NAME OF THE MEDICAL PRODUCT

Suboxone 2 mg/0.5 mg sublingual tablets

Suboxone 8 mg/2 mg sublingual tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SUBOXONE 2 mg/0.5mg tablet contains 2 mg buprenorphine as buprenorphine hydrochloride and 0.5 mg naloxone as naloxone hydrochloride dihydrate.

Each SUBOXONE 8 mg/2mg tablet contains 8 mg buprenorphine as buprenorphine hydrochloride and 2 mg naloxone as naloxone hydrochloride dihydrate.

Excipients: Lactose, mannitol, maize starch, povidone K 30, citric acid anhydrous, sodium citrate, magnesium stearate, acesulfame potassium and natural lemon and lime flavor.

PHARMACEUTICAL FORM

Sublingual tablet

Suboxone 2mg/0.5mg Sublingual Tablet

White hexagonal biconvex tablets of 6.5 mm x 5.9 mm AF (across face), embossed with a “N2” on one side of the tablet

Suboxone 8mg/2mg Sublingual Tablet

White hexagonal biconvex tablets of 11.0 mm x 10.1 mm AF (across face), embossed with a “N8” on one side of the tablet

The sublingual formulation is not designed to be split or broken.

MECHANISM OF ACTION

Buprenorphine is an opioid partial agonist/antagonist which binds to the μ (mu) and κ (kappa) receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible properties with the μ receptors, which over a prolonged period, might minimize the need of addicted patients for drugs.

Opioid agonist ceiling effects were observed during clinical pharmacology studies in opioid-dependent persons.

Naloxone is an antagonist at μ (mu)-opioid receptors. Because of its almost complete first pass metabolism, naloxone administered orally or sublingually has no detectable

pharmacological activity. However, when administered intravenously to opioid dependent persons, naloxone may produce marked opioid antagonist effects and opioid withdrawal.

PRECLINICAL SAFETY DATA

The combination of buprenorphine and naloxone has been investigated in acute and repeated dose (up to 90 days in rats) toxicity studies in animals. No synergistic enhancement of toxicity has been observed. Undesirable effects were based on the known pharmacological activity of opioid agonistic and/or antagonistic substances.

The combination (4:1) of buprenorphine hydrochloride and naloxone hydrochloride was not mutagenic in a bacterial mutation assay (Ames test), and was not clastogenic in an *in vitro* cytogenetic assay in human lymphocytes or in an intravenous micronucleus test in the rat.

Reproduction studies by oral administration of buprenorphine: naloxone (ratio 1:1) indicated that embryo lethality occurred in rats in the presence of maternal toxicity at all doses. The lowest dose studied represented exposure multiples of 1x for buprenorphine and 5x for naloxone at the maximum human therapeutic dose calculated on a mg / m^2 basis. No developmental toxicity was observed in rabbits at maternally toxic doses. Further, no teratogenicity has been observed in either rats or rabbits. A peri-postnatal study has not been conducted with SUBOXONE; however, maternal oral administration of buprenorphine at high doses during gestation and lactation resulted in difficult parturition (possible as a result of the sedative effect of buprenorphine), high neonatal mortality and a slight delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats.

Dietary administration of SUBOXONE in the rat at dose levels of 500 ppm or greater produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (estimated exposure approximately 2.4x for buprenorphine at a human dose of 24 mg SUBOXONE based on AUC, plasma levels of naloxone were below the limit of detection in rats) had no adverse effect on fertility in females.

A carcinogenicity study with SUBOXONE was conducted in rats at doses of 7, 30 and 120 mg/kg/day, with estimated exposure multiples of 3 to 75 times, based on a human daily sublingual dose of 16 mg calculated on a mg/m² basis. Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dosage groups.

PHARMACOKINETIC PROPERTIES:

Buprenorphine:

Absorption: Buprenorphine, when taken orally, undergoes first-pass metabolism with N-dealkylation and glucuroconjugation in the small intestine and the liver. The use of this medicinal product by the oral route is therefore inappropriate.

Peak plasma concentrations are achieved 90 minutes after sublingual administration. Plasma levels of buprenorphine increased with the sublingual dose of SUBOXONE. Both Cmax and AUC of buprenorphine increased with the increase in dose (in the range of 4-16 mg), although the increase was less than dose proportional.

