SCHEDULING STATUS **S6**

1. NAME OF THE MEDICINE

SUBOXONE 2 mg Sublingual Tablets

SUBOXONE 8 mg Sublingual Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SUBOXONE 2 mg Sublingual Tablets: Each tablet contains 2 mg buprenorphine (as buprenorphine hydrochloride) and 0,5 mg naloxone (as naloxone hydrochloride dihydrate)

Excipients with known effect:

Sugar content: Each tablet contains 44,08 mg lactose monohydrate and 30 mg mannitol.

SUBOXONE 8 mg Sublingual Tablets: Each tablet contains 8 mg buprenorphine (as buprenorphine hydrochloride) and 2 mg naloxone (as naloxone hydrochloride dihydrate)

Excipients with known effect:

Sugar content: Each tablet contains 176,32 mg lactose monohydrate and 120 mg mannitol.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SUBOXONE 2 mg Sublingual Tablets: White hexagonal biconvex tablets with N2 debossed on one side.

SUBOXONE 8 mg Sublingual Tablets: White hexagonal biconvex tablets with N8 debossed on one side.

4. CLINICAL PARTICULARS

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4.1 Therapeutic indications

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.

The intention of the naloxone component is to deter intravenous misuse.

SUBOXONE is indicated in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

4.2 Posology and method of administration

Posology

Each SUBOXONE sublingual tablet contains buprenorphine and naloxone. SUBOXONE containing 2 mg buprenorphine and 0,5 mg naloxone is referred to as the “2 mg” tablets. SUBOXONE containing 8 mg buprenorphine and 2 mg naloxone is referred to as the “8 mg” tablets.

Physicians must warn patients that the sublingual route is the only effective and safe route of administration for this medicinal product (see section 4.4). SUBOXONE sublingual tablets are to be placed under the tongue until dissolved, which usually requires 5 to 10 minutes. 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.

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 section 4.5) and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended (see section 4.4).

Induction:

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

To avoid precipitating withdrawal, induction with SUBOXONE or buprenorphine only tablets should be undertaken when objective and clear signs of withdrawal are evident.

Initiation therapy:

The recommended starting dose is one to two tablets of SUBOXONE 2 mg/0,5 mg sublingual tablets. An additional one to two tablets of SUBOXONE 2 mg/0,5 mg sublingual tablets may be administered on day one depending on the individual patient's requirements.

- **Opioid-dependent drug addicts who have not undergone withdrawal:** When treatment starts, the first dose of SUBOXONE should be taken when signs of withdrawal appear, but not less than 6 hours after the patient last used the opioids (e.g. heroin; short acting opioids).

- **Patients receiving methadone:** Before beginning SUBOXONE therapy, the dose of methadone should be reduced to a maximum of 30 mg/day. The first dose of SUBOXONE should be taken when the signs of withdrawal appear, but not less than 24 hours after the patient last used methadone. Buprenorphine may precipitate symptoms of withdrawal in patients dependent on methadone.

Dosage adjustment and maintenance:

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 to 8 mg.

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During the initiation of treatment, daily dispensing of SUBOXONE is recommended. After stabilisation, a reliable patient may be given a supply of SUBOXONE sufficient for several days of treatment. It is recommended that the amount of SUBOXONE be limited to 7 days or according to local requirements.

Less than daily dosing:

In some patients, after a satisfactory stabilisation has been achieved, the frequency of SUBOXONE dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no dose on the intervening days. For example, a patient stabilised to receive a daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 24 mg. Patients requiring a titrated daily dose > 8 mg/day may not find this regimen adequate.

Dosage reduction and termination of treatment: After a satisfactory stabilisation has been achieved, if the patient agrees, the dosage may be reduced gradually to a lower maintenance dose; in some favourable cases, treatment may be discontinued. The availability of the sublingual tablet in doses of 2 mg and 8 mg, allows for a downward titration of the dosage. Patients should be monitored following termination of buprenorphine treatment because of the potential for relapse.

<u>Special populations</u>

Elderly

The safety and efficacy of SUBOXONE in elderly patients over 65 years of age has not been established.

