

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

Company Ref No	Country	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
----------------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**NEONATAL AND INFANCY DISORDERS**

1999-11-0850	FRANCE		3 D		WITHDRAWAL SYNDROME NEONATAL INTESTINAL OBSTRUCTION ABDOMINAL DISTENSION		Not Yet Recovered Hospitalized
--------------	--------	--	-----	--	--	--	-----------------------------------

Source : Non-US, Health Professional, AFSSAPS  
 Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS  
 Indication : DRUG DEPENDENCE

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
8-4MG QD*			
8MG QD			
4MG QD	2 MONTH(S)		

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

Comment: 3 DAY OLD BABY PRESENTED WITH NEONATAL WITHDRAWAL SYNDROME.NO CLEAR EXPLANATION FOR THE DIGESTIVE SYMPTOMATOLOGY WAS PROPOSED. THE REPORTER CONSIDERED THE EVENT POSSIBLY RELATED.

1999-11-1026	FRANCE		8 D		WITHDRAWAL SYNDROME NEONATAL		Recovered Medically Significant
--------------	--------	--	-----	--	------------------------------	--	------------------------------------

Source : Non-US, Health Professional  
 Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS  
 Indication : UNKNOWN

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
UNKNOWN			

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

Comment: 8 DAY OLD PATIENT, WHOSE MOTHER WAS TREATED WITH SUBUTEX (BUPRENORPHINE) DURING HER PREGNANCY, HAD A WITHDRAWAL SYNDROME. AT THE AGE OF 3 MONTHS THE CHILD WAS FINE.

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	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
---------	--------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**NEONATAL AND INFANCY DISORDERS**

1999-11-1027	FRANCE			8 D		WITHDRAWAL SYNDROME NEONATAL		Recovered Medically Significant
--------------	--------	--	--	-----	--	------------------------------	--	------------------------------------

Source : Non-US, Health Professional

Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Indication : UNKNOWN

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

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
UNKNOWN			

Comment: 8 DAY OLD PATIENT, WHOSE MOTHER WAS TREATED WITH SUBUTEX (BUPRENORPHINE) DURING HER PREGNANCY, HAD A WITHDRAWAL SYNDROME. CHILD RECOVERED.

1999-11-1028	FRANCE			8 D		WITHDRAWAL SYNDROME NEONATAL		Recovered Medically Significant
--------------	--------	--	--	-----	--	------------------------------	--	------------------------------------

Source : Non-US, Health Professional

Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Indication : UNKNOWN

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

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
UNKNOWN			

Comment: 8 DAY OLD PATIENT, WHOSE MOTHER WAS TREATED WITH SUBUTEX (BUPRENORPHINE) DURING HER PREGNANCY, HAD A WITHDRAWAL SYNDROME. CHILD RECOVERED.

**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	Country	A	S	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
Ref No		G	E				
		E	X				

**NEONATAL AND INFANCY DISORDERS**

1999-12-0199	FRANCE		1 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 : SUBLINGUAL TABLETS  
 Indication : DRUG DEPENDENCE

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
*4-16MG QD	3 YEAR(S)		
4MG QD	3 YEAR(S)		
16MG QD	3 MONTH(S)		

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

Comment: FRENCH HEALTH AUTHORITY REPORT. NEONATAL WITHDRAWAL SYNDROME.

1999-12-1075	FRANCE		1 W F		WITHDRAWAL SYNDROME NEONATAL		Recovered without sequelae Hospitalized, Drug Abuse/Misuse
--------------	--------	--	-------	--	------------------------------	--	---

Source : Non-US, Health Professional  
 Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS  
 Indication : DRUG DEPENDENCE

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
2 MG DAILY	32 MONTH(S)		.9

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

Comment: WITHDRAWAL SYNDROME NEONATAL REPORTED AT DAY 8 IN A NORMAL FEMALE BABY WHOSE MOTHER WAS INJECTING HERSELF WITH SUBUTEX ON A REGULAR BASIS THROUGHOUT THE PREGNANCY.

**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	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
---------	--------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**NEONATAL AND INFANCY DISORDERS**

1999-12-1080	FRANCE		1	D	F	WITHDRAWAL SYNDROME NEONATAL		Recovered without sequelae Hospitalized
--------------	--------	--	---	---	---	------------------------------	--	---

Source : Non-US, Health Professional, AFSSAPS

Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Indication : DRUG DEPENDENCE

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

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
------------	--------------------	-------------------	--------------------

4MG QD	8 MONTH(S)		
--------	------------	--	--

Comment: FRENCH HEALTH AUTHORITIES REPORT: MOTHER, HEROINE ADDICTED, BECAME PREGNANT, AND INITIATED SUBUTEX (BUPRENORPHINE) 4MG QD ONE MONTH LATER FOR DRUG DEPENDENCE. AFTER 41 WEEKS OF AMENORRHEA, DELIVERY FROM BELOW OF A NORMAL FEMALE BABY. AT DAY 1, WITHDRAWAL SYNDROME (LIPSITZ SCORE AT 7). TREATMENT WITH MORPHINE CHLORHYDRATE 0.8ML\*4 BY DAY WAS INTRODUCED. AT DAY 17, THE PATIENT RECOVERED AND MORPHINE CHLORHYDRATE WAS STOPPED. REPORTER CONSIDERED THE WITHDRAWAL SYNDROME NEONATAL POSSIBLY RELATED TO SUBUTEX.

**PLATELET, BLEEDING AND CLOTTING DISORD**

1999-12-0820	FRANCE		28	Y	M	PURPURA SKIN NECROSIS		Not Yet Recovered Hospitalized
--------------	--------	--	----	---	---	--------------------------	--	--------------------------------

Source : Non-US, Health Professional, AFSSAPS

Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form : TABLETS

Indication : DRUG DEPENDENCE

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

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
------------	--------------------	-------------------	--------------------

16 MG QD	CONTINUING		
----------	------------	--	--

Comment: FRENCH HEALTH AUTHORITY REPORT (BX9900858). THE MEDICAL HISTORY INCLUDED A CHRONIC HEPATITIS C, A TOXICOMANY HISTORY AND A FRACTURE WITH BONE TRANSPLANTATION OF THE SCAPHOID BONE AT THE AGE OF 14. CONCOMITANT TREATMENT : NOZINAN (LEVOMEPROZAMINE), GAVISCON (SODIUM ALGINATE AND BICARBONATE), STILNOX (ZOLPIDEM) AND MOPRAL (OMEPRAZOLE). AFTER 4 YEARS OF USE OF SUBUTEX, THE PATIENT DEVELOPED A PURPURA OF THE FOUR LIMBS WITH NECROSIS OF A FINGER ON THE RIGHT HAND LEADING TO HIS HOSPITALIZATION. A CUTANEOUS BIOPSY REVEALED A IGG AND FIBRIN DEPOSIT ON THE VASCULAR WALL. AT A TIME AS YET UNKNOWN THE PATIENT HAD ANOTHER PURPURIC FLARE-UP WITH A LEFT HAND EDEMA. THE REPORTER EVOKED THE POSSIBILITY OF AN ANGEITIS FOLLOWING THE INJECTION OF 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	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
----------------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**PSYCHIATRIC DISORDERS**

1999-08-0545	FRANCE	21 Y	M		SUICIDE ATTEMPT MYDRIASIS CONVULSIONS		Unknown Hospitalized, Overdose, Drug Abuse/Misuse
--------------	--------	------	---	--	---	--	--

Source : Non-US, Health Professional, AFSSAPS  
 Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS  
 Indication : DRUG DEPENDENCE

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
UNKNOWN	UNKNOWN		

Other Suspect Drug(s)/Dosage Form/ Dose(s):  
 EFFEXOR TABLETS UNKNOWN  
 XANAX TABLETS UNKNOWN

Comment: PATIENT WITH HISTORY OF DRUG ABUSE WAS TREATED WITH SUBUTEX (BUPRENORPHINE HCL) FOR DRUG SUBSTITUTION THERAPY. SUBUTEX WAS ADMINISTERED INTRAVENOUSLY. PATIENT HAD ALSO EFFEXOR (VENLAFAXINE) FOR NEUROTIC DEPRESSION AND XANAX. MYDRIASIS OCCURRED AFTER HE MADE A SUICIDE ATTEMPT WITH EFFEXOR, THEN AT DAY +7, CONVULSIVE CRISIS APPEARED. THE NUMBER OF TABLETS HE TOOK WAS UNKNOWN. NO LAB TEST AVAILABLE, BECAUSE THE PATIENT REFUSED TO BE HOSPITALIZED. IT WAS REPORTED THAT AE APPEARED ON 99 AND LASTED THREE HOURS. THE PATIENT WAS LOST OF SIGHT. REPORTER CONSIDERED EVENTS DOUBTFULLY RELATED TO SUBUTEX, EFFEXOR AND XANAX.

1999-10-0003	FRANCE	31 Y	F		DRUG DEPENDENCE		Not Yet Recovered Hospitalized, Drug Abuse/Misuse
--------------	--------	------	---	--	-----------------	--	---

Source : Non-US, Health Professional, AFSSAPS  
 Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS  
 Indication : UNKNOWN

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
18 MG QD	UNKNOWN		

Other Suspect Drug(s)/Dosage Form/ Dose(s):  
 ROHYPNOL 0.5 MG

Comment: PATIENT WAS SNIFFING AND INJECTING SUBUTEX WITH ROHYPNOL. NO AE WAS REPORTED. PATIENT WAS HOSPITALIZED FOR AN UNKNOWN REASON.

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

Company	Ref No	Country	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
---------	--------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**PSYCHIATRIC DISORDERS**

1999-10-1089	FRANCE	31 Y	M		DRUG DEPENDENCE WEIGHT DECREASE RAYNAUD'S DISEASE VOMITING	/	Not Yet Recovered Hospitalized, Drug Abuse/Misuse
--------------	--------	------	---	--	---	---	---

Source : Non-US, Health Professional, AFSSAPS  
 Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS  
 Indication : DRUG DEPENDENCE  
 Other Suspect Drug(s)/Dosage Form/ Dose(s):

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
UNKNOWN	UNKNOWN		

Comment: PATIENT WITH HISTORY OF ALCOHOL ABUSE, DRUG DEPENDENCE AND CHRONIC HEPATITIS NOTED POST-PRANDIAL VOMITING SINCE 6 MONTHS. A WEIGHT LOSS OF 22KG WITHIN 1 AND A HALF YEAR WAS ALSO REPORTED. SINCE 8 MONTHS, PATIENT WAS ONLY FEEDING HIMSELF WITH LIQUIDS. A RAYNAUD'S SYNDROME WAS NOTED SINCE 1 MONTH. PATIENT WAS ADMITTED IN INTERNAL MEDICINE DEPT. FOR WEANING FROM ALCOHOL. UNTIL 8 DAYS BEFORE, HE WAS MISUSING SUBUTEX (BUPRENORPHINE) BY INJECTING IT BY IV ROUTE. REPORTER CONSIDERED DRUG DEPENDENCE, DRUG ABUSE AND DRUG MISUSE DOUBTFULLY RELATED WITH SUBUTEX.

1999-12-0345	UNITED KINGDOM		M		AGGRESSIVE REACTION		Unknown Medically Significant
--------------	----------------	--	---	--	---------------------	--	----------------------------------

Source : Non-US, Health Professional  
 Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS  
 Indication : UNKNOWN  
 Other Suspect Drug(s)/Dosage Form/ Dose(s):

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
UNKNOWN	UNKNOWN		

Comment: REPORTER IS A DRUGS ADVISOR WHO HAS BEEN ASKED BY A BARRISTER TO GIVE AN EXPERT OPINION ON POTENTIAL OF SUBUTEX TO CAUSE A PERSON TO COMMIT MURDER. BARRISTERS CLIENT HAD EITHER COMPLETED OR WAS STILL UNDERGOING DETOX WITH SUBUTEX, HAS BEEN CONVICTED OF MURDER. NO OTHER DETAILS KNOWN AT PRESENT. FOLLOW-UP HAS BEEN REQUESTED.

