-1077	FRANCE	28 Y	F		RETINITIS	—	Improved Hospitalized, Drug Abuse/Misuse
					INFECTION FUNGAL	—	

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
TABLETS	8 MG QD	UNKNOWN	—	

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT ADDICTED TO HEROINE SINCE THE AGE OF 13 YEARS. IN JAN1999 SHE WAS GIVEN SUBUTEX (BUPRENORPHINE) AT DOSE 8 MG QD AS SUBSTITUTIVE TREATMENT BUT USED SUBUTEX TABLET INTRAVENOUSLY. ON — 1999 SHE BECAME PREGNANT. THE PATIENT REPORTED THAT HER LAST IV INJECTION WITH SUBUTEX WAS IN AUG1999. IN — .999, SHE DEVELOPED AN UNILATERAL CHORIORETINITIS WITH CANDIDA LEADING TO HER HOSPITALISATION. NO CARDIAC DISORDER WAS FOUND. SHE RECEIVED FUNGIZONE (AMPHOTERICINE B) AND TRIFLUCAN (FLUCONAZOLE) AS SYMPTOMATIC TREATMENT. A VITRECTOMY WAS REPORTED (NOS). HER CONDITION IMPROVED SLOWLY AND A SURGERY WAS CONSIDERED AT THE END OF HER PREGNANCY. A CUTANEOUS CANDIDA WAS ALSO DIAGNOSED WHICH REGRESSED.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
DISORDERS OF THE EYE							
2000-01-1104	FRANCE	22 Y	M		RETINAL DISORDER FEVER SKIN NODULE RIGORS VOMITING SWEATING INCREASED		Recovered with sequelae Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL SOLUTION	UNKNOWN	UNKNOWN	01/06/1998	

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT INITIATED DRUG SUBSTITUTION THERAPY WITH SUBUTEX (BUPRENORPHINE). PATIENT WAS MISUSING SUBUTEX BY IV INJECTION AND BY NASAL INHALATION. ONE WEEK AFTER ONE INJECTION OF SUBUTEX, SEPTIC PICTURE WITH FEVER, CHILLS, SWEATING, VOMITING AND THEN ERUPTION OF SUBCUTANEOUS NODULES ON THE SCALP AND VISUAL DISORDERS OCCURRED. PATIENT WAS HOSPITALIZED. A LEFT CHORIORETINITIS WAS DISCOVERED. INFECTION WITH CANDIDA ALBICANS WAS SUSPECTED. PATIENT WAS ALSO TAKING OCCASIONALLY LSD, ECSTASY AND PSYCHOTROPIC DRUGS. NO INFORMATION WAS PROVIDED ON HOW SUBUTEX WAS PREPARED BEFORE THE INJECTIONS. REPORTER CONSIDERED RETINOPATHY, FEVER AND CHILLS DOUBTFULLY RELATED WITH SUBUTEX.

DISORDERS OF THE IMMUNE SYSTEM							
1999-11-1094	FRANCE	35 Y	M		SCLERODERMA	— —	Not Yet Recovered Medically Significant, Drug Abuse/Misuse

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	UNKNOWN	CONTINUING	00/00/1995	

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT HAS BEEN INJECTING SUBUTEX SINCE 1995. SCLERODERMA WAS DIAGNOSED ON — .999.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)
Dosage form(s): ALL DOSES
Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
DISORDERS OF THE REPRODUCTIVE SYSTEM AND							
1999-09-0362	FRANCE	24 Y	F		AMENORRHEA	00/06/1999	Unchanged Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	2 MG DAILY	CONTINUING		

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: AMENORRHEA ASSOCIATED WITH AN INCREASE OF PROLACTIN WAS REPORTED ON —99 IN A PATIENT TREATED WITH SUBUTEX SINCE MORE THAN 3 YEARS. DATE OF LATE MENSES NOTED ON —99.

1999-09-0363	FRANCE	34 Y	M		GYNECOMASTIA	—	Not Yet Recovered Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	6-7 MG QD	CONTINUING	00/00/1997	

Indication : DRUG DEPENDENCE NO
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: A PATIENT HAD A PULMONARY TUBERCULOSIS IN 1990 AND A HISTORY OF HEPATITIS C, NOT TREATED, CONSIDERED AS RECOVERED. HE ABUSED WITH SUBUTEX (BUPRENORPHINE HCL) SINCE 1997 — HE WAS CATERING WITH SUBUTEX ILLEGALLY. AT THE PRESENT TIME HE WAS TAKING 6-7 MG QD OF SUBUTEX BY SUB-LINGUAL ROUTE. ON — 1999 THE PHYSICIAN — . NOTED A GYNECOMASTIA. HE CONSIDERED IT POSSIBLY RELATED TO SUBUTEX.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
DISORDERS OF THE REPRODUCTIVE SYSTEM AND							
1999-09-0634	FRANCE		F		HYDRAMNIOS	00/06/1999	Unknown Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	0.8 MG QD	UNKNOWN		

Indication : DRUG DEPENDENCE

Other Suspect Drug(s)/Dosage Form/ Dose(s):
SOLUPRED UNKNOWN — UNKNOWN

Comment: HYDRAMNIOS WAS DIAGNOSED DURING BIRTH. ACUTE ADRENAL INSUFFICIENCY OCCURRED IN THE BABY.