Patients with impaired hepatic function

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The effects of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study. Since both active medicines are extensively metabolised, the plasma levels were found to be higher 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.

As SUBOXONE pharmacokinetics may be altered in patients with hepatic insufficiency, lower initial doses and careful dose titration in patients with mild to moderate hepatic impairment are recommended (see section 5).

Patients with impaired renal function

Modification of the SUBOXONE dose is not required in patients with renal insufficiency. Caution is recommended when dosing patients with severe renal impairment (CLcr < 30 ml/min) (see section 5).

Paediatric population

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

Method of administration

Administration is sublingual.

Treatment must be under the supervision of a physician experienced in the management of opiate dependence/addiction.

4.3 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*.

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4.4 Special warnings and precautions for use

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

Patients should be closely monitored during the switching period from buprenorphine or methadone to SUBOXONE since withdrawal symptoms have been reported.

Diversion:

Diversion refers to the introduction of buprenorphine into the illicit market either by patients or by individuals who obtain the medicinal product through theft from patients or pharmacies.

This diversion may lead to new drug dependent individuals using buprenorphine as the primary drug of abuse, with the risks of overdose, spread of blood borne viral infections, respiratory depression and hepatic injury.

Sub-optimal treatment with SUBOXONE may prompt 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 minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing SUBOXONE such as avoiding prescribing multiple refills early in treatment, and conducting patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability.

Because the naloxone in the combination tablet precipitated immediate and intense withdrawal symptoms in individuals dependent on heroin, methadone, or other opioid full agonists, SUBOXONE is expected to be less likely to be diverted for intravenous use.

Patients dependent upon concomitant CNS-active substances, including alcohol, should not be treated with the increased doses required by the less-than-daily dosing regimen intended for use in a supervised dose setting. Patients with sporadic use of

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concomitant non-opioid medications should be monitored closely, and all patients dosed on a less-than-daily basis should be observed for at least 1,5 hours following the first multi-dose administration initiating less-than-daily dosing or whenever treated with doses higher than 48 mg.

Sleep-related breathing disorders:

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Respiratory Depression:

A number of cases of death due to respiratory depression have been reported, particularly when SUBOXONE was used in combination with benzodiazepines (see section 4.5), when high dose SUBOXONE was administered to non-opioid dependent individuals who had not developed a tolerance to the effects of opioids or when SUBOXONE was not used according to the prescribing information.
Deaths have been reported in association with concomitant administration of SUBOXONE and other CNS depressants such as alcohol or other opioids.

SUBOXONE may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. Protect children against exposure.

SUBOXONE should be used with caution in patients with compromised respiratory function (e.g. chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression, or kyphoscoliosis).

Patients with the physical and/or pharmacological risk factors above should be monitored, and dose reduction may be considered.

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CNS depression:

SUBOXONE may cause drowsiness, particularly when used together with alcohol or other central nervous system depressants (such as benzodiazepines, tranquilisers, sedatives or hypnotics) (see sections 4.5 and 4.7).

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of SUBOXONE and sedative medicines such as benzodiazepines or related medicines may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe SUBOXONE concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Serotonin syndrome:

Concomitant administration of SUBOXONE and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic medicines is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

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If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Dependence:

Buprenorphine is a partial agonist of the μ -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.

Discontinuation of treatment may result in a withdrawal syndrome that may be delayed.

Hepatitis, hepatic events:

Cases of acute hepatic injury have been reported in opioid-dependent patients both in clinical trials and in post-marketing adverse event 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 and 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 and chronic hepatitis C, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicines, or ongoing drug use by injection) may have a causative or contributory role.

Patients who are positive for viral hepatitis, on concomitant medicinal products (see section 4.5) and/or have existing liver dysfunction are at greater risk of liver injury, and these underlying factors must be taken into consideration before prescribing SUBOXONE and during treatment (see section 4.2).

When a hepatic event is suspected, further biological and etiological evaluation is required. Depending upon these findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent return to illicit drug use. If the drug treatment is continued, hepatic function should be monitored closely.