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

Company Ref No	Country	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
----------------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**RENAL & URINARY SYSTEM DISORDERS**

1999-08-0908	FRANCE	45 Y	M		NEPHROSIS DISEASE PROGRESSION	/	Recovered without sequelae Hospitalized
--------------	--------	------	---	--	----------------------------------	---	--

Source : Non-US, Health Professional, AFSSAPS

Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Indication : DRUG DEPENDENCE

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

INTERFERON ALFA-2A INJECTABLE 3MIU TIW

INTERFERON ALFA-2A INJECTABLE 3MIU TIW

FUROSEMIDE TABLETS 40MG QD

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
------------	--------------------	-------------------	--------------------

16MG QD CONTINUING

SUBCUTANEOUS For 3 WEEK(S)

SUBCUTANEOUS CONTINUING

ORAL UNKNOWN

Comment: PATIENT WITH HISTORY OF VIRAL HEPATITIS, DRUG ABUSE AND NEPHROTIC SYNDROME INITIATED DRUG SUBSTITUTION THERAPY WITH SUBUTEX (BUPRENORPHINE) SL 16MG QD. THEN, PATIENT INITIATED TREATMENT FOR NEPHROTIC SYNDROME WITH FUROSEMIDE PO 40MG QD AND FOR VIRAL HEPATITIS WITH INTERFERON ALFA-2A (NOT PRECISED) SC 3MIU TIW. AGGRAVATION OF THE NEPHROTIC SYNDROME WAS NOTED AND WAS ASSOCIATED WITH EXTENDED EDEMA, ANEMIA AT 8.8G/DL, PROTEIN LEVEL AT 30G/L AND VERY LOW ALBUMINEMIA. PATIENT WAS GIVEN 2 UNITS OF RED BLOOD CELLS AND HIGH DOSES OF LASILIX (FUROSEMIDE). INTERFERON WAS INTERRUPTED FOR 2 WEEKS AND THEN REINTRODUCED AT THE SAME DOSE. NO AGGRAVATION OF THE NEPHROTIC SYNDROME WAS FURTHER NOTED. REPORTER CONSIDERED AGGRAVATION OF THE NEPHROTIC SYNDROME DOUBTFULLY RELATED WITH INTERFERON ALFA-2A, FUROSEMIDE AND SUBUTEX.

2000-01-1100	FRANCE	30 Y	M		BLOOD CREATININE INCREASED PROCEDURE	/	Unknown Hospitalized
--------------	--------	------	---	--	---	---	-------------------------

Source : Non-US, Health Professional

Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Indication : DRUG DEPENDENCE

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

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
------------	--------------------	-------------------	--------------------

UNKNOWN UNKNOWN

Comment: FRENCH AGENCY REPORT(LY9900719), REFERRING TO A MALE WITH HISTORY OF DRUG ADDICTION. AT A TIME AS YET UNKNOWN, HE WAS STARTED WITH SUBUTEX (BUPRENORPHINE) AT UNSPECIFIED DOSE. THE PATIENT WAS ALSO TAKING REGULARLY NEO CODION (CODEINE CAMPHOSULFONATE) SYRUP APPROXIMATELY 310 MG DAILY. IN 1999, HE WAS HOSPITALIZED FOR AN APPENDECTOMY. ON 1999, THE ADMISSION BLOOD WORK REVEALED A BLOOD CREATININE INCREASED AT 250 (UNITS AND BASELINE NOT PROVIDED). THE REPORTER EVOKED NEO CODION OR SUBUTEX AS THE POSSIBLE ETHIOLOGY.



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

Company	Country	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
---------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

RESPIRATORY SYSTEM DISORDERS

1999-08-0226	FRANCE	1	D	M	ACUTE RESPIRATORY DISTRESS CYANOSIS NEONATAL HYPOTONIA NEONATAL WITHDRAWAL SYNDROME NEONATAL		Recovered without sequelae Hospitalized
--------------	--------	---	---	---	---	--	--

Source : Non-US, Health Professional, AFSSAPS  
 Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS  
 Indication : DRUG DEPENDENCE

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
1.2-1MG QD*	UNKNOWN		
1.2MG QD	8 MONTH(S)		
1 MG QD	UNKNOWN		

Other Suspect Drug(s)/Dosage Form/ Dose(s):  
 PROZAC      CAPSULES 60 MG /WEEK      ORAL      UNKNOWN

Comment: FRENCH HEALTH AUTHORITY REPORT: BABY'S MOTHER HAD HISTORY OF DRUG ABUSE WITH HEROIN AND WAS TREATED DURING ALL HER PREGNANCY WITH 8MG-TABLET DOSE OF SUBUTEX (BUPRENORPHINE HCL) 1.2MG QD AND WITH PROZAC (FLUOXETINE) 60 MG WEEKLY SINCE 28MAY1999 OR BEFORE PREGNANCY (EXACT DATE UNKNOWN). SHE GAVE BIRTH TO A MALE BABY WHO PRESENTED AT HOUR 1 RESPIRATORY DISTRESS, ATONIA AND EXTREME CYANOSIS (APGAR SCORE = 3). A FEW DAYS LATER NEONATAL WITHDRAWAL SYNDROME OCCURRED. SYMPTOMATIC TREATMENT WAS GIVEN. BABY RECOVERED WITHOUT SEQUELAE. REPORTER CONSIDERED EVENTS POSSIBLY RELATED TO SUBUTEX AND PROZAC.FOLLOW-UP: BABY RECOVERED .

1999-10-0074	FRANCE	28	Y	F	EMPHYSEMA		Not Yet Recovered Hospitalized, Drug Abuse/Misuse
--------------	--------	----	---	---	-----------	--	--

Source : Non-US, Health Professional  
 Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS  
 Indication : UNKNOWN

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
UNKNOWN	12 MONTH(S)		

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

Comment: PATIENT WHO USED SUBUTEX BY INHALATION HAD A VOLUMINOUS DESTROYING EMPHYSEMA.

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

Company	Country	A	S	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
Ref No		G	E				
		E	X				

**RESPIRATORY SYSTEM DISORDERS**

1999-10-0846	FRANCE	54 Y	F		BRADYPNEA SOMNOLENCE APNEA MIOSIS NAUSEA		Recovered without sequelae Life Threatening, Hospitalized
--------------	--------	------	---	--	--	--	---

Source : Non-US, Health Professional, AFSSAPS

Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Indication : HEADACHE

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

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
1 SL TAB	1 DOSE(S)		

Comment: 4 HOURS AFTER INITIATING 1 SL TABLET OF SUBUTEX, THE PATIENT ARRIVED AT ER, WITH SOMNOLENCE, MIOSIS, NAUSEA, APNEA AND BRADYPNEA. THE PATIENT WAS TREATED WITH NARCAN (NALOXONE). THE PATIENT RECOVERED. THE REPORTER CONSIDERED SOMNOLENCE AND RESPIRATORY DIORDERS PROBABLY RELATED TO SUBUTEX.

1999-11-0591	UNITED KINGDOM	31 Y			DYPSPNEA DYSPEPSIA	08/11/1999	Improved Non Serious
--------------	----------------	------	--	--	-----------------------	------------	-------------------------

Source : Non-US, Health Professional

Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form : CAPSULES

Indication : UNKNOWN

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

HEROIN

Comment: NONE

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
8MG	UNKNOWN		

**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	Country	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
---------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**RESPIRATORY SYSTEM DISORDERS**

1999-12-0018	FRANCE	35 Y	M		SLEEP APNEA SYNDROME DYSPNEA CONVULSIONS	00/00/1997 00/00/1999	Recovered Medically Significant
--------------	--------	------	---	--	--	--------------------------	------------------------------------

Source : Non-US, Health Professional

Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
------------	--------------------	-------------------	--------------------

Indication : DRUG DEPENDENCE

6-10MG QD	CONTINUING	00/00/1996	
-----------	------------	------------	--

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

UNKNOWN

UNKNOWN

Comment: PATIENT INITIATED SUBUTEX (BUPRENORPHINE) 6 TO 10 MG QD IN 1996 FOR DRUG DEPENDENCE. IN APPROXIMATELY 1997, THE PATIENT HAD A POSSIBLE SLEEP APNEA SYNDROME, WHEN HE TOOK ALSO BENZODIAZEPINS. BENZODIAZEPINS WERE DISCONTINUED. DURING THE NIGHT OF ' ' SPASMS AND RESPIRATORY PAUSE OF ABOUT 1 MINUTE OCCURRED. THE PATIENT DID NOT TAKE BENZODIAZEPINS. THE PHYSICIAN SUSPECTED A SLEEP APNEA SYNDROME.

1999-12-0170	FRANCE	25 Y	F		PULMONARY EDEMA		Died - drug may be contributory Died, Overdose, Drug Abuse/Misuse
--------------	--------	------	---	--	-----------------	--	---

Source : Non-US, Health Professional

Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
------------	--------------------	-------------------	--------------------

Indication : UNKNOWN

UNKNOWN	UNKNOWN		
---------	---------	--	--

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

UNKNOWN

ORAL

UNKNOWN

Comment: PATIENT DIED DUE TO PULMONARY EDEMA THE REPORTER NOTED THAT THE DEATH OCCURRED IN HOURS FOLLOWING INJECTION OF SUBUTEX 8MG. TAKING OF NORDAZEPAM PO AND ALCOHOL WAS ALSO NOTED. CAUSE OF DEATH WAS ACCIDENTAL DEATH BY OVERDOSE DUE TO ASSOCIATION OF SUBUTEX, NORDAZEPAM AND ALCOHOL. REPORTER CONSIDERED THE DEATH PROBABLY RELATED TO SUBUTEX, AND SPECIFIED THAT, ALONE, BUPRENORPHINE PRESENTED FEW RISKS, BUT THAT ASSOCIATED TO OTHER DEPRESSORS OF CNS AS ALCOHOL AND BENZODIAZEPINS, AND USED BY INJECTION (OF CRUSHED TABLETS), BUPRENORPHINE IS LIKELY TO LEAD TO DEATH BY OVERDOSE.



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

Company Ref No	Country	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
----------------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**RESPIRATORY SYSTEM DISORDERS**

1999-12-0171	FRANCE	16 Y	F		RESPIRATORY DEPRESSION	—	Died - drug may be contributory Died, Overdose, Drug Abuse/Misuse
--------------	--------	------	---	--	------------------------	---	---

Source : Non-US, Health Professional

Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Total Dose

Treatment Duration

Admin. Start Date

Admin. Finish Date

Indication : UNKNOWN

UNKNOWN

UNKNOWN

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

NORDAZEPAM

UNKNOWN

ORAL

UNKNOWN

Comment: REPORTER CONSIDERED THE DEATH PROBABLY RELATED TO SUBUTEX, AND SPECIFIED THAT, IN ASSOCIATION WITH OTHER PSYCHOTROPICS AS A BENZODIAZEPIN (DEPRESSOR OF THE CNS), BUPRENORPHINE IS LIKELY TO LEAD TO DEATH BY DEEP RESPIRATORY DEPRESSION.

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS**

1999-12-0390	FRANCE	35 Y	M		PRURITUS	00/11/1999	Unknown Non Serious
--------------	--------	------	---	--	----------	------------	------------------------

Source : Non-US, Health Professional

Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Total Dose

Treatment Duration

Admin. Start Date

Admin. Finish Date

Indication : DRUG DEPENDENCE

\*IV-SL

CONTINUING

00/00/1998

!V

00/00/1998

00/10/1999

2MG BID

CONTINUING

00/10/1999

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

Comment: PATIENT TREATED WITH SUBUTEX (BUPRENORPHINE) FOR DRUG SUBSTITUTION FOR AT LEAST A YEAR. THERE IS NO ALLERGY HISTORY IN THIS PATIENT. IN 1999, A PHARMACIST REPORTED THAT THE PATIENT HAD BEEN USING SUBUTEX IN IV UP UNTIL TWO MONTHS AGO. SINCE THEN, HE STARTED TO USE SUBUTEX AT DOSE 2 MG BID IN SUBLINGUAL ROUTE (MORNING AND EVENING). DURING THE LAST MONTH THE PATIENT HAS BEEN COMPLAINING ABOUT PRURITUS ON HIS LIMBS THAT HAPPENED 45 MINUTES ONLY AFTER HE TOOK THE TABLET IN THE EVENING AFTER HE SHOWERED. PRURITUS EPISODES ABATED SPONTANEOUSLY 1 HOUR 10 MIN LATER.