1999-10-1157	FRANCE	34 Y	M		SPERM DISORDER	—	Unknown Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	4 MG QD	2 YEAR(S)	00/00/1996	00/10/1998
	4 MG QD	CONTINUING	10/10/1999	

Indication : DRUG DEPENDENCE

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: MALE PATIENT, TREATED WITH SUBUTEX 4MG QD (BUPRENORPHINE) FROM 1996 TO OCT1998, REINITIATED SUBUTEX ON 10OCT1999 FOR DRUG DEPENDENCE. HIS SPERMOGRAM OF —99 WAS NORMAL. ON — NO SPERMAZOON WAS FOUND DURING INTRAVAGINAL EXAM OF HIS PARTNER. A SPERMOGRAM WAS PLANNED. REPORTER CONSIDERED THE EVENT POSSIBLY RELATED TO SUBUTEX.

APPEARS THIS WAY
ON ORIGINAL

Drug(s): SUBUTEX (BUPRENORPHINE HCL)
Dosage form(s): ALL DOSES
Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
DISORDERS OF THE REPRODUCTIVE SYSTEM AND							
2000-01-0581	FRANCE		M		PRIAPISM		Unknown Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)
Dosage Form : SUBLINGUAL TABLETS — **Total Dose:** UNKNOWN — **Treatment Duration:** UNKNOWN — **Admin. Start Date:** — **Admin. Finish Date:** —
Indication : UNKNOWN
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT REPORTED PRIAPISM WHILE TAKING SUBUTEX.

ENDOCRINE DISORDERS							
1999-09-0556	FRANCE	1 D			ADRENAL INSUFFICIENCY	—	Recovered Medically Significant

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)
Dosage Form : SUBLINGUAL TABLETS — **Total Dose:** 0.8 MG QD — **Treatment Duration:** UNKNOWN — **Admin. Start Date:** — **Admin. Finish Date:** —
Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: A MOTHER WHO HAD A HISTORY OF DRUG ABUSE AND HEPATITIS C, WAS TREATED WITH SUBUTEX (BUPRENORPHINE HCL) 0.8MG QD FOR DRUG SUBSTITUTION THERAPY AND WITH SOLUPRED (PREDNISOLONE) FOR HEPATITIS C DURING HER PREGNANCY. SHE GAVE BIRTH TO A BABY IN — 1999. HYDRAMNIOS WAS DIAGNOSED AT THE BIRTH. THE ETIOLOGIC EXPLORATION (NOT PRECISED) WAS NEGATIVE. THE BABY DIDN'T HAVE A NEONATAL WITHDRAWAL SYNDROME, BUT AN ACUTE ADRENAL INSUFFICIENCY OCCURRED AT THE BIRTH. ACCORDING TO THE PHYSICIAN, IT COULD BE RELATED TO THE TREATMENT WITH SOLUPRED THAT THE MOTHER TOOK DURING HER PREGNANCY. IT WAS REPORTED ON — 99 THAT AT THE PRESENT TIME, THE BABY WAS DOING WELL.

APPEARS THIS WAY
ON ORIGINAL

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
ENDOCRINE DISORDERS							
1999-11-0857	FRANCE	36 Y	M		HYPERTHYROIDISM SWEATING INCREASED TACHYCARDIA ANOREXIA	—	Not Yet Recovered Hospitalized

Source : Non-US, Health Professional, AFSSAPS

Main Schering Drug : REBETOL (RIBAVIRIN)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
TABLETS				
Indication : UNKNOWN	1000 MG QD	4 MONTH(S)	—	—

Other Suspect Drug(s)/Dosage Form/ Dose(s):

VIRAFERON	INJECTABLE SUSPENSION 3 MU WEEKLY	SUBCUTANEOUS	For 8 MONTH(S)
SUBUTEX (BUPRENORPHINE HCL)	SUBLINGUAL TABLETS 3 MG QD	SUBLINGUAL	For 8 WEEK(S)
VISKEN	TABLETS 5 MG QD	ORAL	
DAFALGAN	CAPSULES 3000 MG/WEEK	ORAL	For 8 MONTH(S)