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Precipitated withdrawal:

When initiating treatment with buprenorphine, it is important to 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 section 4.2). Conversely withdrawal symptoms may also be associated with suboptimal dosing.

Hepatic impairment:

The effects 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 which may require dose adjustments. 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 moderate to severe hepatic impairment (see section 5).

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 (CLcr <30 ml/min) (see section 4.2 and section 5).

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,

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angioedema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to SUBOXONE use.

General opioid class warnings:

- 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, in other circumstances where cerebrospinal pressure may be increased, or in patients with a history of seizure.
- Opioid-induced miosis, changes in the level of consciousness, or changes in the perception of pain as a symptom of disease and 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 should be used with caution in patients with toxic psychoses, acute alcoholism, or delirium tremens.
- Opioids should be used with caution in patients with hypotension, prostatic hypertrophy or urethral stricture.
- 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.

Athletes must be aware that this medicine may cause a positive reaction to ‘anti-doping’ tests.

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

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Excipients:

SUBOXONE contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

SUBOXONE should not be taken together with alcoholic drinks or medications containing alcohol as alcohol increases the sedative effect of buprenorphine (see section 4.4).

SUBOXONE should be used cautiously when co-administered with:

- **Benzodiazepines:** The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Therefore, dosages must be limited and this combination must be avoided in cases where there is a risk of misuse (see section 4.4). 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 prescribed (see section 4.4).

- **Other central nervous system depressants**, other opioid derivatives (e.g. methadone, analgesics and antitussives), certain antidepressants, sedative H_1-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.

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- **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. Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving SUBOXONE.

  Conversely, the potential for overdose should be considered with higher than usual doses of full agonist opioids, such as methadone or level III analgesics, 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 section 4.4).

- Serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

- **Naltrexone:** Naltrexone is an opioid antagonist that can block the pharmacological effects of buprenorphine.

  For opioid dependent patients currently receiving SUBOXONE treatment, the naltrexone antagonist may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms.

  For patients currently receiving naltrexone treatment, the intended therapeutic effects of SUBOXONE administration may be blocked by the naltrexone antagonist.

- **CYP3A4 inhibitors:** An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in an increased Cmax and AUC (area under the curve) of buprenorphine (approximately 50 % and 70%

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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, macrolide antibiotics or azole antifungals such as ketoconazole or itraconazole).

- CYP3A4 inducers: Concomitant use of CYP3A4 inducers with buprenorphine may decrease buprenorphine plasma concentrations, potentially resulting in under-treatment of opioid dependence with buprenorphine. Therefore it is recommended that patients receiving SUBOXONE should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered, and the dose of buprenorphine or CYP3A4 inducer may need to be adjusted accordingly.

To date, no notable interaction has been observed with cocaine, the agent most frequently used by multi-drug abusers in association with opioids.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is very limited experience with SUBOXONE in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Towards the end of pregnancy high doses of buprenorphine may produce respiratory depression in the neonate even after a short period of administration. Long-term administration of buprenorphine during the last three months of pregnancy may cause a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions) in the neonate.
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.

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SUBOXONE should not be used during pregnancy.

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.

Breastfeeding

It is unknown whether naloxone is excreted in human breast milk. Buprenorphine and its metabolites are excreted in human breast milk. In rats buprenorphine has been found to inhibit lactation. Therefore, breast-feeding should be discontinued during treatment with SUBOXONE.

Fertility

No data on male and female fertility is available.

4.7 Effects on ability to drive and use machines

In general SUBOXONE has minor to moderate influence on the ability to move safely in traffic, use machines, or perform other hazardous activities. SUBOXONE may cause drowsiness, dizziness, or impaired thinking, particularly when taken together with alcohol or central nervous system depressants. Therefore, caution is advised when performing the above-mentioned activities (see section 4.4 and section 4.5).

4.8 Undesirable effects

a. Summary of the safety profile

Clinical Trial Data:

The most common treatment related undesirable effects reported during clinical studies with SUBOXONE were those related to withdrawal symptoms (e.g. abdominal pain, diarrhoea, muscle aches, anxiety, sweating).