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

Company	Country	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
---------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**VASCULAR (EXTRACARDIAC) DISORDERS**

1999-09-1086	FRANCE		F		VASCULAR DISORDER		Not Yet Recovered Non Serious
--------------	--------	--	---	--	-------------------	--	----------------------------------

Source : Non-US, Health Professional, —  
 Main Schering Drug : SUBUTEX (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS  
 Indication : DRUG DEPENDENCE  
 Other Suspect Drug(s)/Dosage Form/ Dose(s):

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
UNKNOWN	CONTINUING		

**Comment:** A PATIENT INITIATED 2 OR 3 YEARS AGO SUBUTEX (BUPRENORPHINE HCL) FOR DRUG SUBSTITUTION THERAPY. IT WAS ADMINISTRED ESSENTIALLY BY SUBLINGUAL WAY, BUT SOMETIMES THE PATIENT INJECTED IT INTRAVENOUSLY. ACROSYNDROME WAS NOTED (DATE UNKNOWN). IT WAS REPORTED THAT PATIENT HAD RED AND HOT FINGERS AND ERYTHROCYANOSIS. THERE WAS NEITHER ABCES, NOR NECROTIC LESIONS AT THE INJECTION SITES. SEROLOGIES FOR HIV, HCV AND HBV WERE NEGATIVE. A DOPPLER ULTRASOUND EXAMINATION WAS SCHEDULED. REPORTER CONSIDERED AE DOUBTFULLY RELATED TO SUBUTEX.

**APPEARS THIS WAY  
ON ORIGINAL**



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

Company	A	S				
Ref No	G	E	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
	E	X				

**Study Phase Decodes:**

- CG = COOPERATIVE GRP STDY
- CM = COMPASS
- CO = CO-OP
- GA = GOVERMENTAL AGENCIES
- IS = INVESTIGATR INITIATD
- LO = LOCAL
- MI = MARKETING INITIATED
- OB = OBSERVATIONAL
- OT = OTHER
- P1 = PHASE I
- P2 = PHASE II
- P3 = PHASE III
- P4 = PHASE IV
- PM = POST-MARKETING

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

Body System: APPLICATION SITE DISORDERS

- Adverse Reaction: **INJECTION SITE ABSCESS**
  - 1999-09-0247 for Case Summary see: APPLICATION SITE DISORDERS
  - 1999-10-0447 for Case Summary see: APPLICATION SITE DISORDERS
- Adverse Reaction: **INJECTION SITE PAIN**
  - 1999-09-0830 for Case Summary see: APPLICATION SITE DISORDERS
- Adverse Reaction: **INJECTION SITE REACTION**
  - 1999-10-1144 for Case Summary see: APPLICATION SITE DISORDERS

Body System: BODY AS A WHOLE (GENERAL DISORDERS)

- Adverse Reaction: **ANOREXIA**
  - 1999-09-0243 for Case Summary see: METABOLIC AND NUTRITIONAL DISORDERS
  - 1999-11-0857 for Case Summary see: ENDOCRINE DISORDERS
- Adverse Reaction: **ASTHENIA**
  - 1999-08-0887 for Case Summary see: GASTRO-INTESTINAL SYSTEM DISORDERS
  - 1999-11-0031 for Case Summary see: DISORDERS OF BLOOD AND LYMPHATIC SYSTEM
- Adverse Reaction: **CYANOSIS NEONATAL**
  - 1999-08-0226 for Case Summary see: RESPIRATORY SYSTEM DISORDERS
- Adverse Reaction: **DISEASE PROGRESSION**
  - 1999-08-0908 for Case Summary see: RENAL & URINARY SYSTEM DISORDERS
- Adverse Reaction: **DIZZINESS**
  - 1999-09-0243 for Case Summary see: METABOLIC AND NUTRITIONAL DISORDERS
- Adverse Reaction: **EDEMA**
  - 1999-09-0559 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS
  - 1999-09-0639 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS
  - 1999-09-0640 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS
  - 1999-09-0641 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS
- Adverse Reaction: **EDEMA PERIPHERAL**
  - 1999-09-0816 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS
  - 2000-01-0002 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS

**BEST POSSIBLE COPY**

**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: FEVER**

- 1999-10-0062 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS
- 1999-10-1085 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS
- 2000-01-1104 for Case Summary see: DISORDERS OF THE EYE
- 2000-01-1149 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS

**Adverse Reaction: PAIN**

- 1999-08-0887 for Case Summary see: GASTRO-INTESTINAL SYSTEM DISORDERS

**Adverse Reaction: RIGORS**

- 1999-10-0062 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS
- 2000-01-1104 for Case Summary see: DISORDERS OF THE EYE

**Adverse Reaction: WITHDRAWAL SYNDROME**

- 1999-08-0178 for Case Summary see: METABOLIC AND NUTRITIONAL DISORDERS
- 1999-10-0499 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS
- 1999-11-1060 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS
- 1999-11-1061 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS
- 1999-12-1093 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS
- 2000-01-1149 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS

**Body System: CARDIOVASCULAR DISORDERS, GENERAL**

**Adverse Reaction: MYOCARDIAL ISCHEMIA**

- 1999-09-0013 for Case Summary see: CARDIOVASCULAR DISORDERS, GENERAL

**Body System: CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS**

**Adverse Reaction: COMA**

- 1999-11-1059 for Case Summary see: LIVER AND BILIARY SYSTEM DISORDERS

**Adverse Reaction: CONVULSIONS**

- 1999-08-0545 for Case Summary see: PSYCHIATRIC DISORDERS
- 1999-12-0018 for Case Summary see: RESPIRATORY SYSTEM DISORDERS

**Adverse Reaction: HYPOTONIA NEONATAL**

- 1999-08-0226 for Case Summary see: RESPIRATORY SYSTEM DISORDERS

**Adverse Reaction: PARESTHESIA**

APPEARS THIS WAY  
ON ORIGINAL

**BEST POSSIBLE COPY**



Drug(s):  
SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s):  
ALL DOSES

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

1999-09-0559 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS

Adverse Reaction: SOMNOLENCE

1999-10-0646 for Case Summary see: RESPIRATORY SYSTEM DISORDERS

Body System: DISORDERS OF BLOOD AND LYMPHATIC SYSTEM

Adverse Reaction: POLYCYTHEMIA

1999-11-0031 for Case Summary see: DISORDERS OF BLOOD AND LYMPHATIC SYSTEM

Body System: DISORDERS OF THE EAR AND LABYRINTH

Adverse Reaction: DEAFNESS

2000-01-0415 for Case Summary see: DISORDERS OF THE EAR & LABYRINTH

Adverse Reaction: TINNITUS

1999-09-0243 for Case Summary see: METABOLIC AND NUTRITIONAL DISORDERS

Body System: DISORDERS OF THE EYE

Adverse Reaction: MIOSIS

1999-10-0646 for Case Summary see: RESPIRATORY SYSTEM DISORDERS

1999-11-1059 for Case Summary see: LIVER AND BILIARY SYSTEM DISORDERS

Adverse Reaction: MYDRIASIS

1999-08-0545 for Case Summary see: PSYCHIATRIC DISORDERS

Adverse Reaction: RETINAL DISORDER

2000-01-1104 for Case Summary see: DISORDERS OF THE EYE

Adverse Reaction: RETINITIS

1999-12-1077 for Case Summary see: DISORDERS OF THE EYE

Body System: DISORDERS OF THE IMMUNE SYSTEM

Adverse Reaction: SCLERODERMA

1999-11-1094 for Case Summary see: DISORDERS OF THE IMMUNE SYSTEM

Body System: DISORDERS OF THE REPRODUCTIVE SYSTEM AND

Adverse Reaction: AMENORRHEA

1999-09-0362 for Case Summary see: DISORDERS OF THE REPRODUCTIVE SYSTEM AND

Adverse Reaction: GYNECOMASTIA

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

1999-09-0363 for Case Summary see: DISORDERS OF THE REPRODUCTIVE SYSTEM AND  
Adverse Reaction: **HYDRAMNIOS**

1999-09-0634 for Case Summary see: DISORDERS OF THE REPRODUCTIVE SYSTEM AND  
Adverse Reaction: **PRIAPISM**

2000-01-0581 for Case Summary see: DISORDERS OF THE REPRODUCTIVE SYSTEM AND  
Adverse Reaction: **SPERM DISORDER**

1999-10-1157 for Case Summary see: DISORDERS OF THE REPRODUCTIVE SYSTEM AND

**Body System: ENDOCRINE DISORDERS**

Adverse Reaction: **ADRENAL INSUFFICIENCY**

1999-09-0556 for Case Summary see: ENDOCRINE DISORDERS

Adverse Reaction: **HYPERTHYROIDISM**

1999-11-0857 for Case Summary see: ENDOCRINE DISORDERS

**Body System: FOETAL DISORDERS**

Adverse Reaction: **CLEFT LIP**

1999-08-1019 for Case Summary see: FOETAL DISORDERS

**Body System: GASTROINTESTINAL SYSTEM DISORDERS**

Adverse Reaction: **ABDOMINAL DISTENSION**

1999-11-0850 for Case Summary see: NEONATAL AND INFANCY DISORDERS

Adverse Reaction: **ABDOMINAL PAIN**

1999-10-0062 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS

1999-12-1093 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS

Adverse Reaction: **DIARRHEA**

1999-08-0887 for Case Summary see: GASTRO-INTESTINAL SYSTEM DISORDERS

Adverse Reaction: **DYSPEPSIA**

1999-11-0591 for Case Summary see: RESPIRATORY SYSTEM DISORDERS

Adverse Reaction: **INTESTINAL OBSTRUCTION**

1999-11-0850 for Case Summary see: NEONATAL AND INFANCY DISORDERS

Adverse Reaction: **MELENA**

53

**BEST POSSIBLE COPY**



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

1999-08-0887 for Case Summary see: GASTRO-INTESTINAL SYSTEM DISORDERS

Adverse Reaction: NAUSEA

1999-09-0243 for Case Summary see: METABOLIC AND NUTRITIONAL DISORDERS

1999-10-0062 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS

1999-10-0646 for Case Summary see: RESPIRATORY SYSTEM DISORDERS

Adverse Reaction: VOMITING

1999-08-0887 for Case Summary see: GASTRO-INTESTINAL SYSTEM DISORDERS

1999-09-0243 for Case Summary see: METABOLIC AND NUTRITIONAL DISORDERS

1999-10-0062 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS

1999-10-1089 for Case Summary see: PSYCHIATRIC DISORDERS

2000-01-1104 for Case Summary see: DISORDERS OF THE EYE

Body System: HEARD RATE AND RHYTHM DISORDERS

Adverse Reaction: TACHYCARDIA

1999-11-0857 for Case Summary see: ENDOCRINE DISORDERS

2000-01-1149 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS

Body System: INFECTION AND INFESTATIONS

Adverse Reaction: INFECTION FUNGAL

1999-12-1077 for Case Summary see: DISORDERS OF THE EYE

Adverse Reaction: SEPSIS

1999-10-1096 for Case Summary see: INFECTION AND INFESTATIONS

Body System: LIVER AND BILIARY SYSTEM DISORDERS

Adverse Reaction: HEPATIC DISORDER NOS

1999-11-1059 for Case Summary see: LIVER AND BILIARY SYSTEM DISORDERS

Adverse Reaction: HEPATIC ENZYMES INCREASED

1999-08-0810 for Case Summary see: LIVER AND BILIARY SYSTEM DISORDERS

Adverse Reaction: HEPATITIS

1999-08-0810 for Case Summary see: LIVER AND BILIARY SYSTEM DISORDERS

1999-11-0903 for Case Summary see: LIVER AND BILIARY SYSTEM DISORDERS

Adverse Reaction: JAUNDICE

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

1999-08-0810 for Case Summary see: LIVER AND BILIARY SYSTEM DISORDERS

**Body System: METABOLIC AND NUTRITIONAL DISORDERS**

- Adverse Reaction: **CALCINOSIS**  
1999-08-0593 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS
- Adverse Reaction: **DEHYDRATION**  
1999-10-0374 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- Adverse Reaction: **HYPOKALEMIA**  
1999-10-0374 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- Adverse Reaction: **WEIGHT DECREASE**  
1999-08-0178 for Case Summary see: METABOLIC AND NUTRITIONAL DISORDERS  
1999-08-1054 for Case Summary see: METABOLIC AND NUTRITIONAL DISORDERS  
1999-09-0243 for Case Summary see: METABOLIC AND NUTRITIONAL DISORDERS  
1999-09-0553 for Case Summary see: METABOLIC AND NUTRITIONAL DISORDERS  
1999-09-0830 for Case Summary see: APPLICATION SITE DISORDERS  
1999-10-1089 for Case Summary see: PSYCHIATRIC DISORDERS  
2000-01-0925 for Case Summary see: METABOLIC AND NUTRITIONAL DISORDERS
- Adverse Reaction: **WEIGHT INCREASE**  
1999-09-0820 for Case Summary see: METABOLIC AND NUTRITIONAL DISORDERS