Comment: PATIENT TREATED WITH VISKEN (PINDOLOL) 5MG QD (DATE UNKNOWN), WITH VIRAFERON (INTERFERON ALFA 2B) 3MUI BY WEEK AND DAFALGAN (PARACETAMOL) 3000MG BY WEEK SINCE 15JAN1999, WITH RIBAVIRIN (UNDER TEMPORARY AUTHORIZATION OF USE) 1000MG QD SINCE 15MAY, AND WITH SUBUTEX (BUPRENORPHINE) 3MG QD SINCE 15JUL. SINCE : —— , IT WAS NOTED SIGNS OF HYPERTHYROIDISM WITH THYROID GOITER AND BIOLOGICAL HYPERTHYROIDISM, DUE TO TREATMENT WITH VIRAFERON, ACCORDING TO THE REPORTER. IT WAS REPORTED TREMBLING OF EXTREMITIES, PALPITATIONS WITH TACHYCARDIA OF REST, SLEEP DISORDERS, IRRITABILITY, VASOMOTOR DISORDERS (SWEATING INCREASED, THERMOPHOBIA), DIFFUSE GOITER, RUBBERY, ASYMMETRICAL, WITHOUT BREATH OR THRILL, ASTHENIA, ANOREXIA. ALL DRUGS WERE DISCONTINUED ON 15SEP. REPORTER CONSIDERED THE HYPERTHYROIDISM DOUBTFULLY RELATED TO DRUGS.

APPEARS THIS WAY
ON ORIGINAL

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
FOETAL DISORDERS							
1999-08-1019	FRANCE		F		CLEFT LIP	—	Not Yet Recovered Hospitalized, Congenital Anomaly

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form :	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	UNKNOWN	UNKNOWN		

Indication : UNKNOWN
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT WITH HISTORY OF CHRONIC HEPATITIS C WAS TAKING SUBUTEX (BUPRENORPHINE) DURING HER PREGNANCY. AT 22-23 WEEKS OF AMENORRHEA, ULTRASOUND REVALED AN ISOLATED LABIOPALATINE CLEFT. INDUCED DELIVERY WAS PERFORMED AT 35 WEEKS OF AMENORRHEA DUE TO PREMATURE MEMBRANES RUPTURE. A FEMALE BABY WITH AN UNILATERAL LABIO-MAXILLAR CLEFT. BABY'S CARYOTYPE WAS 46 XX. REPORTER CONSIDERED LABIAL CLEFT DOUBTFULLY RELATED WITH SUBUTEX.

GASTRO-INTESTINAL SYSTEM DISORDERS							
1999-08-0887	FRANCE	25 Y	M		MELENA ASTHENIA DYSPNEA PAIN DIARRHEA SWEATING INCREASED VOMITING		Not Yet Recovered Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form :	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	2 MG	1 DOSE(S)	—	

Indication : UNKNOWN
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT WITH NO HISTORY OF MELENA TOOK 1/4 OF AN 8MG DOSAGE TABLET OF SUBUTEX (BUPRENORPHINE) FROM A FRIEND WHO WAS TREATED WITH SUBUTEX THINKING HE WAS TAKING PARACETAMOL. ABOUT HALF AN HOUR LATER, SWEATING, VOMITING, PAIN IN THE ARM, DYSPNEA AT EXERTION (PATIENT WAS DYSPNEIC WHEN CLIMBING STAIRS), ASTHENIA AND DIARRHEA WITH BLACK STOOLS OCCURRED. 2 DAYS LATER, ALL EVENTS HAD RESOLVED EXCEPT DIARRHEA WITH BLACK STOOLS, ASTHENIA AND DYSPNEA AT EXERTION. IF BLACK STOOLS HAD TO PERSIST, REPORTER STATED HE WOULD PERFORM A CHECK UP FOR MELENA. REPORTER CONSIDERED SWEATING, VOMITING, PAIN IN THE ARM, DYSPNEA AT EXERTION, ASTHENIA AND DIARRHEA POSSIBLY RELATED WITH SUBUTEX, BUT COULD NOT ASSESS A CAUSALITY FOR THE BLACK STOOLS.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
INFECTION AND INFESTATIONS							
1999-10-1096	FRANCE	36 Y	M		SEPSIS		Recovered without sequelae Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	8MG QD	6 MONTH(S)	15/09/1998	02/04/1999

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: FRENCH HEALTH AUTHORITIES REPORT: PATIENT, ADDICTED TO DRUGS, TREATED WITH SUBUTEX 8MG QD (BUPRENORPHINE) DURING 6 MONTHS. DILUTED SUBUTEX SL TABLET WITH HIS SALIVA, AND HAD INJECTED IT BY IV ROUTE. HOSPITALIZED (DATE UNKNOWN) FOR ASTHENIA, FEVER AND CARDIAC MURMUR. SEPSIS WITH STREPTOCCOCUS WAS DIAGNOSED. THE SAME STREPTOCOCCUS WAS FOUND IN HIS SALIVA DURING A LATER EXAM. RECOVERED. REPORTER CONSIDERED THE SEPSIS POSSIBLY RELATED TO SUBUTEX.