In the pivotal clinical study of SUBOXONE, 342 of 472 patients (72,5 %) reported treatment related adverse events. These reactions are listed in Table 1 by system,

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organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

b. Tabulated summary of adverse reactions

System organ class	***Frequency***	***Adverse Event***
Infections and infestations	Common	Infection
	Uncommon	Vaginitis
Blood and lymphatic system disorders	Uncommon	Anaemia, thrombocytopenia, leucopenia, Lymphadenopathy, leukocytosis
Immune system disorders	Uncommon	Allergic reaction
Metabolism and Nutrition disorders	Common	Peripheral oedema, weight decreased
	Uncommon	Hyperglycaemia, hyperlipemia, hypoglycaemia
Psychiatric disorders	Common	Anxiety, nervousness, depression, libido decreased, thinking abnormal
	Uncommon	Drug dependence, amnesia, hostility; speech disorder, depersonalisation, abnormal dreams, apathy, euphoria

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Nervous System disorders	Very common	Insomnia
	Common	Somnolence, dizziness, paresthesia, hypertonia Convulsion, agitation, tremor, hyperkinesia
Eye disorders	Common	Lacrimation disorder, amblyopia
	Uncommon	Miosis, conjunctivitis
Cardiac disorders	Uncommon	Myocardial infarction, angina pectoris, palpitation, tachycardia, bradycardia
Vascular disorders	Common	Vasodilation, hypertension, migraine
	Uncommon	Hypotension, heat stroke
Respiratory thoracic and mediastinal disorders	Common	Rhinitis, pharyngitis, cough increased
	Uncommon	Dyspnoea, asthma, yawn
Gastrointestinal disorders	Very common	Constipation, nausea
	Common	Vomiting, dyspepsia, diarrhoea, anorexia, flatulence
	Uncommon	Ulcerative stomatitis, tongue discolouration
Hepatobiliary system disorders	Common	Liver function abnormal
Skin and subcutaneous tissue disorders	Very common	Sweating
	Common	Rash, pruritis, urticaria

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	Uncommon	Exfoliative dermatitis, acne, skin nodule, alopecia, dry skin
Musculoskeletal, connective tissue and bone disorders	Common	Arthralgia, myalgia, leg cramps
	Uncommon	Arthritis
Renal and urinary system disorders	Common	Albuminuria, urine abnormality
	Uncommon	Haematuria, kidney calculus, increased creatinine, urinary tract infection, dysuria, urinary retention
Reproductive system and breast disorders	Uncommon	Impotence, amenorrhoea, abnormal ejaculation, menorrhagia, metrorrhagia
General disorders and administrative site conditions	Very common	Withdrawal syndrome, headache
	Common	Asthenia, fever, flu syndrome, malaise, accidental injury, chills, chest pain, abdominal pain, back pain, pain
Injury, poisoning and procedural complications	Uncommon	Hypothermia

Post-Marketing Data:

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Table 2 lists the most commonly reported adverse reactions reported during post-marketing surveillance. Events occurring in at least 1 % of reports by healthcare professionals and considered to be at least possibly related to treatment are included.

Table 2: Spontaneous adverse drug reactions collected through post-marketing surveillance reported by body system	
System Organ Class	**Preferred term**
Psychiatric disorders	Anxiety
Nervous system disorders	Headache
Gastrointestinal disorders	Nausea Vomiting
Skin and subcutaneous disorders	Rash Urticaria Hyperhidrosis
General disorders and administration site conditions	Drug withdrawal syndrome Oedema peripheral Oedema

c. Description of selected adverse reactions

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:

- 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 section 4.4).
- Respiratory depression has occurred. Death due to respiratory depression has been reported, particularly when buprenorphine products were used in combination with benzodiazepines (see section 4.5), or when buprenorphine

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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 section 4.4 and section 4.5).