Values in the table represent the mean and (coefficient of variation in %).

Distribution: The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of 2 to 5 hours).

Table 1: Pharmacokinetic Parameters of SUBOXONE

Pharmacokinetic Parameter	**SUBOXONE 4 mg**	**SUBOXONE 8 mg**	**SUBOXONE 16 mg**
Cmax · ng/ml	1.84 (39)	3.0 (51)	5.95 (38)
AUC0-48 hour · ng/ml	12.52 (35)	20.22 (43)	34.89 (33)

Biotransformation and elimination: Buprenorphine is metabolized by 14-N-dealkylation and glucuroconjugation of the parent molecule and the dealkylated metabolite. Clinical data confirm that CYP3A4 is responsible for the N-dealkylation of buprenorphine. N-dealkylbuprenorphine is a μ (mu)-opioid agonist with weak intrinsic activity.

Elimination of buprenorphine is bi- or tri-exponential, and has a mean half-life from plasma of 32 hours. Buprenorphine is eliminated in the feces by biliary excretion of the glucuroconjugated metabolites (70 %), the rest being eliminated in the urine.

Naloxone:

Absorption and distribution: Following intravenous administration, naloxone is rapidly distributed (distribution half-life ~ 4 minutes). Following oral administration, naloxone is barely detectable in plasma; following sublingual administration of SUBOXONE, plasma naloxone concentrations are

low and decline rapidly.

Biotransformation and elimination: The drug is metabolized in the liver, primarily by glucuronide conjugation, and excreted in the urine. Naloxone has a mean half-life from plasma of 1.2 hours.

Special Populations:

Elderly: No pharmacokinetic data in elderly patients are available.

Renal impairment: Renal elimination plays a relatively small role (~30 %) in the overall clearance of SUBOXONE. No dose modification based on renal function is generally required but caution is recommended when dosing subjects with severe renal impairment.

Hepatic impairment: The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study. Table 2 summarizes the results from a clinical trial in which the exposure after single-dose administration of Suboxone 2.0/0.5mg (buprenorphine/naloxone) sublingual tablet was determined in healthy subjects, and in subjects with hepatic impairment.

Table 2. Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine and naloxone following SUBOXONE administration (change relative to healthy subjects)

PK Parameter	Mild Hepatic Impairment (Child-Pugh Class A) (n=9)	Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)	Severe Hepatic Impairment (Child-Pugh Class C) (n=8)
Buprenorphine			
C_{max}	1.2-fold increase	1.1-fold Increase	1.7-fold increase
AUC_{last}	Similar to control	1.6-fold increase	2.8-fold increase
Naloxone			
C_{max}	Similar to control	2.7-fold increase	11.3-fold increase
AUC_{last}	0.2-fold decrease	3.2-fold increase	14.0-fold increase

Overall, buprenorphine plasma exposure increased approximately 3-fold in patients with severely impaired hepatic function, while naloxone plasma exposure increased 14-fold with severely impaired hepatic function.

CLINICAL EFFICACY

Efficacy and safety data for SUBOXONE are primarily derived from a one-year clinical trial, comprising a 4week randomized double blind comparison of SUBOXONE, buprenorphine and placebo tablets followed by a 48-week safety study of SUBOXONE. In this trial, 326 heroin-addicted subjects were randomly assigned to either SUBOXONE 16 mg per day, 16 mg buprenorphine per day or placebo tablets. For subjects randomized to either active treatment, dosing began with one 8 mg tablet of buprenorphine on Day 1, followed by 16 mg (two 8 mg tablets) of buprenorphine on Day 2. On Day 3, those randomized to receive SUBOXONE were switched to the combination tablet. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Take-home doses were provided for weekends. The primary study comparison was to assess the efficacy of buprenorphine and SUBOXONE individually against placebo. The percentage of thrice-weekly urine samples that were negative for non-study opioids was statistically higher for both SUBOXONE versus placebo ($p < 0.0001$) and buprenorphine versus placebo ($p < 0.0001$).

