# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Subutex 300 mg prolonged-release solution for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1.5 mL prolonged-release solution for injection in a prefilled syringe contains 300 mg buprenorphine (as buprenorphine base).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Prolonged-release solution for injection.

Clear, viscous, colourless to yellow to amber sterile solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

Subutex prolonged-release injection is indicated in adults (16 years and older) who have agreed to be treated for opioid addiction.

### 4.2 Posology and method of administration

Administration of Subutex prolonged-release injection is restricted to healthcare professionals. Appropriate precautions, such as to conduct patient follow-up visits with clinical monitoring according to the patient's needs, should be taken when

prescribing and dispensing buprenorphine. Take-home use or self-administration of the medicinal product by patients is not allowed.
Subutex prolonged-release injection is not interchangeable with other buprenorphine prolonged-release solutions for injection.

Posology
Patients should first undergo induction and stabilization by initiating a transmucosal buprenorphine-containing product, delivering the equivalent of 8 mg/day to 24 mg/day of buprenorphine for a minimum of 7 days. Dosing and induction with this transmucosal buprenorphine-containing product should be based on instructions in its appropriate product label. Dosing should be stopped on the day of the first Subutex prolonged-release injection.
Following stabilisation on a transmucosal buprenorphine-containing product, the patient should be given an initial dose of 300 mg Subutex prolonged-release injection. 1 month later, a second dose of 300 mg Subutex prolonged-release injection should be given. 1 month later, the patient should commence the monthly maintenance dose of 100 mg Subutex prolonged-release injection.
In clinical trials, randomisation to the 300-mg maintenance dose group did not provide additional efficacy as compared to randomisation to the 100-mg maintenance dose group (see section 5.1); however, patients who tolerate the 100-mg maintenance dose but do not show a satisfactory clinical response may receive a monthly maintenance dose of 300 mg.

Transition of patients established on long-term treatment with transmucosal buprenorphine
Patients established on long-term treatment with transmucosal buprenorphine (8 mg/day to 24 mg/day) and whose disease symptoms are controlled can be transitioned directly to Subutex prolonged-release injection [see Table 1 for treatment initiation]. At steady-state, plasma buprenorphine concentrations achieved with the 100-mg maintenance dose are contained within the range obtained with transmucosal treatment; peak concentrations may be lower, while average and trough concentrations may be higher [see Figure 2 in section 5.2]. These levels need to be taken into consideration when transitioning a patient established on long-term treatment with transmucosal buprenorphine to Subutex prolonged-release injection.

**Table 1 Transition of patients established on long-term treatment with transmucosal buprenorphine whose disease symptoms are controlled**

| **Transmucosal Buprenorphine Doses** | Subutex **prolonged-release injection** | | |
|---|---|---|---|
| | **Injection 1** | **Injection 2** | **Maintenance Dose** |
| 8 mg/day to 18 mg/day | 300 mg | 100 mg* | 100 mg |
| 20 mg/day to 24 mg/day | 300 mg | 300 mg | 100 mg |

* For patients still experiencing craving or withdrawal symptoms after the initial 300-mg dose, consider giving 300 mg as the second dose.

Frequency of dosing
In consideration of its long half-life, Subutex prolonged-release injection should be administered once monthly and separated by a minimum of 26 days between doses.

Missed doses

A patient who misses a dose should receive the next dose as soon as possible. Unavoidable occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.

Treatment goals and discontinuation

Before initiating treatment with Subutex, a treatment strategy including treatment duration and treatment goals, should be agreed together with the patient. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. There is no maximum recommended duration of maintenance treatment. The need for continuing medication-assisted treatment should be re-evaluated periodically.

When a patient no longer requires therapy with buprenorphine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.4). If Subutex is discontinued, its extended. If Subutex prolonged-release injection is discontinued, its extended-release characteristics should be considered (see section 5.2) and the patient should be monitored for several months for signs and symptoms of withdrawal and treated appropriately After steady-state has been achieved, patients discontinuing Subutex prolonged-release injection may have detectable plasma levels of buprenorphine for twelve months or longer. The correlation between plasma concentrations of buprenorphine and those detectable in urine is not known.