**Body System: MUSCULO-SKELETAL SYSTEM DISORDERS**

- Adverse Reaction: **ARTHRITIS**  
2000-01-1155 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS
- Adverse Reaction: **ARTHROPATHY**  
1999-10-0062 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS
- Adverse Reaction: **JOINT DISORDER**  
1999-08-0593 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS
- Adverse Reaction: **SPONDYLITIS**  
2000-01-1129 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS
- Adverse Reaction: **TENDON DISORDER**  
1999-08-0365 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS

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

- 1999-08-0407 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS
- 1999-08-0408 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS
- 1999-08-0409 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS

**Body System: NEONATAL AND INFANCY DISORDERS**

**Adverse Reaction: MATERNAL DRUG EXPOSURE**

- 1999-08-0365 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS
- 1999-09-0188 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-10-0499 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS

**Adverse Reaction: WITHDRAWAL SYNDROME NEONATAL**

- 1999-08-0226 for Case Summary see: RESPIRATORY SYSTEM DISORDERS
- 1999-09-0188 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-09-0473 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-10-0374 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-10-0506 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-10-1272 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-10-1273 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-11-0358 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-11-0850 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-11-1026 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-11-1027 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-11-1028 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-12-0199 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-12-1075 for Case Summary see: NEONATAL AND INFANCY DISORDERS
- 1999-12-1080 for Case Summary see: NEONATAL AND INFANCY DISORDERS

**Body System: PLATELET, BLEEDING AND CLOTTING DISORD**

**Adverse Reaction: PURPURA**

- 1999-12-0820 for Case Summary see: PLATELET, BLEEDING AND CLOTTING DISORD

**Body System: PSYCHIATRIC DISORDERS**

**Adverse Reaction: AGGRESSIVE REACTION**

- 1999-12-0345 for Case Summary see: PSYCHIATRIC DISORDERS

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

Adverse Reaction: **AGITATION**

1999-12-1093 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS

Adverse Reaction: **DRUG DEPENDENCE**

1999-10-0003 for Case Summary see: PSYCHIATRIC DISORDERS

1999-10-1085 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS

1999-10-1089 for Case Summary see: PSYCHIATRIC DISORDERS

Adverse Reaction: **IMPOTENCE**

1999-11-0031 for Case Summary see: DISORDERS OF BLOOD AND LYMPHATIC SYSTEM

Adverse Reaction: **INSOMNIA**

1999-08-0409 for Case Summary see: MUSCULO-SKELETAL SYSTEM DISORDERS

Adverse Reaction: **SUICIDE ATTEMPT**

1999-08-0545 for Case Summary see: PSYCHIATRIC DISORDERS

**Body System: RENAL & URINARY SYSTEM DISORDERS**Adverse Reaction: **BLOOD CREATININE INCREASED**

2000-01-1100 for Case Summary see: RENAL &amp; URINARY SYSTEM DISORDERS

Adverse Reaction: **NEPHROSIS**

1999-08-0908 for Case Summary see: RENAL &amp; URINARY SYSTEM DISORDERS

Adverse Reaction: **RENAL INSUFFICIENCY**

1999-10-0374 for Case Summary see: NEONATAL AND INFANCY DISORDERS

**Body System: RESPIRATORY SYSTEM DISORDERS**Adverse Reaction: **ACUTE RESPIRATORY DISTRESS**

1999-08-0226 for Case Summary see: RESPIRATORY SYSTEM DISORDERS

Adverse Reaction: **APNEA**

1999-10-0646 for Case Summary see: RESPIRATORY SYSTEM DISORDERS

Adverse Reaction: **BRADYPNEA**

1999-10-0646 for Case Summary see: RESPIRATORY SYSTEM DISORDERS

Adverse Reaction: **DYSYPNEA**

1999-08-0887 for Case Summary see: GASTRO-INTESTINAL SYSTEM DISORDERS

1999-11-0591 for Case Summary see: RESPIRATORY SYSTEM DISORDERS

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

1999-12-0018 for Case Summary see: RESPIRATORY SYSTEM DISORDERS  
Adverse Reaction: EMPHYSEMA  
1999-10-0074 for Case Summary see: RESPIRATORY SYSTEM DISORDERS  
Adverse Reaction: PULMONARY EDEMA  
1999-12-0170 for Case Summary see: RESPIRATORY SYSTEM DISORDERS  
Adverse Reaction: RESPIRATORY DEPRESSION  
1999-11-1059 for Case Summary see: LIVER AND BILIARY SYSTEM DISORDERS  
1999-12-0171 for Case Summary see: RESPIRATORY SYSTEM DISORDERS  
Adverse Reaction: SLEEP APNEA SYNDROME  
1999-12-0018 for Case Summary see: RESPIRATORY SYSTEM DISORDERS

**Body System: SKIN AND SUBCUTANEOUS TISSUE DISORDERS**

Adverse Reaction: ERYTHEMA  
1999-09-0559 for Case Summary see: BODY AS A WHOLE - GENERAL DISORDERS  
Adverse Reaction: PRURITUS  
1999-12-0390 for Case Summary see: SKIN AND SUBCUTANEOUS TISSUE DISORDERS  
Adverse Reaction: SKIN NECROSIS  
1999-12-0820 for Case Summary see: PLATELET, BLEEDING AND CLOTTING DISORDERS  
Adverse Reaction: SKIN NODULE  
2000-01-1104 for Case Summary see: DISORDERS OF THE EYE  
Adverse Reaction: SWEATING INCREASED  
1999-08-0887 for Case Summary see: GASTRO-INTESTINAL SYSTEM DISORDERS  
1999-11-0857 for Case Summary see: ENDOCRINE DISORDERS  
2000-01-1104 for Case Summary see: DISORDERS OF THE EYE

**Body System: SURGICAL AND MEDICAL PROCEDURES**

Adverse Reaction: PROCEDURE  
2000-01-1100 for Case Summary see: RENAL & URINARY SYSTEM DISORDERS

**Body System: VASCULAR (EXTRACARDIAC) DISORDERS**

Adverse Reaction: RAYNAUD'S DISEASE  
1999-10-1089 for Case Summary see: PSYCHIATRIC DISORDERS



Drug(s):  
SUBUTEX (BUPRENORPHINE HCL)

Dosage form(s):  
ALL DOSES

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

Adverse Reaction: **VASCULAR DISORDER**

1999-09-1086 for Case Summary see: **VASCULAR (EXTRACARDIAC) DISORDERS**

**APPEARS THIS WAY  
ON ORIGINAL**

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

Adverse Reaction:	Count
<b>CENTR AND PERIPH NERV SYST DISORDERS</b>	
CONFUSION	1
NEUROPATHY	1
SOMNOLENCE	1
TREMOR NEONATAL	1
<b>Total Adverse Reaction Count for CENTR AND PERIPH NERV SYST DISORDERS</b>	<b>4</b>
<b>Total Patient Count for CENTR AND PERIPH NERV SYST DISORDERS</b>	<b>4</b>
<b>DISORDERS OF THE IMMUNE SYSTEM</b>	
ANGIOEDEMA	2
<b>Total Adverse Reaction Count for DISORDERS OF THE IMMUNE SYSTEM</b>	<b>2</b>
<b>Total Patient Count for DISORDERS OF THE IMMUNE SYSTEM</b>	<b>2</b>
<b>DISORDERS OF THE REPRODUCTIVE SYSTEM AND</b>	
SEMEN ABNORMAL	1
<b>Total Adverse Reaction Count for DISORDERS OF THE REPRODUCTIVE SYSTEM AND</b>	<b>1</b>
<b>Total Patient Count for DISORDERS OF THE REPRODUCTIVE SYSTEM AND</b>	<b>1</b>
<b>GASTRO-INTESTINAL SYSTEM DISORDERS</b>	
ABDOMINAL PAIN	1
CONSTIPATION	1
INTESTINAL OBSTRUCTION	1
VOMITING	1
<b>Total Adverse Reaction Count for GASTRO-INTESTINAL SYSTEM DISORDERS</b>	<b>4</b>
<b>Total Patient Count for GASTRO-INTESTINAL SYSTEM DISORDERS</b>	<b>2</b>
<b>INFECTION AND INFESTATIONS</b>	
SEPSIS	1



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

<u>Adverse Reaction:</u>	<u>Count</u>
Total Adverse Reaction Count for INFECTION AND INFESTATIONS	1
Total Patient Count for INFECTION AND INFESTATIONS	1
<b>NEONATAL AND INFANCY DISORDERS</b>	
WITHDRAWAL SYNDROME NEO	1
Total Adverse Reaction Count for NEONATAL AND INFANCY DISORDERS	1
Total Patient Count for NEONATAL AND INFANCY DISORDERS	1
<b>PSYCHIATRIC DISORDERS</b>	
DRUG DEPENDENCE	1
HALLUCINATION	1
Total Adverse Reaction Count for PSYCHIATRIC DISORDERS	2
Total Patient Count for PSYCHIATRIC DISORDERS	2
<b>RENAL &amp; URINARY SYSTEM DISORDERS</b>	
URINE DISCOLORATION	1
Total Adverse Reaction Count for RENAL & URINARY SYSTEM DISORDERS	1
Total Patient Count for RENAL & URINARY SYSTEM DISORDERS	1
<b>RESPIRATORY SYSTEM DISORDERS</b>	
SLEEP APNEA SYNDROME	1
Total Adverse Reaction Count for RESPIRATORY SYSTEM DISORDERS	1
Total Patient Count for RESPIRATORY SYSTEM DISORDERS	1
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>	
URTICARIA	1
Total Adverse Reaction Count for SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1
Total Patient Count for SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1

---

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

---

<u>Adverse Reaction:</u>	<u>Count</u>
Total # Adverse Reactions in this Report	18
Total # of Patients in this Report	11

APPEARS THIS WAY  
ON ORIGINAL

Drug(s):  
TEMGESIC (BUPRENORPHINE HCL)

Dosage form(s):  
ALL DOSES

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

**Body System: CENTR AND PERIPH NERV SYST DISORDERS**

Adverse Reaction: **CONFUSION**  
1999-10-0667 for Case Summary see: CENTR AND PERIPH NERV SYST DISORDERS

Adverse Reaction: **NEUROPATHY**  
1999-11-0137 for Case Summary see: CENTR AND PERIPH NERV SYST DISORDERS

Adverse Reaction: **SOMNOLENCE**  
1999-12-0214 for Case Summary see: RESPIRATORY SYSTEM DISORDERS

Adverse Reaction: **TREMOR NEONATAL**  
1999-12-1082 for Case Summary see: NEONATAL AND INFANCY DISORDERS

**Body System: DISORDERS OF THE IMMUNE SYSTEM**

Adverse Reaction: **ANGIOEDEMA**  
1999-12-0996 for Case Summary see: DISORDERS OF THE IMMUNE SYSTEM  
2000-01-0881 for Case Summary see: DISORDERS OF THE IMMUNE SYSTEM

**Body System: DISORDERS OF THE REPRODUCTIVE SYSTEM AND**

Adverse Reaction: **SEMEN ABNORMAL**  
1999-11-0840 for Case Summary see: RENAL & URINARY SYSTEM DISORDERS

**Body System: GASTRO-INTESTINAL SYSTEM DISORDERS**

Adverse Reaction: **ABDOMINAL PAIN**  
1999-10-0523 for Case Summary see: GASTRO-INTESTINAL SYSTEM DISORDERS

Adverse Reaction: **CONSTIPATION**  
1999-10-0523 for Case Summary see: GASTRO-INTESTINAL SYSTEM DISORDERS