In a double-blind, double-dummy, parallel-group study comparing buprenorphine ethanolic solution to a full agonist active control, 162 subjects were randomized to receive the ethanolic sublingual solution of buprenorphine at 8 mg/day (a dose which is roughly comparable to a dose of 12 mg/day of SUBOXONE), or two relatively low doses of active control, one of which was low enough to serve as an alternative to placebo, during a 3 to 10 day induction phase, a 16-week maintenance phase and a 7-week detoxification phase. Buprenorphine was titrated to maintenance dose by Day 3; active control doses were titrated more gradually. Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, buprenorphine was more effective than the low dose of the control in keeping heroin addicts in treatment and in reducing their use of opioids while in treatment. The effectiveness of buprenorphine, 8 mg per day was similar to that of the moderate active control dose, but equivalence was not demonstrated.

THERAPEUTIC INDICATIONS

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

POSOLOGY AND METHOD OF ADMINISTRATION

Administration is sublingual.

It is recommended that SUBOXONE treatment be prescribed as part of comprehensive management for opioid drug dependence. The result of the treatment depends on the dosage prescribed as well as on the combined medical, psychological, social and educational measures taken in monitoring the patient. Treatment must be under the supervision of a physician experienced in the management of opiate dependence/addiction.

Method of administration

Physicians must warn patients that the sublingual route is the only effective and safe route of administration for this medicinal product (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE). SUBOXONE sublingual tablets are to be placed under the tongue until completely dissolved, which usually requires 5 to 10 minutes. Patients should not swallow or consume food or drink until the tablet is completely dissolved.

The dose is made up from Suboxone 2 mg/0.5 mg and SUBOXONE 8 mg/2 mg sublingual tablets, which may be taken all at the same time or in two divided portions; the second portion to be taken directly after the first portion has dissolved.

Posology

Precautions to be taken before induction

Adults:

Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medicines (see INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS) and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Induction:

Prior to treatment 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 of opioid dependence. There are no adequate and well-controlled studies using Suboxone as initial medication. Subutex contains no naloxone and is preferred for use during induction. Following induction, Suboxone, due to the presence of naloxone, is preferred.

Dosage adjustment and maintenance therapy:

The dose of SUBOXONE should be increased progressively according to the clinical effect of the individual patient and should not exceed a maximum single daily dose of 24 mg. The dosage is titrated according to reassessment of the clinical and psychological status of the patient and should be made in steps of 2-8 mg.

Daily dispensing of buprenorphine is recommended.

During maintenance therapy, it may be necessary to periodically restabilise the patient to a new maintenance dose in response to changing patient needs.

Switching between Subutex and Suboxone sublingual tablets

When used sublingually, SUBOXONE and SUBUTEX have similar clinical effects and are interchangeable; however, when switching between SUBOXONE and SUBUTEX, the prescriber, patient and treatment staff should agree to the change, and the patient should be monitored in case a need to readjust the dose occurs.

Dosage reduction and medical withdrawal:

The decision to discontinue therapy with SUBOXONE after a period of maintenance or brief stabilisation should be made as part of a comprehensive treatment plan. To avoid withdrawal symptoms and potential relapse to illicit drug use, the SUBOXONE dose may be progressively decreased over time in favourable cases until treatment can be discontinued. The availability of the sublingual tablet in doses of 2 mg/0.5mg and 8 mg/2mg allows for a downward titration of dosage. For patients who may require a lower buprenorphine dose, buprenorphine 0.4 mg sublingual tablets may be used. Patients should be monitored following medical withdrawal because of the potential for relapse.

Special populations

Elderly: The safety and efficacy of SUBOXONE in elderly patients over 65 years of age have not been established. No recommendation on posology can be made.

Paediatric population: SUBOXONE is not recommended for use in children below age 15 years due to lack of data on safety and efficacy.

Hepatic impairment: The effects of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study. Both active medicines are extensively metabolized in the liver, and the plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment compared with healthy subjects. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and/or buprenorphine. SUBOXONE should be used with caution in patients with hepatic impairment (see CONTRAINDICATIONS and PHARMACOKINETIC PROPERTIES).

Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy.