Special populations

*Elderly*

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

Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients, the decision to prescribe Subutex prolonged-release injection should be made cautiously in individuals 65 years of age or older and these patients should be monitored for signs and symptoms of toxicity or overdose.

*Hepatic impairment*

Plasma levels are increased in moderate and severe hepatic impairment compared to healthy subjects (see section 5.2). Subutex prolonged-release injection should be used with caution in patients with moderate hepatic impairment (see section 4.4). Patients should be monitored with regard to signs and symptoms for toxicity or overdose caused by increased levels of buprenorphine (see section 4.4). Subutex prolonged-release injection is contraindicated in patients with severe hepatic impairment (see section 4.3).

*Renal impairment*

Modification of the buprenorphine dose is not required for patients with renal impairment. Caution is recommended when dosing patients with severe renal impairment (creatinine clearance < 30 mL/min) (see sections 4.4 and 5.2).

*Paediatric population*

No data are available in individuals less than 16 years of age; therefore, Subutex prolonged-release injection should not be used in children or adolescents under the age of 16 years.

Method of administration
For abdominal subcutaneous injection only.
Subutex prolonged-release injection should be administered by subcutaneous injection in the abdominal region by a healthcare professional. Each injection should be administered only using the syringe and safety needle included with the product. To avoid irritation, rotate injection sites using all four quadrants of the abdomen, provided there is adequate subcutaneous tissue (see Package Leaflet for more details).
For detailed, stepwise instruction on preparation and administration of Subutex prolonged-release injection, see section 6.6 and in the document **INFORMATION FOR HEALTHCARE PROFESSIONALS ONLY**.

## 4.3 Contraindications

- Hypersensitivity to buprenorphine or to any of the excipients listed in section 6.1
- Severe respiratory insufficiency
- Severe hepatic impairment
- Acute alcoholism or delirium tremens

## 4.4 Special warnings and precautions for use

Subutex prolonged-release injection is recommended only for the treatment of opioid drug dependence. It is also recommended that treatment is prescribed by a physician who ensures comprehensive management of the opioid-dependent patient(s).

Risk of Serious Harm or Death with Intravenous Administration (Incorrect Administration)
Intravenous injection presents significant risk of serious harm or death as Subutex prolonged-release injection forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, could result if administered intravenously. Do not administer intravenously or intramuscularly.

Drug dependence, tolerance and potential for abuse
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 or localised 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 or if the medicine is not safeguarded against theft.

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as buprenorphine. Abuse or intentional misuse of buprenorphine may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with buprenorphine and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2).

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psychoactive drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Subutex prolonged-release injection is injected as a solution and following administration, the poly (DL-lactide-co-glycolide) polymer creates a depot which contains buprenorphine. After initial formation of the depot, buprenorphine is released via diffusion from, and the biodegradation of, the depot. Clinical monitoring for evidence at the injection site of tampering or attempting to remove the depot should be ongoing throughout treatment.

Pain Management

While on Subutex prolonged-release injection, situations may arise where patients need acute pain management, or may require anaesthesia (including regional/local anaesthesia). Treat patients receiving Subutex prolonged-release injection with a non-opioid analgesic whenever possible. Patients requiring opioid therapy for analgesia may be treated with a high-affinity full opioid analgesic under the supervision of a healthcare professional, with particular attention to respiratory function. Titration of full opioid analgesics to the desired analgesic effect might require higher doses. Therefore, a higher potential for toxicity exists with opioid administration and the patient should be monitored during treatment. If opioid therapy is required as part of anaesthesia, patients should be continuously monitored by anaesthesia staff not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy should be provided by individuals specifically trained in the use of anaesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent/open airway and giving of assisted/controlled ventilation.

Advise patients of the importance of instructing their family members and close friends, in the event of emergency, to inform the treating healthcare professional or emergency room staff that the patient is physically dependent on an opioid and that the patient is being treated with Subutex prolonged-release injection.

The above guidance should also be considered for any patient who has discontinued Subutex prolonged-release injection within the last 6 months.