LIVER AND BILIARY SYSTEM DISORDERS							
1999-08-0810	FRANCE	42 Y	M		HEPATITIS JAUNDICE HEPATIC ENZYMES INCREASED	—	Not Yet Recovered Hospitalized, Medically Significant

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	8MG QD	CONTINUING		

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: AE: HEPATITIS; JAUNDICE; HEPATIC ENZYMES INCREASED: PATIENT RECOVERING FROM HEPATITIS B WITHOUT TREATMENT, WITH HEPATITIS C STABLE, UNTREATED, HIV POSITIVE AND PULMONARY TUBERCULOSIS, INITIATED AT LEAST ONE YEAR AGO SUBUTEX (BUPRENORPHINE) FOR DRUG SUBSTITUTION THERAPY. AT THE PRESENT TIME THE DOSE OF SUBUTEX WAS 8MG QD. ICTERUS APPEARED AND BILIRUBINEMIA WAS MEASURED AT 53µMOL/L. ANTITUBERCULOUS TREATMENT WITH RIFATER WAS DISCONTINUED. ONE MONTH LATER HEPATIC CHECK-UP (ULTRASONOGRAPHY) DIDN'T SHOW AN OBSTRUCTION OF BILIARY WAYS. TREATMENT WITH SUBUTEX WAS STILL ONGOING AS OF THE DAY OF THIS REPORT AND IT WAS THE ONLY MEDICATION PATIENT WAS TAKING. THE PATIENT HAS RECEIVED ANTITUBERCULOUS MEDICATION IN THE PAST WITHOUT ANY PROBLEMS. THE PATIENT ALSO PRESENTED WITH THE SAME SYMPTOMS PREVIOUSLY WHEN HE HAD ACTIVE HEPATITIS C AND B AND WHEN HE HAD TREATMENT WITH ANTITUBERCULOUS DRUGS. THE PHYSICIAN CONSIDERED THAT IT WAS A DRUG INDUCED HEPATITIS, UNLIKELY RELATED TO SUBUTEX.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)
Dosage form(s): ALL DOSES
Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
LIVER AND BILIARY SYSTEM DISORDERS							
1999-11-0903	FRANCE		M		HEPATITIS		Unknown Medically Significant

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)
Dosage Form : SUBLINGUAL TABLETS — **Total Dose:** UNKNOWN — **Treatment Duration:** UNKNOWN — **Admin. Start Date:** — **Admin. Finish Date:** —
Indication : UNKNOWN
Other Suspect Drug(s)/Dosage Form/ Dose(s):
COCAINE — UNKNOWN
Comment: PATIENT, TREATED WITH SUBUTEX (BUPRENORPHINE), HAD ACUTE HEPATITIS. HE ALSO INJECTED COCAINE.

1999-11-1059	FRANCE	28 Y	M		HEPATIC DISORDER NOS COMA MIOSIS RESPIRATORY DEPRESSION		Recovered Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)
Dosage Form : SUBLINGUAL TABLETS — **Total Dose:** UNKNOWN — **Treatment Duration:** UNKNOWN — **Admin. Start Date:** — **Admin. Finish Date:** —
Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):
Comment: PATIENT, TREATED WITH SUBUTEX (BUPRENORPHINE) FOR DRUG DEPENDENCE, HOSPITALIZED FOR A PICTURE OF OPIATE POISONNING (COMA, RESPIRATORY DEPRESSION, MIOSIS) AND SEVERE HEPATIC DISORDER. CHECK-UP ONGOING. REPORTER DIDN'T PROVIDED CAUSALITY FOR THE EVENT.

APPEARS THIS WAY
ON ORIGINAL

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
METABOLIC AND NUTRITIONAL DISORDERS							
1999-08-0178	FRANCE	26 Y	F		WEIGHT DECREASE WITHDRAWAL SYNDROME	00/00/1999 —	Not Yet Recovered Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	10 MG QD	CONTINUING	—	

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT TREATED SINCE MAY1999 WITH SUBUTEX (BUPRENORPHINE HCL) 10 MG QD FOR DRUG SUBSTITUTION, REPORTED THAT SINCE THE BEGINNING OF THE TREATMENT SHE HAD A WEIGH LOSS OF 10 KG. ON — AFTER SHE TOOK A 10 MG- DOSE OF SUBUTEX, SHE HAD A WITHDRAWAL SYNDROME. REPORTER CONSIDERED EVENTS PROBABLY RELATED TO SUBUTEX.

1999-08-1054	FRANCE	31 Y	M		WEIGHT DECREASE		Unknown Hospitalized

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	0.4MG BID	UNKNOWN	00/00/1998	

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT WITH HISTORY OF HEROIN ADDICTION INITIATED SUBSTITUTION THERAPY WITH SUBUTEX (BUPRENORPHINE) 0.4MG BID ONE YEAR AGO. WEIGHT LOSS OF 20KG WAS NOTED. PATIENT WAS HOSPITALIZED TO EXPLORE THE WEIGHT LOSS AND FOR WEANING FROM SUBUTEX.