Patients who are positive for viral hepatitis, on concomitant medicinal products (See INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION) and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended (See section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment: Modification of the SUBOXONE dose is not generally required in patients with renal impairment. Caution is recommended when dosing patients with severe renal impairment (CLcr < 30 ml/min) (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE and PHARMACOKINETIC PROPERTIES).

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:

SUBOXONE should not be taken together with:

• Alcoholic drinks or medications containing alcohol, as alcohol increases the sedative effect of buprenorphine (see Effects on ability to drive and use machines).

SUBOXONE should be used cautiously when co-administered with:

- Benzodiazepines: This combination may result in death due to respiratory depression of central origin. Therefore, dosages must be limited and this combination must be avoided in cases where there is a risk of misuse. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking this product, and should also be cautioned to use benzodiazepines concurrently with this product only as directed by their physician (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Other central nervous system depressants, other opioid derivatives (e.g. methadone, analgesics and antitussives), certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances: these combinations increase central nervous system depression. The reduced level of alertness can make driving and using machines hazardous.
- Opioid analgesics: The analgesic properties of other opioids such as methadone and level III analgesics may be reduced in patients receiving treatment with SUBOXONE for opioid dependence.

  Furthermore, adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving SUBOXONE. Therefore, the potential to overdose with a full agonist exists, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining.

  Patients with a need for analgesia and opioid dependence treatment may be best managed by multidisciplinary teams that include both pain and opioid dependence treatment specialists (See also Precipitation of opioid withdrawal syndrome).
- Naltrexone and other opioid antagonists: Concomitantly administered opioid antagonists such as naltrexone can reduce or block the pharmacological effects of buprenorphine. For opioid dependent patients currently receiving SUBOXONE treatment, the antagonist may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms. For patients currently

receiving treatment, the intended therapeutic effects of SUBOXONE administration may be blocked by the opioid antagonist.

- CYP3A4 inhibitors: an interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax and AUC (area under the curve) of buprenorphine (approximately 50 % and 70 % respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving SUBOXONE should be closely monitored, and may require dose-reduction if combined with potent CYP3A4 inhibitors (e.g., protease inhibitors like ritonavir, nelfinavir or indinavir or azole antifungals such as ketoconazole, itraconazole, or macrolide antibiotics).
- CYP3A4 inducers: Concomitant use of CYP3A4 inducers with buprenorphine may decrease buprenorphine plasma concentrations, potentially resulting in sub-optimal treatment of opioid dependence with buprenorphine. It is recommended that patients receiving SUBOXONE should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered. The dose of buprenorphine or the CYP3A4 inducer may need to be adjusted accordingly.

UNDESIRABLE EFFECTS:

Summary of the safety profile

The most common-treatment related undesirable effects reported during clinical trials with SUBOXONE were constipation and those related to withdrawal symptoms (e.g., insomnia, headache, nausea and hyperhidrosis). Some reports of seizure, vomiting, diarrhoea, and elevated liver function tests were considered serious.

In the pivotal clinical study of SUBOXONE, 342 of 472 patients (72.5 %) reported treatment related adverse reactions. These reactions are listed in Table 1 by system, organ class and frequency (very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000 to ≤ 1/100)).

Table 3: Treatment-related undesirable effects reported in the pivotal clinical study of SUBOXONE (≥ 0.1% of SUBOXONE-treated patients)

Very common **(≥1/10)**	**Common** **(≥1/100 to <1/10)**	**Uncommon** **(≥1/1000 to <1/100)**
Infections and infestations		
	Influenza Infection Pharyngitis Rhinitis	Urinary tract infection Vaginal infection
Blood and lymphatic system disorders		
		Anaemia Leukocytosis Leukopenia Lymphadenopathy Thrombocytopenia
Immune system disorders		
		Hypersensitivity
Metabolism and nutrition disorders		
		Hyperglycaemia Hyperlipidaemia Hypoglycaemia Decreased appetite
Psychiatric disorders		
Insomnia	Anxiety Depression Libido decreased Nervousness Thinking abnormal	Abnormal dreams Agitation Apathy Depersonalisation Drug dependence Euphoric mood Hostility