Adverse Reaction: **INTESTINAL OBSTRUCTION**  
1999-12-1081 for Case Summary see: INFECTION AND INFESTATIONS

Adverse Reaction: **VOMITING**  
1999-12-1081 for Case Summary see: INFECTION AND INFESTATIONS

**Body System: INFECTION AND INFESTATIONS**

Adverse Reaction: **SEPSIS**  
1999-12-1081 for Case Summary see: INFECTION AND INFESTATIONS

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

**Body System: NEONATAL AND INFANCY DISORDERS**

Adverse Reaction: **WITHDRAWAL SYNDROME NEONATAL**  
1999-12-1082 for Case Summary see: NEONATAL AND INFANCY DISORDERS

**Body System: PSYCHIATRIC DISORDERS**

Adverse Reaction: **DRUG DEPENDENCE**  
1999-09-0014 for Case Summary see: PSYCHIATRIC DISORDERS

Adverse Reaction: **HALLUCINATION**  
1999-08-0038 for Case Summary see: PSYCHIATRIC DISORDERS

**Body System: RENAL & URINARY SYSTEM DISORDERS**

Adverse Reaction: **URINE DISCOLORATION**  
1999-11-0840 for Case Summary see: RENAL & URINARY SYSTEM DISORDERS

**Body System: RESPIRATORY SYSTEM DISORDERS**

Adverse Reaction: **SLEEP APNEA SYNDROME**  
1999-12-0214 for Case Summary see: RESPIRATORY SYSTEM DISORDERS

**Body System: SKIN AND SUBCUTANEOUS TISSUE DISORDERS**

Adverse Reaction: **URTICARIA**  
1999-12-0996 for Case Summary see: DISORDERS OF THE IMMUNE SYSTEM

**APPEARS THIS WAY  
ON ORIGINAL**

**BEST POSSIBLE COPY**

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

Company	Country	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
---------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**CENTR AND PERIPH NERV SYST DISORDERS**

1999-10-0667	FRANCE	70 Y	M		CONFUSION	15/08/1999	Unknown Hospitalized
--------------	--------	------	---	--	-----------	------------	----------------------

Source : Non-US, Health Professional, AFSSAPS

Main Schering Drug : TEMGESIC (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Indication : UNKNOWN

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

DEPAKINE CHRONO (SODIUM VALPROATE)

SUSTAINED RELEASE TABLETS 1 G QD

ORAL

For 6 WEEK(S)

DEROXAT

TABLETS 20 MG QD

ORAL

For 7 WEEK(S)

Comment: A 70 YEAR OLD PATIENT, WITH HISTORY OF BRONCHIAL CANCER AND CEREBELLAR LESIONS, INITIATED DEROXAT, DEPAKINE CHRONO (VALPROIC ACID) AND TEMGESIC (BUPRENORPHINE) 0.4MG QD. CONFUSION WAS NOTED. TEMGESIC, DEROXAT AND DEPAKINE WERE DISCONTINUED. THE REPORTER CONSIDERED THE CONFUSION DOUBTFULLY RELATED TO DEPAKINE, TEMGESIC AND DEROXAT.

1999-11-0137	FRANCE	30 Y	M		NEUROPATHY	00/00/1999	Not Yet Recovered Medically Significant
--------------	--------	------	---	--	------------	------------	---

Source : Non-US, Health Professional

Main Schering Drug : TEMGESIC (BUPRENORPHINE HCL)

Dosage Form : INJECTABLE

Indication : UNKNOWN

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

Comment: PATIENT, WITH HISTORY OF SCIATICA, WAS OPERATED ON RACHIS AND WAS TREATED FOR POST-OPERATIVE PAIN WITH MORPHINE. FIVE DAYS AFTER SURGERY, MORPHINE WAS REPLACED BY TEMGESIC INJECTABLE (BUPRENORPHINE). NINE DAYS AFTER SURGERY, A CAUDA EQUINA SYNDROME WAS DIAGNOSED. TEMGESIC WAS DISCONTINUED. MYELOGRAPHY WAS NORMAL. 8 MONTHS AFTER DIAGNOSTIC, DISORDERS WERE STILL PERSISTING. AS THERE WERE NO EXPLANATION FOR THE CAUSALITY OF THE SYNDROME, REPORTER WAS ASKING IF TEMGESIC CAN INDUCE URETROPROSTATIC DISORDERS, LIKE DYSURIA AND URINARY RETENTION.

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

Company		A	S				
Ref No	Country	G	E	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
		E	X				

**DISORDERS OF THE IMMUNE SYSTEM**

1999-12-0996	SWEDEN	42 Y	F	ANGIOEDEMA URTICARIA	—	Recovered without sequelae Hospitalized
--------------	--------	------	---	-------------------------	---	---

Source : Non-US, HEALTH AUTHO

Main Schering Drug : TEMGESIC (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Indication : BACKACHE NOS

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

KETOGAN      TABLETS 5 MD QD

Total Dose

0.8 MG QD

Treatment Duration

6 MONTH(S)

Admin. Start Date

For 1 DAY(S)

Admin. Finish Date

ORAL

Comment: PATIENT DEVELOPED ANGIOEDEMA AND URTICARIA AFTER SIX MONTHS TREATMENT WITH TEMGESIC. PATIENT WAS ACUTELY IMPAIRED AND ADMITTED TO HOSPITAL. TREATMENT DISCONTINUED AND SYMPTOMS DISAPPEARED.

2000-01-0881	FINLAND	80 Y	F	ANGIOEDEMA	—	Recovered Life Threatening
--------------	---------	------	---	------------	---	-------------------------------

Source : Non-US, Health Professional

Main Schering Drug : TEMGESIC (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Indication : GENERAL SYMPTOMS NEC

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

ATROPINE      1 ML

Total Dose

0.2 MG

Treatment Duration

1 DOSE(S)

Admin. Start Date

For 1 DOSE(S)

Admin. Finish Date

INTRAVENOUS

Comment: AN 80 YEAR OLD FEMALE PATIENT RECEIVED ATROPINE AND TEMGESIC AT NIGHT. AT 6:30 AM, SHE EXPERIENCED ANGIOEDEMA. SHE WAS TREATED SOLUCORTEF IV AND TRAMAL FOR PAIN.

APPEARS THIS WAY  
ON ORIGINAL

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

Company Ref No	Country	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
----------------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**GASTRO-INTESTINAL SYSTEM DISORDERS**

1999-10-0523	FRANCE	44 Y	M		ABDOMINAL PAIN CONSTIPATION	/	Unknown Hospitalized
--------------	--------	------	---	--	--------------------------------	---	-------------------------

Source : Non-US, Health Professional  
 Main Schering Drug : TEMGESIC (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS      Total Dose      Treatment Duration      Admin. Start Date      Admin. Finish Date  
 Indication : GENERAL SYMPTOMS NEC      0.4MG QD      6 MONTH(S)  
 Other Suspect Drug(s)/Dosage Form/ Dose(s):  
 Comment: PATIENT WAS HOSPITALIZED FOR STUBBORN CONSTIPATION AND ABDOMINAL PAIN THAT OCCURRED SUDDENLY. LAXATIVES WERE GIVEN IN HOSPITAL. TEMGESIC WAS DISCONTINUED. BARIUM ENEMA WAS PERFORMED. SCANNER WAS SCHEDULED. PATIENT WAS DISCHARGED AFTER 7 DAYS. SURGEON IN HOSPITAL CONSIDERED EVENTS POSSIBLY RELATED WITH TEMGESIC.

**INFECTION AND INFESTATIONS**

1999-12-1081	FRANCE	88 Y	M		SEPSIS INTESTINAL OBSTRUCTION VOMITING	/	Died - unrelated to drug Died
--------------	--------	------	---	--	--	---	-------------------------------------

Source : Non-US, Health Professional, AFSSAPS  
 Main Schering Drug : TEMGESIC (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS      Total Dose      Treatment Duration      Admin. Start Date      Admin. Finish Date  
 Indication : UNKNOWN      UNKNOWN      UNKNOWN  
 Other Suspect Drug(s)/Dosage Form/ Dose(s):  
 Comment: FRENCH HEALTH AUTHORITIES REPORT: PATIENT, TREATED WITH TEMGESIC (BUPRENORPHINE), WAS HOSPITALIZED FOR BLACKISH VOMITING (FECALOID). A SUB-OBSTRUCTION PICTURE WAS NOTED. 2HOURS LATER, STOOLS WERE MOULDED AND PASTY. TEMGESIC WAS DISCONTINUED. NEXT DAY, EVOLUTION WAS GOOD AND HEMODYNAMIC WAS STABLE. THE PATIENT DIED (DATE UNKNOWN) DUE TO SEPSIS. REPORTER CONSIDERED THE GASTROINTESTINAL OBSTRUCTION AND THE VOMITING DOUBTFULLY RELATED TO TEMGESIC AND THE DEATH NOT RELATED TO THE ADVERSE EVENT.

67

**APPEARS THIS WAY  
ON ORIGINAL**

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

Company	Ref No	Country	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
---------	--------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**NEONATAL AND INFANCY DISORDERS**

1999-12-1082	FRANCE	1 D	F		WITHDRAWAL SYNDROME NEONATAL TREMOR NEONATAL	/	Recovered without sequelae Hospitalized
--------------	--------	-----	---	--	---	---	--

Source : Non-US, Health Professional, AFSSAPS  
 Main Schering Drug : TEMGESIC (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS  
 Indication : GENERAL SYMPTOMS NEC  
 Other Suspect Drug(s)/Dosage Form/ Dose(s):

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
0.6-1.2MG	UNKNOWN		

Comment: FRENCH HEALTH AUTHORITIES REPORT : MOTHER, WHO TOOK REGULARLY 3 TO 6 TABLETS OF TEMGESIC 0.2MG DURING PREGNANCY, GAVE BIRTH BY CESAREAN SECTION AT 38 WEEKS OF FERTILIZATION AGE. WEIGHT AT BIRTH WAS 2.970KG FOR 47CM AND A CRANIAL PERIMETER OF 33. APGAR WAS AT 10-10-10. THE CHILD SHOWED NONE RESPIRATORY DISTRESS, THE CARDIORESPIRATORY ADAPTATION WAS WITHOUT PROBLEM. THE CLINICAL EXAMINATION WAS NORMAL. THE CHILD WAS SUPERVISED WITH A FINNEGAN SCORE ADAPTED, DONE EVERY 6 HOURS. THE SCORE REMAINED LESS THAN 7 AND DID NOT NEED ANY DRUG ADMINISTRATION. ONLY SOME TRANSIENT TREMORS WERE NOTED AT DAY 3. THE CHILD RECOVERED WITHOUT SEQUELAE. THE REPORTER CONSIDERED THE EVENTS POSSIBLY RELATED TO TEMGESIC.

**PSYCHIATRIC DISORDERS**

1999-08-0038	NETHERLANDS	36 Y	F		HALLUCINATION	09/07/1999	Recovered Medically Significant
--------------	-------------	------	---	--	---------------	------------	------------------------------------

Source : Non-US, Health Professional  
 Main Schering Drug : TEMGESIC (BUPRENORPHINE HCL)  
 Dosage Form : SUBLINGUAL TABLETS  
 Indication : UNKNOWN  
 Other Suspect Drug(s)/Dosage Form/ Dose(s):

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
0.2 MG	2 DAY(S)	09/07/1999	10/07/1999

Comment: THIS REPORT WAS RECEIVED FROM THE NETHERLANDS HEALTH AUTHORITY. MORE INFORMATION CAN NOT BE REQUESTED BUT THEY WILL SEND US UPDATES IF THEY RECEIVE THEM.