APPEARS THIS WAY
ON ORIGINAL

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
METABOLIC AND NUTRITIONAL DISORDERS							
1999-09-0243	FRANCE	33 Y	M		WEIGHT DECREASE TINNITUS DIZZINESS NAUSEA VOMITING ANOREXIA		Improved Hospitalized

Source : Non-US, Health Professional
Main Schering Drug : RIBAVIRIN
Dosage Form : CAPSULES
Indication : HPT C ACUTE WO HPAT COMA

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
1000 MG QD	8 DAY(S)		
600 MG QD	11 DAY(S)		

Other Suspect Drug(s)/Dosage Form/ Dose(s):

INTRONA (INTERFERON ALFA-2B RECOMBINANT)	INJECTABLE 3 MU QOD	SUBCUTANEOUS	For 8 DAY(S)
INTRONA (INTERFERON ALFA-2B RECOMBINANT)	INJECTABLE 3 MU QOD	SUBCUTANEOUS	For 11 DAY(S)
SUBUTEX (BUPRENORPHINE HCL)	SUBLINGUAL TABLETS 0.4 MG X6/DAY		
RETROVIR	TABLETS 300 MG BID	ORAL	
VIDEX	TABLETS 2 TAB. QD	ORAL	
INVIRASE	TABLETS 1800MG QD	ORAL	

Comment: A PATIENT WITH HISTORY OF HIV AND HCV POSITIVE, INITIATED AROUND — 1999 INTRONA (INTERFERON ALFA 2B) 3MIU EVERY 2 DAYS AND RIBAVIRIN 1G QD FOR HEPATITIS C. IT WAS REPORTED ON — 99 THAT ABOUT ONE WEEK AGO NASEA AND VOMITING APPEARED. PATIENT COMPLAINED OF INSTABILITY WHILE STANDING, HE WAS FEELING WELL WHEN HE WAS LYING. EAR ROARING PRECEEDING NAUSEA WAS ALSO REPORTED. A WEIGHT LOSS OF 4 KG WITHIN 15 DAYS WAS NOTED. TREATMENT WAS DISCONTINUED FOR 4 DAYS AND RE-INITIATED ON — '99 AT THE DOSE OF 3MIU EVERY 2 DAYS FOR INTRONA AND 600 MG QD FOR RIBAVIRIN. ON — '99 HE HAD A VISIT WITH THE PHYSICIAN AND HE WAS DOING BETTER. REPORTER CONSIDERED EVENTS POSSIBLY RELATED TO INTRONA AND RIBAVIRIN.

APPEARS THIS WAY
ON ORIGINAL

Drug(s): SUBUTEX (BUPRENORPHINE HCL)
Dosage form(s): ALL DOSES
Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
METABOLIC AND NUTRITIONAL DISORDERS							
1999-09-0553	FRANCE	42 Y	M		WEIGHT DECREASE	—	Not Yet Recovered Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form :	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication :				
DRUG DEPENDENCE	2 MG QD	CONTINUING	00/05/1999	

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: A PATIENT WITH HISTORY OF DRUG ABUSE WITH HEROIN INITIATED IN MAY1998 DRUG SUBSTITUTION THERAPY WITH SUBUTEX (BUPRENORPHINE HCL). AT THE PRESENT TIME THE DOSE OF SUBUTEX WAS 2MG QD. ' — .1999 THE PATIENT NOTED A WEIGHT DECREASE AND AS OF — 99 HE LOST 5KG SINCE THE INITIATION OF TREATMENT WITH SUBUTEX.

1999-09-0820	FRANCE	35 Y	F		WEIGHT INCREASE		Not Yet Recovered Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form :	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication :				
UNKNOWN	16 MG QD	UNKNOWN		

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: A PATIENT WITH HISTORY OF VIRAL HEPATITIS, DRUG DEPENDENCE TO MORPHINE-LIKE DRUGS AND TOBACCO ABUSE, WAS HOSPITALIZED FOR ALTERATION OF HER GENERAL STATE AND WEIGHT INCREASE OF 30 KG WITHIN 6 MONTHS. FOR ONE YEAR SHE USED TO INJECTE HERSELF INTRAVENOUSLY 1 TO 2 TABLETS DAILY(=16 MG QD) OF SUBUTEX. REPORTER CONSIDERED EVENTS DOUBTFULLY RELATED TO SUBUTEX.