Nervous system disorders		
Headache	Migraine Dizziness Hypertonia Paraesthesia Somnolence	Amnesia Convulsion Hyperkinesia Speech disorder Tremor
Eye disorders		
	Amblyopia Lacrimal disorder	Conjunctivitis Miosis
Cardiac disorders		
		Angina Pectoris Bradycardia Myocardial infarction Palpitations Tachycardia
Vascular disorders		
	Hypertension Vasodilatation	Hypotension
Respiratory, thoracic and mediastinal disorders		
	Cough	Asthma Dyspnoea Yawning
Gastrointestinal disorders		
Constipation Nausea	Abdominal Pain Diarrhoea Dyspepsia Flatulence Vomiting	Mouth ulceration Tongue discolouration
Skin and subcutaneous tissue disorders		
Hyperhidrosis	Pruritus Rash Urticaria	Acne Alopecia Dermatitis exfoliative

		Dry skin Skin mass
Musculoskeletal and connective tissue disorders		
	Back Pain Arthralgia Muscle spasms Myalgia	Arthritis
Renal and urinary disorders		
	Urine Abnormality	Dysuria Haematuria Nephrolithiasis Urinary retention Albuminuria
Reproductive system and breast disorders		
	Erectile dysfunction	Amenorrhoea Ejaculation disorder Menorrhagia Metrorrhagia
General disorders and administration site conditions		
Drug withdrawal syndrome	Asthenia Chest Pain Chills Pyrexia Malaise Pain Oedema peripheral	Hypothermia
Investigations		
	Liver function test abnormal Weight decreased	Blood creatinine increased
Injury, poisoning and procedural complications		
	Injury	Heat stroke

The most common adverse drug reactions reported during post-marketing surveillance are also captured in Table 3.

Description of other selected adverse reactions observed post-marketing

The following is a summary of other post-marketing adverse event reports that are considered serious or otherwise noteworthy, some of which may have only been observed with buprenorphine alone in the treatment of opioid dependence:

- Respiratory depression has occurred. Death due to respiratory depression has been reported, particularly when buprenorphine products were used in combination with benzodiazepines (See section INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION), or when buprenorphine products were not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine products and other CNS depressants such as alcohol or other opioids (see INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION and SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- Hepatic transaminase increase, hepatitis, acute hepatitis, cytolytic hepatitis, jaundice, hepatorenal syndrome, hepatic encephalopathy, and hepatic necrosis have occurred (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- Hallucinations, orthostatic hypotension, syncope and vertigo have been reported.
- The most common signs and symptoms of hypersensitivity include rashes, urticaria, and pruritus. Cases of bronchospasm, respiratory depression, angioedoema and anaphylactic shock have been reported (see CONTRAINDICATIONS).

In cases of drug abuse or intentional drug misuse, some adverse experiences attributed to the act of misuse rather than the medicinal product have included: local reactions, such as cellulitis or abscess that are sometimes septic, potentially serious acute hepatitis, pneumonia, endocarditis and other serious infections (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

Spontaneous abortion has been reported with both buprenorphine and buprenorphine-naloxone. It is not possible to establish a causal relationship since cases typically involve other drug use or risk

factors for spontaneous abortion (see USAGE DURING FERTILITY, PREGNANCY AND LACTATION). A neonatal abstinence syndrome has been reported among newborns of women who have received buprenorphine during pregnancy. The syndrome may be milder and more protracted than that from short acting full μ-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history (see FERTILITY, PREGNANCY AND LACTATION).

CONTRAINDICATIONS:

SUBOXONE is contraindicated in the following instances:

- hypersensitivity to buprenorphine, to naloxone, or to any of the excipients,
- severe respiratory insufficiency,
- severe hepatic insufficiency,
- acute alcoholism or *delirium tremens*.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Misuse, abuse and diversion: Buprenorphine can be misused or abused in a manner similar to other opioids, legal or illicit. Some risks of misuse and abuse include overdose, spread of blood borne viral infections, respiratory depression and hepatic injury.

Buprenorphine misuse by someone other than the intended patient poses the additional risk of new drug dependent individuals using buprenorphine as the primary drug of abuse, and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicine is not safeguarded against theft.

Sub-optimal treatment with SUBOXONE may prompt medication misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with SUBOXONE may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines.