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

Company	Ref No	Country	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
---------	--------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**PSYCHIATRIC DISORDERS**

1999-09-0014	FRANCE	45 Y	F		DRUG DEPENDENCE			Not Yet Recovered Medically Significant, Drug Abuse/Misuse
--------------	--------	------	---	--	-----------------	--	--	--

Source : Non-US, Health Professional

Main Schering Drug : TEMGESIC (BUPRENORPHINE HCL)

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

Indication :	MALIGN NEOPL BREAST NOS	1.2 MG QD	CONTINUING	00/00/1988	
--------------	-------------------------	-----------	------------	------------	--

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

Comment: FEMALE PATIENT ABOUT 45 YEAR-OLD UNDERWENT SURGERY FOR BREAST CANCER 11 YEARS AGO, FOLLOWED BY RADIOTHERAPY. SHE INITIATED TEMGESIC (BUPRENORPHINE HCL) INJECTABLE ROUTE AND AFTER THAT PO FOR PAIN IN THE ARM OCCURRING AFTER THE SURGICAL INTERVENTION. SINCE THEN PATIENT WAS SELF-MEDICATING WITH TEMGESIC FOR A PAIN IN THE ARM. SHE MADE AN ATTEMPT TO DISCONTINUE THAT DRUG FOR 3 DAYS AND SHE HAD HEADACHES AND MALAISES, SO SHE RE-INITIATED TEMGESIC. AT THE PRESENT TIME SHE SAID THAT SHE WAS TAKING 6 TABLETS QD (1.2MG QD). SHE WISHES TO STOP TEMGESIC.

**RENAL & URINARY SYSTEM DISORDERS**

1999-11-0840	GERMANY		M		URINE DISCOLORATION SEMEN ABNORMAL			Unknown Non Serious
--------------	---------	--	---	--	---------------------------------------	--	--	------------------------

Source : Non-US, Health Professional,

Main Schering Drug : TEMGESIC (BUPRENORPHINE HCL)

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

Indication :	UNKNOWN	UNKNOWN			
--------------	---------	---------	--	--	--

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

Comment: NONE

APPEARS THIS WAY  
ON ORIGINAL

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

Company Ref No	Country	A G E	S E X	Study Phase	Reaction Description	Onset Date	Patient Status/ AE Outcome
----------------	---------	-------------	-------------	-------------	----------------------	------------	-------------------------------

**RESPIRATORY SYSTEM DISORDERS**

1999-12-0214	DENMARK	52 Y	M		SLEEP APNEA SYNDROME SOMNOLENCE	20/04/1995 20/04/1995	Recovered without sequelae Medically Significant
--------------	---------	------	---	--	------------------------------------	--------------------------	--

Source : Non-US, Health Professional

Main Schering Drug : TEMGESIC (BUPRENORPHINE HCL)

Dosage Form : SUBLINGUAL TABLETS

Indication : GENERAL SYMPTOMS NEC

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

Total Dose	Treatment Duration	Admin. Start Date	Admin. Finish Date
UNKNOWN	5 YEAR(S)	27/06/1994	00/09/1999

Comment: SLEEP APNEA WAS CONSIDERED MEDICALLY SIGNIFICANT BY THE HEALTH AUTHORITY AND SOMNOLENCE WAS NON-SERIOUS. REPORT. NO FURTHER INFORMATION IS AVAILABLE.

**APPEARS THIS WAY  
ON ORIGINAL**

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

Company		A	S			
		G	E			<u>Patient Status/</u>
<u>Ref No</u>	<u>Country</u>	<u>E</u>	<u>X</u>	<u>Study Phase</u>	<u>Reaction Description</u>	<u>Onset Date</u>
						<u>AE Outcome</u>

**Study Phase Decodes:**

- CG = COOPERATIVE GRP STDY
- CM = COMPASS
- CO = CO-OP
- GA = GOVERNMENTAL AGENCIES
- IS = INVESTIGATR INITIATD
- LO = LOCAL
- MI = MARKETING INITIATED
- OB = OBSERVATIONAL
- OT = OTHER
- P1 = PHASE I
- P2 = PHASE II
- P3 = PHASE III
- P4 = PHASE IV
- PM = POST-MARKETING

**APPEARS THIS WAY  
ON ORIGINAL**

PRODUCT = TEMGESIC: CUMULATIVE ADVERSE EVENTS REPORTED POST-MARKETING

EVENT	ORIGINAL	OCT 99		MAY 00	
		TOTAL	NEW	TOTAL	NEW
	Jun-99	Oct-99	Oct-99	May-00	May-00
<b>Application Site Disorders</b>					
Injection Site Inflammation	1		1		1
Injection Site Pain	1		1		1
<b>Total For Application Site Disorders</b>	<b>2</b>	<b>0</b>	<b>2</b>		<b>2</b>
<b>Autonomic Nervous System Disorders</b>					
Hot Flashes	1		1		1
<b>Total For Autonomic Nervous System Disorders</b>	<b>1</b>	<b>0</b>	<b>1</b>		<b>1</b>
<b>Body As A Whole</b>					
Anorexia	1		1		1
Asthenia	4		4		4
Cyanosis	5		5		5
Death	5		5		5
Disease Progression	1		1		1
Dizziness	11		11		11
Edema	4		4		4
Fatigue	1		1		1
Fever	2		2		2
Headache	4	1	5		5
Hypothermia	1		1		1
Malaise	4	1	5		5
Multiple Organ Failure	1		1		1
No Adverse Reaction	2		2		2
Pain	3		3		3
Rigors	1		1		1
Syncope	4		4		4
Therapeutic Response Decrease	2		2		2
Withdrawal Syndrome	1		1		1
<b>Total For Body As A Whole - General Disorders</b>	<b>57</b>	<b>2</b>	<b>59</b>		<b>59</b>
<b>Cardiovascular Disorders, General</b>					
Cardiac Failure	1		1		1
Circulatory Failure	3		3		3
Hypotension	8		8		8
Hypotension Postural	1		1		1
Myocardial Infarction	1		1		1
Pericarditis	1		1		1
<b>Total For Cardiovascular Disorders, General</b>	<b>15</b>	<b>0</b>	<b>15</b>		<b>15</b>
<b>Central And Periph Nerv Syst Disorders</b>					
Agitation Neonatal	2		2		2
Ataxia	1		1		1
Coma	6	1	7		7
Confusion	19		19	1	20
Convulsions	1		1		1
Delirium	3		3		3
Dementia Aggravated	1		1		1
Encephalopathy	1		1		1

PRODUCT = TEMGESIC: CUMULATIVE ADVERSE EVENTS REPORTED POST-MARKETING

EVENT	ORIGINAL	OCT 99	MAY 00		
Loss of Consciousness		1	1		1
Myoclonus	1		1		1
Neuropathy				1	1
Paresthesia	3		3		3
Somnolence	9		9	1	10
Speech Disorder	2		2		2
Stupor	2		2		2
Tremor	2		2		2
Tremor Neonatal	1		1	1	2
<b>Total For Centr And Periph Nerv Syst Disorders</b>	<b>54</b>	<b>2</b>	<b>56</b>	<b>4</b>	<b>60</b>
<b>Disorders Of Blood And Lymphatic System</b>					
Anemia	3		3		3
Anemia Hemolytic	1		1		1
Eosinophilia	2		2		2
Lymphocytosis	1		1		1
Neutropenia	1		1		1
Pancytopenia	1	1	2		2
<b>Total For Disorders Of Blood And Lymphatic System</b>	<b>9</b>	<b>1</b>	<b>10</b>		<b>10</b>
<b>Disorders Of The Ear And Labyrinth</b>					
Tinnitus	1		1		1
Vertigo	5		5		5
<b>Total For Disorders Of The Ear And Labyrinth</b>	<b>6</b>	<b>0</b>	<b>6</b>		<b>6</b>
<b>Disorders Of The Eye</b>					
Miosis	2		2		2
Mydriasis	3		3		3
Myopia		1	1		1
Vision Blurred	1		1		1
Vision Disorder		1	1		1
<b>Total For Disorders Of The Eye</b>	<b>6</b>	<b>2</b>	<b>8</b>		<b>8</b>
<b>Disorders Of The Immune System</b>					
Angioedema				2	2
<b>Total For Disorders Of The Immune System</b>				<b>2</b>	<b>2</b>
<b>Disorders Of The Reproductive System</b>					
Gynecomastia	1		1		1
Priapism	1		1		1
Semen Abnormal				1	1
<b>Total For Disorders Of The Reproductive System</b>	<b>2</b>	<b>0</b>	<b>2</b>	<b>1</b>	<b>3</b>
<b>Foetal Disorders</b>					
Congenital Anomaly Nos	1		1		1
Stillbirth	1		1		1
<b>Total For Foetal Disorders</b>	<b>2</b>	<b>0</b>	<b>2</b>		<b>2</b>
<b>Gastro-Intestinal System Disorders</b>					
Abdominal Pain	1		1	1	2

PRODUCT = TEMGESIC: CUMULATIVE ADVERSE EVENTS REPORTED POST-MARKETING

EVENT	ORIGINAL	OCT 99	MAY 00
Constipation	1	1	2
Diarrhea	2	2	2
Dyspepsia	1	1	1
Hemorrhage Gastro-Intestinal Tract	1	1	1
Intestinal Obstruction			1
Melena	1	1	1
Nausea	28	1	29
Pancreatitis	1	1	2
Stomatitis	1	1	1
Vomiting	27	1	28
<b>Total For Gastro-Intestinal System Disorders</b>	<b>64</b>	<b>3</b>	<b>67</b>
<b>Heart Rate And Rhythm Disorders</b>			
AV Block	1	1	1
Bradycardia	8	8	8
Cardiac Arrest	4	4	4
Tachycardia	2	2	2
Tachycardia Supraventricular	1	1	1
<b>Total For Heart Rate And Rhythm Disorders</b>	<b>16</b>	<b>0</b>	<b>16</b>
<b>Infection And Infestations</b>			
Abscess		1	1
Dermatitis Fungal	1	1	1
Infection	2	2	2
Infection Parasitic		1	1
Pneumonia	2	2	2
Sepsis			1
Septic Arthritis Nos.		1	1
<b>Total For Infection And Infestations</b>	<b>5</b>	<b>3</b>	<b>8</b>
<b>Injury And Poisoning</b>			
Injury Accidental	2	1	3
Misuse	4	4	4
Trauma	1	1	1
<b>Total For Injury And Poisoning</b>	<b>7</b>	<b>1</b>	<b>8</b>
<b>Liver And Biliary System Disorders</b>			
Bilirubinemia	1	1	1
Cholangitis	1	1	1
Coma Hepatic	2	2	2
Gamma-GT Increased	1	1	1
Hepatic Encephalopathy	1	1	1
Hepatic Enzymes Increased	3	3	3
Hepatitis	2	2	2
Hepatitis Cholestatic	1	1	1
SGOT Increased	1	1	1
<b>Total For Liver And Biliary System Disorders</b>	<b>13</b>	<b>0</b>	<b>13</b>
<b>Metabolic And Nutritional Disorders</b>			
Creatine Phosphokinase Increased	1	1	1
Hyperkalemia	1	1	1
Hypoglycemia	1	1	1

PRODUCT = TEMGESIC: CUMULATIVE ADVERSE EVENTS REPORTED POST-MARKETING

EVENT	ORIGINAL	OCT 99	MAY 00		
Hyponatremia	1		1		1
LDH Increased	1		1		1
Phosphatase Alkaline Increased		1	1		1
<b>Total For Metabolic And Nutritional Disorders</b>	<b>5</b>	<b>1</b>	<b>6</b>		<b>6</b>
<b>Musculo-Skeletal System Disorders</b>					
Arthralgia		1	1		1
Myalgia	1		1		1
Rhabdomyolysis	1		1		1
Tendon Disorder	1		1		1
<b>Total For Musculo-Skeletal System Disorders</b>	<b>3</b>	<b>1</b>	<b>4</b>		<b>4</b>
<b>Neonatal And Infancy Disorders</b>					
Small For Gestational Age	1		1		1
Withdrawal Syndrome Neonatal	6		6	1	7
<b>Total For Neonatal And Infancy Disorders</b>	<b>7</b>	<b>0</b>	<b>7</b>	<b>1</b>	<b>8</b>
<b>Platelet, Bleeding And Clotting Disord</b>					
Hematoma	2		2		2
Prothrombin Decreased	1		1		1
Thrombocythemia	1		1		1
Thrombocytopenia	3		3		3
<b>Total For Platelet, Bleeding And Clotting Disord</b>	<b>7</b>	<b>0</b>	<b>7</b>		<b>7</b>
<b>Psychiatric Disorders</b>					
Aggressive Reaction	2		2		2
Agitation	7		7		7
Amnesia	1		1		1
Anxiety	3		3		3
Behavior Disorder	2		2		2
Drug Dependence	4		4	1	5
Hallucination	10		10	1	11
Impotence		1	1		1
Insomnia	1		1		1
Nervousness	2		2		2
Psychosis	1		1		1
Suicide Attempt	2		2		2
<b>Total For Psychiatric Disorders</b>	<b>35</b>	<b>1</b>	<b>36</b>	<b>2</b>	<b>38</b>
<b>Renal And Urinary System Disorders</b>					
Anuria	2		2		2
Blood Creatinine Increased	2		2		2
Glomerulonephritis	1		1		1
Oliguria	1		1		1
Renal Failure Acute	1	1	2		2
Renal Function Abnormal	1		1		1
Uremia	1		1		1
Urine Discoloration				1	1
Urinary Retention	5		5		5
<b>Total For Renal And Urinary System Disorders</b>	<b>14</b>	<b>1</b>	<b>15</b>	<b>1</b>	<b>16</b>
<b>Respiratory System Disorders</b>					