APPEARS THIS WAY
ON ORIGINAL

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
METABOLIC AND NUTRITIONAL DISORDERS							
2000-01-0925	FRANCE	27 Y	F		WEIGHT DECREASE		Unchanged Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication : DRUG DEPENDENCE	6MG QD	CONTINUING	00/06/1999	

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT INITIATED SUBUTEX (BUPRENORPHINE) 6MG QD, 18 MONTHS AGO, FOR DRUG DEPENDANCE. WEIGHT LOSS OF APPROXIMATELY 10KG WAS REPORTED. REPORTER CONSIDERED THE WEIGHT LOSS POSSIBLY RELATED TO SUBUTEX.

MUSCULO-SKELETAL SYSTEM DISORDERS							
1999-08-0365	FRANCE	31 Y	F		TENDON DISORDER	00/02/1999	Unchanged Non Serious
					MATERNAL DRUG EXPOSURE	00/04/1999	

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication : DRUG DEPENDENCE	6-0.5 MG QD	UNKNOWN	00/02/1999	
	6MG QD	2 MONTH(S)	00/02/1999	00/04/1999
	2MG QD	CONTINUING	00/04/1999	00/00/1999
	1 MG QD	CONTINUING	00/00/1999	00/12/1999
	0.5MG QD	UNKNOWN	00/12/1999	

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PREGNANCY. MOTHER GAVE BIRTH TO A NORMAL CHILD IN GOOD HEALTH ON [redacted],999

APPEARS THIS WAY
ON ORIGINAL

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
MUSCULO-SKELETAL SYSTEM DISORDERS							
1999-08-0407	FRANCE	38 Y	F		TENDON DISORDER	00/05/1999	Not Yet Recovered Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication : DRUG DEPENDENCE	8 MG QD	CONTINUING	16/04/1999	

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: FEMALE PATIENT WITH DIAGNOSIS OF HEPATITIS C 3 MONTHS AGO, STILL NOT TREATED, INITIATED 4 MONTHS AGO SUBUTEX (BUPRENORPHINE HCL) 8MG QD FOR DRUG SUBSTITUTION THERAPY. 2 MONTHS LATER PATIENT WAS DIAGNOSED WITH CARPAL TUNNEL SYNDROME AND AS OF THE DAY OF THE REPORT THE SYMPTOMS STILL PERSIST. REPORTER CONSIDERED EVENT POSSIBLY RELATED TO SUBUTEX.

1999-08-0408	FRANCE	25 Y	M		TENDON DISORDER	—	Not Yet Recovered Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication : DRUG DEPENDENCE	8 MG QD	CONTINUING	16/04/1999	

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT INITIATED ON 16APR1999 SUBUTEX (BUPRENORPHINE HCL) 8MG QD FOR DRUG SUBSTITUTION THERAPY. ON — PATIENT WAS DIAGNOSED WITH RIGHT CARPAL TUNNEL SYNDROME WITH NOCTURNAL PARESTHESIA. BETWEEN — 99 AND — 99 PATIENT DIDN'T WORK. SINCE — IS WORKING AS — AND HIS ACHES RELATED WITH CARPAL TUNNEL SYNDROME WERE INCREASED SINCE THEN. AS OF — 99 THE SYMPTOMS STILL PERSIST. REPORTER CONSIDERED EVENT POSSIBLY RELATED TO SUBUTEX. CASE SWITCHED FROM SERIOUS TO NON-SERIOUS. PATIENT WAS NOT DISABLED. HE WAS — FROM / — . PATIENT HAS NOT RECOVERED YET.

APPEARS THIS WAY
ON ORIGINAL

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
MUSCULO-SKELETAL SYSTEM DISORDERS							
1999-08-0409	FRANCE	24 Y	M		TENDON DISORDER INSOMNIA	00/06/1999	Not Yet Recovered Non Serious

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	2 MG QD	CONTINUING	00/04/1999	

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: MALE PATIENT TREATED WITH SUBUTEX (BUPRENORPHINE HCL) 2MG QD FOR DRUG SUBSTITUTION THERAPY SINCE —, WAS DIAGNOSED WITH CARPAL TUNNEL SYNDROME ON THE RIGHT HAND THREE MONTHS AFTER THE INTIATION OF TREATMENT. SUBUTEX WAS NOT DISCONTINUED. AS OF — THE PATIENT HAD PARTIALLY RECOVERED. THE REPORTER CONSIDERED EVENT POSSIBLY RELATED TO SUBUTEX.

1999-08-0593	FRANCE	39 Y	M		JOINT DISORDER CALCINOSIS	—	Recovered Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	16 MG QD	CONTINUING	00/00/1998	

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT WAS HOSPITALIZED O — 1999. CHONDROCALCINOSIS WAS DIAGNOSED. THE REPORTER CONSIDERED THE EVENT NOT RELATED TO SUBUTEX.