To minimize the risk of misuse, abuse and diversion, physicians should take appropriate precautions when prescribing and dispensing buprenorphine, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's needs.

Combining buprenorphine with naloxone in SUBOXONE is intended to deter misuse and abuse of the buprenorphine. Intravenous or intranasal misuse of SUBOXONE is expected to be less likely

than buprenorphine alone since the naloxone in SUBOXONE can precipitate withdrawal in individuals dependent on heroin, methadone, or other opioid agonists.

Precipitation of opioid withdrawal syndrome: When initiating treatment with SUBOXONE, the physician must be aware of the partial agonist profile of buprenorphine and that it can precipitate withdrawal in opioid-dependent patients particularly if administered less than 6 hours after the last use of heroin or other short acting opioid, or if administered less than 24 hours after the last dose of methadone (see POSOLOGY AND METHOD OF ADMINISTRATION). Patients should be closely monitored during the switching period from buprenorphine or methadone to SUBOXONE since withdrawal symptoms have been reported. Conversely, withdrawal symptoms may also be associated with suboptimal dosing.
The risk of serious undesirable effects such as overdose or treatment dropout is greater if a patient is under dosed with SUBOXONE and continues to self-medicate with opioids, alcohol or other sedative-hypnotics in particular benzodiazepines.

Dependence: Buprenorphine is a partial agonist at the μ (mu)-opiate receptor and chronic administration produces dependence of the opioid type. Studies in animals, as well as clinical experience, have demonstrated that buprenorphine may produce dependence but at a lower level than morphine.
Abrupt discontinuation of treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset.

CNS depression: SUBOXONE may cause drowsiness, particularly when taken together with alcohol or central nervous system depressants (such as benzodiazepines, tranquilizers, sedatives or hypnotics) (see INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS).

Respiratory depression: A number of cases of death due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines (see INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS), or when buprenorphine was not used according to prescribing information. Deaths have been reported in association with concomitant administration of buprenorphine and

other depressants such as alcohol or other opioids. If buprenorphine is administered to some non-opioid dependent individuals, who are not tolerant to the effects of opioids, potentially fatal respiratory depression may occur.

This product should be used with caution in patients with compromised respiratory function (e.g. asthma, chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis (curvature of spine leading to potential shortness of breath). Patients with the physical and/or pharmacological risk factors above should be monitored, and dose reduction may be considered.

SUBOXONE may cause severe, possibly fatal, respiratory depression in children and non-dependent persons in case of accidental or deliberate ingestion. Patients must be warned to store the blister safely, to never open the blister in advance, to keep them out of the reach of children and other household members, and not to take this medicine in front of children. An emergency unit should be contacted immediately in case of accidental ingestion or suspicion of ingestion.

Hepatitis and hepatic events: Cases of acute hepatic injury have been reported in opioid-dependent addicts both in clinical trials and in post marketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases the presence of pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, viral infection such as hepatitis B or chronic hepatitis C, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicines, and ongoing injecting drug use) may have a causative or contributory role. Patients who are positive for viral hepatitis, on concomitant medicinal products (see INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS) and/or have existing liver dysfunction are at greater risk of liver injury. These underlying factors must be taken into consideration before prescribing SUBOXONE and during treatment. When a hepatic event is suspected, further biological and etiological evaluation is required. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If the treatment is continued, hepatic function should be monitored closely.

Hepatic impairment: The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study. Since both buprenorphine and naloxone are extensively metabolized, plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment after single-dose administration. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and/or buprenorphine. SUBOXONE sublingual tablets should be used with caution in patients with hepatic impairment (See CONTRAINDICATIONS and PHARMACOKINETIC PROPERTIES).

Renal impairment: Renal elimination plays a relatively small role in the overall clearance of buprenorphine; therefore, no dose modification based on renal function is generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (creatinine clearance <30 ml/min) (See POSOLOGY AND METHOD OF ADMINISTRATION and PHARMACOKINETIC PROPERTIES).

Use in adolescents (Age 15 ≤18): Due to the lack of data in adolescents (age 15≤18), SUBOXONE should be used only with caution in this age group.

Allergic reactions: Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, urticaria, and pruritus. Cases of bronchospasm, angioedema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to SUBOXONE use.