PRODUCT = TEMGESIC: CUMULATIVE ADVERSE EVENTS REPORTED POST-MARKETING

EVENT	ORIGINAL	OCT 99	MAY 00		
Apnea	3		3		3
Bradypnea	1		1		1
Bronchospasm		1	1		1
Chest X-Ray Abnormal	1		1		1
Dyspnea	6	1	7		7
Hypertension Pulmonary	1		1		1
Hypoventilation	1		1		1
Pleural Effusion	1		1		1
Respiratory Arrest	1	1	2		2
Respiratory Depression	5		5		5
Respiratory Disorder	1		1		1
Respiratory Insufficiency	5		5		5
Sleep Apnea Syndrome				1	1
<b>Total For Respiratory System Disorders</b>	<b>26</b>	<b>3</b>	<b>29</b>	<b>1</b>	<b>30</b>
<b>Skin And Subcutaneous Tissue Disorders</b>					
Bullous Eruption	1	1	2		2
Epidermal Necrolysis	1		1		1
Erythema	4		4		4
Face Edema	1		1		1
Pruritus	5		5		5
Rash	2	1	3		3
Rash Erythematous	1		1		1
Skin Ulceration	1		1		1
Sweating Increased	4		4		4
Urticaria	1	1	2	1	3
<b>Total For Skin And Subcutaneous Tissue Disorders</b>	<b>21</b>	<b>3</b>	<b>24</b>	<b>1</b>	<b>25</b>
<b>Special Senses Other, Disorders</b>					
Taste Loss	1		1		1
<b>Total For Special Senses Other, Disorders</b>	<b>1</b>	<b>0</b>	<b>1</b>		<b>1</b>
<b>Surgical And Medical Procedures</b>					
Amputation	1		1		1
<b>Total For Surgical And Medical Procedures</b>	<b>1</b>	<b>0</b>	<b>1</b>		<b>1</b>
<b>Vascular (Extracardiac) Disorders</b>					
Embolism Arterial	1		1		1
Ischemia	1		1		1
Necrosis Ischemic	1		1		1
Peripheral Ischemia	1		1		1
Vasospasm	1		1		1
<b>Total For Vascular (Extracardiac) Disorders</b>	<b>5</b>	<b>0</b>	<b>5</b>		<b>5</b>
<b>TOTAL OF EVENTS</b>	<b>384</b>	<b>24</b>	<b>408</b>	<b>18</b>	<b>426</b>
<b>NUMBER OF SUBJECTS</b>	<b>110</b>	<b>13</b>	<b>123</b>	<b>11</b>	<b>134</b>



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS**  
**HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 (301)827-7410**

**REVIEW AND EVALUATION OF CLINICAL AND STATISTICAL DATA**

**NDA #:** 20-733  
**Supplement #:** Response to Approvable  
**Sponsor:** Reckitt & Colman Pharmaceuticals  
**Generic Name:** Buprenorphine HCl/Naloxone Sublingual  
Tablets  
**Proprietary Name:** Suboxone (TBD)  
**Pharmacologic Class:** Opioid  
**Proposed Indication:** Treatment of Opioid Dependence  
**Submission Date:** 7/28/00  
**Dosage forms:** Buprenorphine 2 mg/Naloxone 0.5 mg  
sublingual tablet;  
Buprenorphine 8 mg/Naloxone 2 mg  
sublingual tablet  
**Route:** Sublingual  
**Clinical Reviewer:** Celia Jaffe Winchell, M.D.  
**Completion Date:** 12/28/00

**APPEARS THIS WAY  
ON ORIGINAL**

<b>1</b>	<b>BACKGROUND</b> .....	<b>2</b>
<b>2</b>	<b>DEFICIENCIES AND RESPONSES</b> .....	<b>5</b>
2.1	— CHILD-PROOF PACKAGING .....	5
2.2	STABILITY DATA.....	5
2.3	POTENTIAL FOR INTENTIONAL DEGRADATION OF NALOXONE.....	5
2.4	DRAFT LABELING.....	6
2.4.1	Proprietary Tradename SUBOXONE .....	6
2.4.2	Use Of Buprenorphine + Naloxone .....	7
2.4.3	.....	8
2.4.4	Administration Of Doses Requiring More Than Two Tablets In Combination.....	11
2.4.5	Response .....	11
2.4.6	Assessment .....	11
2.4.7	Conclusions/Labeling Review .....	12
<b>3</b>	<b>OTHER ISSUES REQUIRING REVIEW</b> .....	<b>12</b>
3.1	HEPATOTOXICITY.....	12
3.1.1	Background.....	12
3.1.2	Assessment .....	14
3.1.3	Conclusions/Labeling Review .....	20
<b>4</b>	<b>OTHER ISSUES RAISED BY SPONSOR</b> .....	<b>20</b>
4.1	MEDICALLY ASSISTED WITHDRAWAL.....	21
4.1.1	Sponsor's Proposal.....	21
4.1.2	Assessment .....	22
4.1.3	Conclusions/Labeling Review .....	23
4.2	RELATIVE ABUSE POTENTIAL OF BUPRENORPHINE VS BUPRENORPHINE + NALOXONE.....	23
4.2.1	Sponsor's proposal .....	23
4.2.2	Assessment .....	24
4.2.3	Conclusions/Labeling Review .....	24
<b>5</b>	<b>RISK MANAGEMENT/POST-MARKETING SURVEILLANCE PLAN</b> .....	<b>24</b>
<b>6</b>	<b>CONCLUSIONS</b> .....	<b>26</b>
<b>7</b>	<b>RECOMMENDATIONS</b> .....	<b>26</b>

## 1 BACKGROUND

Buprenorphine HCl is a narcotic analgesic which has been marketed since 1982 as Buprenex, an injectable formulation, for the treatment of moderate to severe pain. It is also marketed as an analgesic in sublingual tablets in a number of foreign countries.

For two decades, drug abuse researchers have been exploring the utility of high doses of buprenorphine (>10x the analgesic dose) as a maintenance treatment for opiate addiction. Most of the development has been conducted by the National Institute on Drug Abuse under a cooperative research and development agreement, as well as under more than 40 different investigator-initiated INDs sponsored largely by NIDA grantees. The manufacturer and commercial sponsor is a pharmaceutical company, Reckitt & Colman

Pharmaceuticals, Inc. NIDA and Reckitt & Colman have established a Cooperative Research and Development Agreement (CRADA) for the commercial development of buprenorphine sublingual tablets (sponsor's proposed proprietary name: Subutex, NDA 20-732) and combination tablets containing buprenorphine and naloxone (sponsor's proposed proprietary name: Suboxone; this NDA). Orphan Drug designation and waiver of fees were sought (and granted) based on the projected limited sales revenue.

When the buprenorphine ethanolic solution used in early NIDA-sponsored trials — Reckitt & Colman chose to develop buprenorphine sublingual tablets, Subutex, containing 8 mg, 2 mg, and 0.4 mg for the opiate addiction indication. At the same time, they also elected to develop a second product, Suboxone, which would incorporate naloxone to deter diversion for intravenous abuse, similar to Talwin-Nx. Naloxone is not active orally, and was expected to be poorly bioavailable sublingually and therefore was viewed as an inactive ingredient when the product was used as directed. However, should the product be crushed and injected, the naloxone would precipitate withdrawal in opiate-dependent individuals. The sponsors hope that this will translate into reduced street value and abuse potential, thereby facilitating the use of the product outside the traditional methadone clinic setting. Because the naloxone is not expected to affect the efficacy of buprenorphine when used as directed, the application for both the buprenorphine-only tablets (20-732) and this NDA rely on a common database of safety and efficacy studies, in which buprenorphine was studied alone, in solution and tablet form, and in combination with naloxone.

FDA has previously reviewed both this NDA and NDA 20-732 and found both applications to be approvable. Deficiencies noted in the Subutex NDA (20-732) related chiefly to the lack of pharmacokinetic data necessary to translate the experience with the sublingual solution into meaningful dosing instructions using the sublingual tablet. In addition, no data was provided to support one proposed tablet strength, and certain specific uses recommended in labeling were poorly supported. The sponsor's response to these deficiencies is addressed in a separate review of NDA 20-732.

The original clinical review of this NDA, 20-733, for buprenorphine/naloxone sublingual tablets, was prepared by Dr. Chang Lee under my supervision. Dr. Lee's review, and my own, concluded that the sponsor had submitted substantial evidence of safety and efficacy of buprenorphine, and that their formulation could deliver safe and effective doses. Because much of their evidence was drawn from studies of buprenorphine without naloxone, we also determined that the sponsor had demonstrated that the naloxone in Suboxone was inactive when the product was used as directed in the intended population. In addition, we concluded that there were several assertions made by the sponsor for which adequate support was not provided. Furthermore, pharmacokinetic data suggested that various dose combinations requiring more than two tablets at a time might yield non dose-proportional blood levels, requiring some caution and improvisation on the part of the clinician. Again, we were able to develop labeling more limited than that envisioned by the sponsor.

Significant changes from the sponsor's proposed labeling included:

- Deletion of the proposed proprietary tradename "Suboxone." (The place-holder "Tradename" was used in the division's labeling.)
- Removal of specific dosing recommendations for \_\_\_\_\_, derived from various literature reports and uncontrolled studies
- Recommendation against use of buprenorphine with naloxone as the initial treatment for patients beginning maintenance therapy.
- \_\_\_\_\_
- Addition of adverse event tables
- Inclusion in clinical trials section of only the three trials assessed as adequate and well-controlled.

However, chemistry issues precluded approval of the product even with limited labeling. Concerns were identified regarding the stability of naloxone in the drug product. The naloxone appeared to be \_\_\_\_\_ and it was determined that the identity and toxicity of the degradation products of naloxone had not been completed. The agency requested that the sponsor characterize the degradation products of naloxone and perform safety qualification for those exceeding ICH-specified limits. Additional stability data in packaging which would \_\_\_\_\_ was also needed.

Most concerning, however, was the possibility that the naloxone could be deliberately degraded. The division determined that the stability of naloxone in the product was critical to its approval under 21CFR300.50(a)(2), the Fixed Combination Prescription Drug regulation. Under this regulation, two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component is such that the combination is safe and effective. It is permissible that a component be added to minimize the potential for abuse of the principal active component. Therefore, in order to satisfy the requirements of the combination policy, the naloxone component of Suboxone must be shown to minimize the abuse potential of the buprenorphine component. If the presence and stability of naloxone could not be assured, there would be no basis for approving this product with the addition of naloxone. The division asked the company to evaluate the integrity of the unpackaged product under conditions of intentional degradation, to predict the extent of degradation under abuse conditions.

An action letter designating the application as approvable was sent on January 28, 2000. The deficiencies noted included:

1. Identification and safety qualification (per ICH Q3B) of all degradation products occurring at or above \_\_\_\_\_ of the active ingredient, naloxone.
2. Development and validation of analytical methods and specifications to provide a full accounting for all degradation products of naloxone.
3. Linkage between stability methods used in various studies.

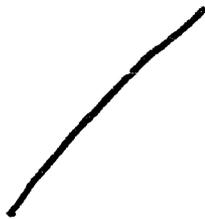
4. Development of [redacted] and child-resistant packaging, with stability data.
5. Stability testing under forced degradation conditions for sufficient time to predict the extent of degradation under abuse conditions, in order to evaluate the integrity of the unpackaged product under conditions of intentional degradation
6. Draft labeling consistent with the division's proposed labeling.