- Hypersensitivity reactions such as bronchospasm, angioedema, or anaphylactic shock have been reported (see section 4.3).
- Transaminase increase, hepatitis, acute hepatitis, cytolytic hepatitis, jaundice, hepatorenal syndrome, hepatic encephalopathy, and hepatic necrosis have occurred (see section 4.4).
- A neonatal abstinence syndrome had 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 section 4.6).
- Hallucination, orthostatic hypotension, syncope, and vertigo, have been reported (see section 4.4).

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 SUBOXONE. It is not possible to establish a causal relationship since cases typically involve other drug use of risk factors for spontaneous abortion (see section 4.6).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com.

4.9 Overdose

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. 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.

The long duration of action of SUBOXONE should be taken into consideration when determining the length of treatment and medical surveillance needed to reverse the effects of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, drugs used in addictive disorders, ATC code: N07BC51

<u>Mechanism of action</u>

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Buprenorphine is an opioid partial agonist/antagonist, which attaches to the μ (mu) and K (kappa) receptors of the brain. It's activity in opioid maintenance treatment is attributed to its slowly reversible properties with the μ receptors.
Opioid agonist ceiling effects are seen.

Naloxone is an antagonist at μ (mu)-opiate 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, the presence of naloxone in buprenorphine/ naloxone produces opiate antagonist effects and opioid withdrawal, thereby deterring intravenous abuse.

5.2 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 increasing the sublingual dose of buprenorphine/ naloxone. Both C_{max} and AUC of buprenorphine increased with the increase in dose (in the range 4 – 16 mg), although the increase was less than dose proportional.

Table 3: Pharmacokinetic Parameters

Values in the table represent the mean and (co-efficient of variation in %).

Pharmaco-kinetic Parameter	**SUBOXONE 4 mg**	**SUBOXONE 8 mg**	**SUBOXONE 16 mg**
C_{max} - ng/ml	1,84 (39)	3,0 (51)	5,95 (38)

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AUC 0-48 hour - ng/ml	12,52 (35)	20,22 (43)	34,89 (33)

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

Metabolism and elimination: Buprenorphine is metabolized by 14-N-dealkylation and glucuroconjugation of the parent molecule and the dealkylated metabolite. 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 faeces 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 buprenorphine/ naloxone, plasma naloxone concentrations are low and decline rapidly.

Metabolism and elimination: The drug is metabolized in the liver, primarily by glucuronide conjugation, and excreted in the urine. Naloxone has a mean elimination half-life from plasma of 1,2 hours.

Special populations

Elderly: No pharmacokinetic data in elderly patients are available.

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

Hepatic impairment: Table 4 summarizes the results from a clinical trial in which the exposure of buprenorphine and naloxone was determined after administering a Suboxone 2 mg/0,5 mg (buprenorphine/naloxone) sublingual tablet in healthy subjects, and in subjects with varied degrees of hepatic impairment.

Table 4. 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			
Cmax	1,2-fold increase	1,1-fold Increase	1,7-fold increase
AUClast	Similar to control	1,6 -fold increase	2,8-fold increase
Naloxone			
Cmax	Similar to control	2,7-fold increase	11,3-fold increase
AUClast	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.

Buprenorphine/naloxone is contraindicated in patients with severe hepatic dysfunction (see section 4.3).

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acesulfame potassium, citric acid anhydrous, lactose monohydrate, maize starch, magnesium stearate, mannitol, natural lemon and lime flavour, povidone K30, sodium citrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep out of reach of children.

Store at or below 30 °C in a dry place protected from light

Do not remove the tablets from the outer carton and blister pack until required for use.

6.5 Nature and contents of container

SUBOXONE 2 mg and 8 mg Sublingual Tablets are packed in a cold form nylon/aluminium/PVC blister pack and placed in cardboard cartons containing 7 or 28 tablets.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd

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Aeroton,

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2013

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8. REGISTRATION NUMBER(S)

SUBOXONE 2 mg Sublingual Tablets: 41/34/1010

SUBOXONE 8 mg Sublingual Tablets: 41/34/1011

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

05 March 2009

10. DATE OF REVISION OF THE TEXT

22 July 2022

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