General warnings relevant to the administration of opioids:
Opioids may produce orthostatic hypotension in ambulatory patients.

Opioids may elevate cerebrospinal fluid pressure, which may cause seizures, so opioids should be used with caution in patients with head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased, or history of seizure.

Athletes must be aware that this medicine may cause a positive reaction to ‘anti-doping’ tests. As with other opioids, caution is requested in patients using buprenorphine and having hypotension, prostatic hypertrophy, toxic psychosis or urethral stenosis.

Opioid-induced miosis, changes in the level of consciousness, or changes in the perception of pain as a symptom of disease may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease.

Opioids should be used with caution in patients with myxoedema, hypothyroidism, or adrenal cortical insufficiency (e.g., Addison's disease).

Opioids have been shown to increase intracholedochal pressure, and should be used with caution in patients with dysfunction of the biliary tract.

Opioids should be administered with caution to elderly or debilitated patients.

The concomitant use of monoamine oxidase inhibitors (MAOI) might produce exaggeration of the effects of opioids, based on experience with morphine.

CYP 3A inhibitors: Medicines that inhibit the enzyme CYP3A4 may give rise to increased concentrations of buprenorphine. A reduction of the SUBOXONE dose may be needed. Patients already treated with CYP3A4 inhibitors should have their dose of Suboxone titrated carefully since a reduced dose may be sufficient in these patients (see INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS).

Effects on ability to drive and use machines: In general, SUBOXONE has moderate influence on the ability to move safely in traffic, use machines, or perform other hazardous activities when administered to opioid dependent patients. SUBOXONE may cause drowsiness, dizziness, or impaired thinking, particularly during treatment induction and dose adjustment. If used together with alcohol or central nervous system depressants, the effect is likely to be more pronounced. Therefore, caution is advised when performing the above mentioned activities until they are reasonably certain that SUBOXONE therapy does not adversely affect the ability to engage in such

activities (see INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS and SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

FERTILITY, PREGNANCY AND LACTATION:

Pregnancy: SUBOXONE should not be used during pregnancy. If it is the prescriber's opinion that therapy in pregnancy is required, the use of buprenorphine may be considered according to the local buprenorphine labeling. In case pregnancy occurs while on SUBOXONE treatment, the mother and the unborn child should be closely monitored and switched to buprenorphine if further treatment is required.

Chronic use of buprenorphine by the mother at the end of pregnancy may cause a withdrawal syndrome in the neonate (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus or convulsions). The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy, to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Breast-feeding: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Suboxone sublingual tablets and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Fertility: Animal studies have shown a reduction in female fertility at high doses (systemic exposure > 2.4 times the human exposure at the maximum recommended dose of 24 mg buprenorphine, based on AUC). See PRECLINICAL SAFETY DATA.

OVERDOSE:

Although the antagonist activity of buprenorphine/naloxone may become manifest at doses somewhat above the recommended therapeutic range, doses in the recommended therapeutic range may produce clinically significant respiratory depression in certain circumstances.

Symptoms: In the event of overdose, general supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. The major symptom requiring

intervention is respiratory depression, which could lead to respiratory arrest and death. Signs of overdose may also include somnolence, amblyopia, miosis, hypotension, nausea, vomiting and/or speech disorders. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

Treatment: Symptomatic treatment of respiratory depression, and standard intensive care measures, should be implemented. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment within which full resuscitation facilities are available.

Use of an opioid antagonist (i.e., naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full agonist opioid agents.

If naloxone is used, the long duration of action of buprenorphine should be taken into consideration when determining the length of treatment and medical surveillance needed to reverse the effects of an overdose. Naloxone can be cleared more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms, so a continuing infusion may be necessary. If infusion is not possible, repeated dosing with naloxone may be required.

NATURE AND CONTENTS OF CONTAINER: Sublingual tablet in blister packs of 7 and 28 tablets.

SPECIAL PRECAUTIONS FOR STORAGE: The shelf-life of SUBOXONE sublingual tablets is 3 years. Store below 30C. No special storage precautions are required.

Keep out of reach of children.

Manufactured by Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull HU8 7DS, UK

Manufactured for Indivior UK Limited

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