APPEARS THIS WAY
ON ORIGINAL

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
MUSCULO-SKELETAL SYSTEM DISORDERS							
1999-10-0062	FRANCE	22 Y	M		ARTHROPATHY ABDOMINAL PAIN FEVER RIGORS NAUSEA VOMITING	—	Recovered without sequelae Hospitalized

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	12 MG	ONCE		

Indication : UNKNOWN
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT INJECTED HIMSELF BY IV ROUTE SUBUTEX 12 MG.ONE HOUR AND HALF AFTER INJECTION PATIENT PRESENTED ARTICULAR BLOCKING, ABDOMINAL PAINS, NAUSEA, VOMITING, CHILLS AND FEVER (40.5 DEGREES CELSIUS) REQUIRING HOSPITALIZATION.PATIENT RECOVERED.REPORTER CONSIDERED AE DOUBTFULLY (POSSIBLY) RELATED TO SUBUTEX.

2000-01-1129	FRANCE	38 Y	M		SPONDYLITIS	—	Not Yet Recovered Hospitalized

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	UNKNOWN	UNKNOWN		

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: FRENCH HEALTH AUTHORITIES REPORT (PP000009): REFERRING TO A 38 YEAR OLD HIV (+), HCV (+) MALE FORMER DRUG ADDICTED. HE WAS STARTED WITH SUBUTEX (BUPRENORPHINE) AS SUBSTITUTIVE TREATMENT. HE WAS REGULARLY USING SUBUTEX IN IV. HE WAS DIAGNOSED WITH AN ANTEROBACTER CLOACAE SPONDYLITIS WITH DISCITIS IN L1 & L2. NO OTHER ENTRY POSSIBILITY WAS FOUND FOR THE INFECTION.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
MUSCULO-SKELETAL SYSTEM DISORDERS							
2000-01-1155	FRANCE	34 Y	M		ARTHRITIS		Not Yet Recovered Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication : DRUG DEPENDENCE	7.5 MG IV QD	15 DAY(S)		

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: FRENCH HEALTH AUTHORITIES REPORT (PP0000013) REFERRING TO A 34 YEAR OLD MALE FORMER HEROIN USER. THERE IS NO RECENT HISTORY OF CUTANEOUS INFECTION IN THIS PATIENT. IN 1996 HE WAS STARTED WITH SUBUTEX (BUPRENORPHINE) AS SUBSTITUTIVE TREATMENT. HE WAS OCCASSIONALY USING SUBUTEX IN IV. IN — 1999, A STERNAL TUMEFACTION WAS NOTICED FOR WHICH A PUNCTURE WAS DONE BUT FAILED ON — 2000. FOR THE PAST 15 DAYS PRIOR TO THE EVENT HE HAD BEEN USING SUBUTEX IN IV TID AT DOSE 7.5 MG QD. ON — HE WAS HOSPITALIZED FOR A CHONDRO STERNAL ARTHRITIS (LAST JOINT).

NEONATAL AND INFANCY DISORDERS							
1999-09-0188	FRANCE	32 Y	F		WITHDRAWAL SYNDROME NEONATAL	00/11/1999	Unknown
					MATERNAL DRUG EXPOSURE	00/00/1999	Medically Significant

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication : DRUG DEPENDENCE	8 MG QD	CONTINUING		

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PREGNANCY .HISTORY OF DRUG ABUSE. DRUG SUBSTITUTION THERAPY WITH SUBUTEX (BUPRENORPHINE HCL) FOR 2-3 YEARS. ONE CHILD IN GOOD HEALTH WAS BORN AFTER AN EXPOSITION TO SUBUTEX DURING THE PREVIOUS PREGNANCY. FOR CURRENT PREGNANCY OUTCOME, IT WAS REPORTED THAT THE THE PATIENT GAVE BIRTH TO A CHILD WITH NEONATAL WITHDRAWAL SYSTEM WHICH LASTED APPROXIMATELY 15 DAYS. THE CHILD THEN RECOVERED.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)
Dosage form(s): ALL DOSES
Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
NEONATAL AND INFANCY DISORDERS							
1999-09-0473	FRANCE				WITHDRAWAL SYNDROME NEONATAL	00/00/1999	Recovered Medically Significant

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	10-4-12 MG QD	CONTINUING	23/11/1996	

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: A NEWBORN BABY, WHICH MOTHER WAS TREATED WITH SUBUTEX DURING HER PREGNANCY (DOSE FROM 10 MG QD TO 4 MG QD AND 8-10 MG QD) HAD A VERY MILD WITHDRAWAL SYNDROME. IT WAS TREATED WITHOUT OPIATES AND RESOLVED WITHIN 2-3 DAYS. BABY WAS DISCHARGED FROM HOSPITAL AND WAS DOING WELL.