The present submission represents the sponsor's response to the approvable letter.

## **2 DEFICIENCIES AND RESPONSES**

The chemistry deficiencies and the adequacy of the sponsor's response have been addressed in detail in the chemistry review. Clinically relevant issues are discussed below.

### **2.1 [redacted] /Child-proof packaging**



### **2.2 Stability data**

The approvable letter identified the following deficiency:

*The stability data provided are not sufficient to assess a reasonable expiry date for the product...*

It appears that insufficient stability data at ICH conditions have been provided to assess a viable shelf life for the product, and that dissolution failure has been noted at early time points. This manufacturing issue does not appear to have been resolved.

### **2.3 Potential for intentional degradation of naloxone**

The approvable letter identified the following deficiency:

*The stability of naloxone in this product is critical to its approval under 21CFR300.50(a)(2), in which it is stated that two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component is such that the combination is safe and effective. It is permissible that a component be added to minimize the potential for abuse of the principal active component. Therefore, in order to satisfy the requirements of the*

*combination policy, the naloxone component of Suboxone must be shown to minimize the abuse potential of the buprenorphine component. If the presence and stability of naloxone cannot be assured, there is no basis for approving this product with the addition of naloxone. In order to evaluate the integrity of the unpackaged product under conditions of intentional degradation, additional testing is required. The tablets should be stressed under forced degradation conditions for sufficient time to predict the extent of degradation under abuse conditions.*

The sponsor demonstrated that naloxone cannot be selectively degraded through "street chemist" methods can be used to separate the components, the naloxone cannot be degraded simply by intentional mis-handling of the tablets. Although it appears that fairly simple

## **2.4 Draft Labeling**

The approvable letter requested draft labeling consistent with the division's version. Significant changes from the sponsor's proposed labeling included:

- Deletion of the proposed proprietary tradename "Suboxone."
- Recommendation against use of buprenorphine with naloxone as the initial treatment for patients beginning maintenance therapy.
- Removal of specific dosing recommendations for
- 
- Addition of adverse event tables
- Inclusion in clinical trials section of only the three trials assessed as adequate and well-controlled.

The sponsor's responses to these changes are found primarily in the proposed labeling provided in this submission, and differences from the division's proposal have not in all cases been explained fully. The last two items were, for the most part, accepted by the sponsor. Other aspects of the label differ significantly from the Division's proposal. These are discussed below.

### **2.4.1 Proprietary Tradename SUBOXONE**

#### **2.4.1.1 Response**

The sponsor has restored the name Suboxone throughout the label.

#### **2.4.1.2 Assessment**

The Division opposes the name Suboxone and proposes \_\_\_\_\_ as an alternative.

The buprenorphine-only and buprenorphine/naloxone products are viewed as "companions." In the only pivotal trial using the combination product, subjects began with two days of treatment with the buprenorphine-only product (to minimize any chance of precipitation of withdrawal), and then switched to the combination product. This has

been described as the planned use of the products by both NIDA and Reckitt & Colman. The combination product is to be recommended for take-home use because of its presumed lesser diversion potential and potential for intravenous misuse, while the buprenorphine-only product is envisioned for induction use (supervised administration or small take-home supplies) and for patients who, for some reason, should not be exposed to naloxone. Both NDAs relied on a common safety and efficacy database, incorporating studies of both tablets and of a sublingual solution tested earlier in development. Therefore, the labels are nearly identical. We believe the best course of action, for clarity, would be to include both products on a single label. Both to facilitate this and to emphasize the relationship between the two products, we believe it would be prudent to use the name \_\_\_\_\_ for the combination product.

We requested the opinion of OPDRA concerning our proposal to substitute the name \_\_\_\_\_ for Suboxone, and to add \_\_\_\_\_ when approved, to the labeling of Subutex. OPDRA endorsed the notion of distinguishing the combination tablet from the buprenorphine-alone products through the use of a suffix such as \_\_\_\_\_ although recommended that both sublingual tablets as well as the parenteral analgesic use the name Buprenex. The Division did not accept this recommendation because Buprenex is not approved for use in addiction treatment, and therefore is not legal to use under laws that govern the treatment of narcotic addiction (e.g. the Narcotic Addict Treatment Act of 1974 and the recently-enacted Drug Addiction Treatment Act). To prevent confusion among practitioners (some of whom are already erroneously using Buprenex off-label), the Division favors distinguishing the sublingual tablets from the parenteral analgesic through the use of a distinct proprietary name, but emphasizing the relationship between buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets through the use of a common name, modified by a suffix.

Furthermore, information relevant to the safety and/or efficacy of both products has been (and will continue to be) drawn from clinical trials and clinical pharmacology studies of tablets, sublingual solutions, intravenous infusions, etc., and from worldwide safety experience with various dosage forms both with and without naloxone. Because the labels are nearly identical, and most changes in labeling are likely to apply to both products, we believe that the use of a common package insert will facilitate, administratively, the maintenance of the labeling. A similar situation prevailed when the 4 mg Nicorette gum was approved in 1992. The product was approved under a separate NDA from the already-marketed 2 mg gum, but was added to the existing label (under the proprietary tradename Nicorette DS). The common package insert facilitated subsequent revisions which applied to both products.

#### 2.4.2 Use Of Buprenorphine + Naloxone

The division proposed the following language in the dosage and administration section of the label:

[ \_\_\_\_\_ ]

(later in text: )

Prior to induction, consideration should be given to the type of opioid dependence (i.e., long- or short-acting opioid), the time since last opioid use, and the degree or level of opioid dependence.

#### 2.4.2.1 Response

The sponsor has proposed deleting that statement and inserting the following language:

Prior to induction, consideration should be given to the type of opioid dependence (i.e., long- or short-acting opioid), the time since last opioid use, and the degree or level of opioid dependence. To avoid precipitating withdrawal, induction with \_\_\_\_\_ should be undertaken when early signs of withdrawal are evident.

#### 2.4.2.2 Assessment

\_\_\_\_\_ in support of this language \_\_\_\_\_

#### 2.4.2.3 Conclusions/Labeling Review

The sponsor's proposed language is not well-supported. The labeling language should remain as previously proposed by the division.

#### 2.4.3

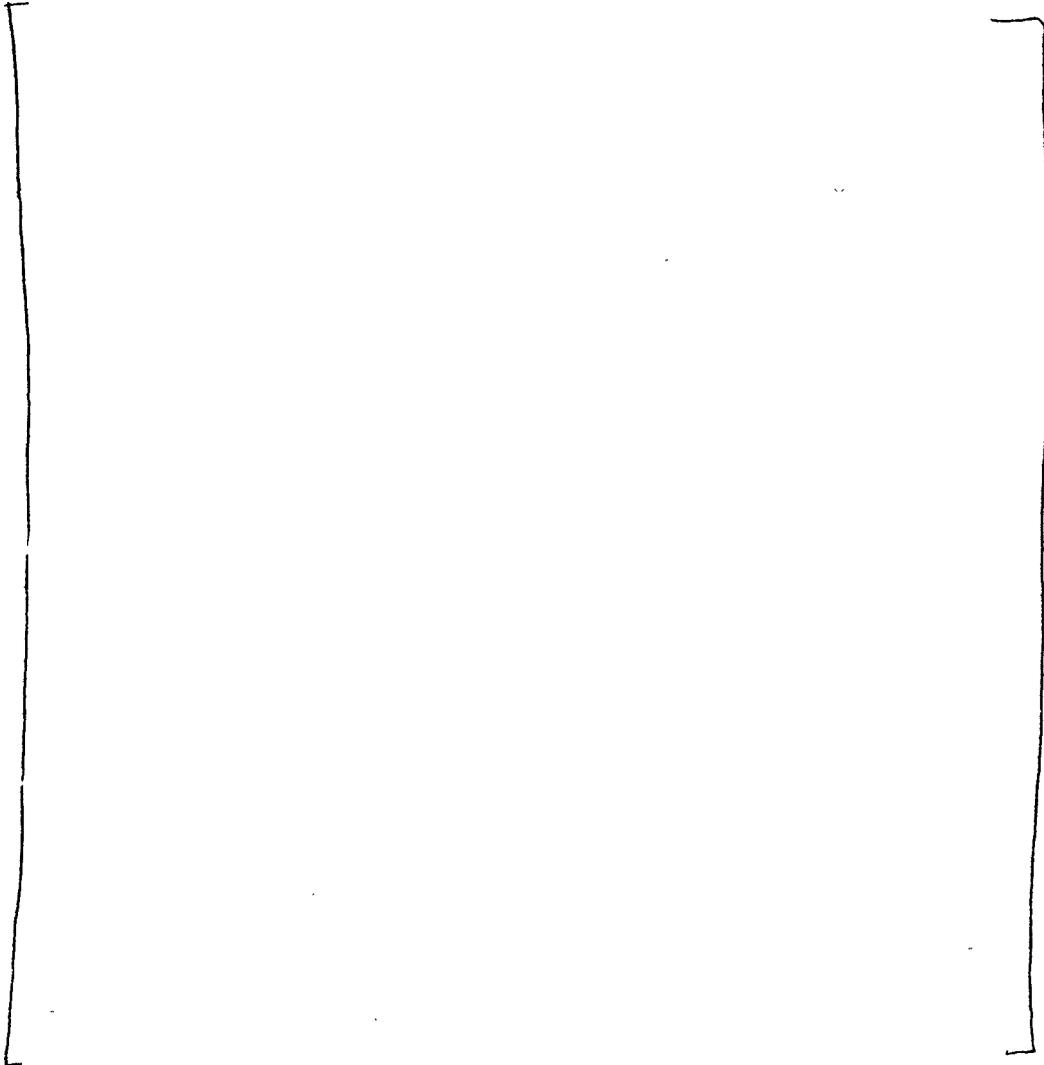
The division's proposed label included the following language:

*Reducing dosage and stopping treatment*

The decision to discontinue therapy with SUBOXONE should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation have been used, but no controlled trials have been undertaken to determine the best method of dose taper at the end of treatment.

**2.4.3.1 Response**

The sponsor proposes the following:

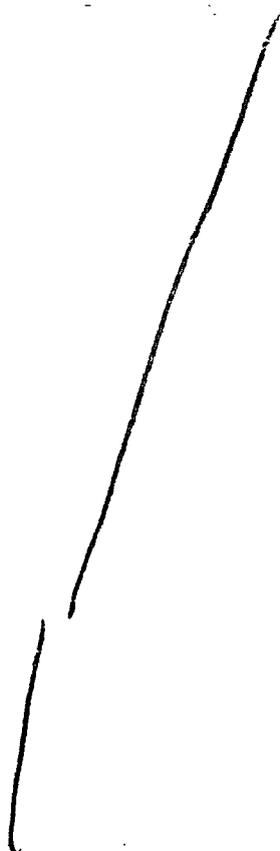


**2.4.3.2 Assessment**

As noted in my review of NDA 20-732, the \_\_\_\_\_ are based on a small, pilot study, which has been reviewed and is not adequate to support specific dosing recommendations.

Regarding the \_\_\_\_\_ it would be simple to dismiss this text as irrelevant to buprenorphine/naloxone combination tablets because

the drug studied in the trials cited was buprenorphine alone. However, after the first few days of treatment, both products might be expected to perform similarly, due to the ineffective competition of naloxone with buprenorphine. With a view toward establishing a common package insert, it is important to consider the adequacy of the presented information. However, as noted in my review of NDA 20-732, the language on \_\_\_\_\_ is both confusing and poorly supported. The section



It remains accurate to say, as the division proposed, that both abrupt and gradual discontinuation have been used. Clearly, clinicians' judgment will be the determining factor in how this product is used in this phase of treatment. The label, as proposed by the division, neither warns against the use of buprenorphine in detoxification, nor provides insufficiently-supported dosing instructions.

#### **2.4.3.3 Conclusions/Labeling Review**

The label should remain as proposed by the division:

##### *Reducing dosage and stopping treatment*

The decision to discontinue therapy with SUBUTEX should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation have been used, but no controlled trials have been undertaken to determine the best method of dose taper at the end of treatment.