1999-10-0374	FRANCE	1 D	F		WITHDRAWAL SYNDROME NEONATAL DEHYDRATION RENAL INSUFFICIENCY HYPOKALEMIA	—	Not Yet Recovered Hospitalized

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	2MG QD	UNKNOWN		

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: AT 40.5 WEEKS OF AMENORRHEA, MOTHER GAVE BIRTH TO A FEMALE BABY WHO WAS TRANSFERRED IN NEONATALOGY DEPARTMENT FOR A WEANING SYNDROME. FUNCTIONAL RENAL INSUFFICIENCY WAS NOTED AT THE THIRD DAY OF LIFE SECONDARY TO DEHYDRATION PROBABLY DUE TO INITIAL FEEDING DIFFICULTIES. A TREATMENT WITH MORPHINE CHLORHYDRATE PO 0.75MG/KG QD WAS INITIATED. ABOUT 1.5 MONTHS LATER, GOOD PSYCHOMOTOR AND PONDOSTATURAL DEVELOPMENT WAS NOTED. REPORTER CONSIDERED NEONATAL WITHDRAWAL SYNDROME PROBABLY RELATED WITH SUBUTEX.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)
Dosage form(s): ALL DOSES
Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
NEONATAL AND INFANCY DISORDERS							
1999-10-0506	FRANCE	1 D			WITHDRAWAL SYNDROME NEONATAL	—	Improved Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	UNKNOWN	DISCONTINUED	00/00/1999	

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: NEONATAL WITHDRAWAL SYNDROME OCCURRED. UNKNOWN TREATMENT WAS GIVEN. THE BABY IMPROVED.

1999-10-1272	FRANCE	2 D	F		WITHDRAWAL SYNDROME NEONATAL	—	Recovered with sequelae Hospitalized

Source : Non-US, Literature, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS	8MG QD			—

Indication : DRUG DEPENDENCE
Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: LITERATURE REPORT: ABSTRACT FROM FIRST EUROPEAN MEETING ON DRUG ABUSE AND DEPENDENCE: C. BEDEN, S.PERQUIN, C. BARJOUX, F. VINCENT, M.MALLARET: "GEMELLARY PREGNANCY ON BUPRENORPHINE: WITHDRAWAL SYNDROME IN NEWBORNS." OCT 25-26, 1999. A FEMALE WHO RECEIVED BUPRENORPHINE DURING PREGNANCY GAVE BIRTH TO TWINS. NEONATAL WITHDRAWAL SYNDROME OCCURRED. WITHDRAWAL SYMPTOMS IMPROVED WITH ORAL DIAZEPAM. THE REPORTER CONSIDERED THE EVENT POSSIBLY RELATED TO SUBUTEX.

Drug(s): SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s): ALL DOSES

Start Date: 01/08/1999
Cutoff Date: 31/01/2000

Company Ref No	Country	AGE	SEX	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
NEONATAL AND INFANCY DISORDERS							
1999-10-1273	FRANCE	2 D	F		WITHDRAWAL SYNDROME NEONATAL	—	Recovered with sequelae Hospitalized

Source : Non-US, Literature, Health Professional
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication : DRUG DEPENDENCE	8MG QD			—

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: LITERATURE REPORT: ABSTRACT FROM FIRST EUROPEAN MEETING ON DRUG ABUSE AND DEPENDENCE..C.BEDEN, S,PERQUIN, C.BARJHOUX, VINCENT M. MALLARET. "GEMELLARY PREGNANCY ON BUPRENORPHINE: WITHDRAWAL SYNDROME IN NEWBORNS". OCT. 25-26, 1999. A FEMALE RECEIVED BUPRENORPHINE DURING HER PREGNANCY. SHE GAVE BIRTH TO TWINS. NEONATAL WITHDRAWAL SYNDROME OCCURRED. WITHDRAWAL SYMPTOMS RESOLVED WITH ORAL DIAZEPAM. THE REPORTER CONSIDERED THE EVENT POSSIBLY RELATED TO SUBUTEX.

1999-11-0358	FRANCE	4 D			WITHDRAWAL SYNDROME NEONATAL	—	Recovered without sequelae Hospitalized, Drug Abuse/Misuse

Source : Non-US, Health Professional, AFSSAPS
Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form	Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
SUBLINGUAL TABLETS				
Indication : DRUG DEPENDENCE	4MG QD	UNKNOWN		

Other Suspect Drug(s)/Dosage Form/ Dose(s):

Comment: PATIENT WAS TAKING SUBUTEX (BUPRENORPHINE) 4MG QD DURING THE WHOLE PREGNANCY. FROM 32ND TO 38TH WEEK OF AMENORHEA, SUBUTEX WAS TAKEN IV AND THEN SL. AT 39 WEEKS OF AMENORRHEA, MALE BABY WAS BORN. NEONATAL WITHDRAWAL SYNDROME WAS REPORTED BY THE HEALTH AUTHORITY. REPORTER CONSIDERED NEONATAL WITHDRAWAL SYNDROME POSSIBLY RELATED WITH SUBUTEX.

APPEARS THIS WAY
ON ORIGINAL