Respiratory depression

Deaths due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines (see section 4.5) or when buprenorphine was not used according to prescribing information. Deaths have

also been reported in association with concomitant administration of buprenorphine and other depressants such as alcohol, gabapentinoids (such as pregabalin and gabapentin) or other opioids.
Subutex prolonged-release injection should be used with care in patients with respiratory insufficiency (e.g. chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis).
Buprenorphine may cause severe, possibly fatal, respiratory depression in children and non-opioid dependent persons who accidentally or deliberately use it. Protect children and non-opioid-dependent persons against exposure.

CNS depression
Buprenorphine may cause drowsiness particularly when used with alcohol or other central nervous system depressants (such as benzodiazepines, gabapentinoids. tranquillisers, sedatives or hypnotics) (see sections 4.5 and 4.7).

Withdrawal signs and symptoms Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with buprenorphine. The decision to maintain a patient on a long-term opioid prescription should be an active decision agreed between the clinician and patient with review at regular intervals (usually at least every three months, depending on clinical progress).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. Withdrawal signs and symptoms were not observed in the month following discontinuation of Subutex prolonged-release injection. Considering the long half-life, any withdrawal signs and symptoms that may occur are delayed. Model simulations indicate that steady-state plasma buprenorphine concentrations decreased slowly over time following the last injection and remained at therapeutic levels (2 ng/mL) for 2 to 5 months on average, depending on the dosage administered (100 or 300 mg, respectively).
Patients who elect to discontinue treatment with Subutex prolonged release injection should be monitored for several months for signs and symptoms of withdrawal and treated appropriately.
The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.
If women take this drug during pregnancy, there is a risk that their new-born infants will experience neonatal withdrawal syndrome.

Precipitation of opioid withdrawal syndrome
When initiating treatment with buprenorphine it is important to be aware of the partial agonist profile of buprenorphine. Buprenorphine products have caused precipitated withdrawal symptoms in opioid-dependent patients when administered before the agonist effects resulting from recent opioid use have subsided. Verify that patients have been induced on a transmucosal buprenorphine-containing product before subcutaneously injecting Subutex prolonged-release injection. To avoid precipitated

withdrawal, induction should be undertaken when objective signs and symptoms of mild to moderate withdrawal are evident. (see section 4.2).

Hepatitis and 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 following the sublingual administration of buprenorphine. 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 liver enzyme abnormalities, genetic disease, infection with hepatitis B or hepatitis C virus, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic drugs and ongoing injecting drug use may have a causative or contributory role. These underlying factors must be taken into consideration before prescribing Subutex prolonged-release injection and during treatment. When a hepatic event is suspected further biological and etiological evaluation is required. Depending on the findings, Subutex prolonged-release injection may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If treatment is continued, hepatic function should be monitored closely.

Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy. All patients should have liver function tests performed at regular intervals.

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of Subutex prolonged-release injection has not been studied.

The effects of impaired hepatic function on the pharmacokinetics of sublingual buprenorphine were evaluated in a clinical study. Since buprenorphine is largely metabolized in the liver, the plasma levels of buprenorphine were higher in patients with moderate and severe hepatic impairment compared to healthy subjects (see section 5.2). Subutex prolonged-release injection should be used with caution in patients with pre-existing moderate hepatic impairment as plasma buprenorphine levels cannot be rapidly lowered. In patients with severe hepatic impairment, the use of buprenorphine is contraindicated (see section 4.3).

Patients with moderate hepatic impairment or who develop moderate-to-severe hepatic impairment while being treated with Subutex prolonged-release injection should be monitored for several months for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. Hepatic function must be monitored regularly during the treatment

Renal impairment

Renal elimination plays a relatively small role (approximately 30 %) in the overall clearance of buprenorphine and metabolites; therefore, no dose modification based on renal function is 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 section 5.2).

Clinical studies of Subutex prolonged-release injection did not include subjects with renal impairment.

QT Prolongation

Caution should be exercised when buprenorphine is co-administered with other medicinal products that prolong the QT interval and in patients with a history of long QT syndrome or other risk factors for QT prolongation.

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 is a contraindication to buprenorphine use.

Serotonin syndrome
Concomitant administration of Subutex prolonged-release injection and other serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs), tricyclic antidepressants or MAO inhibitors may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).
If concomitant treatment with other serotonergic agents 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.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Risks from concomitant use of sedative medicines such as benzodiazepines or related medicinal products
Concomitant use of Subutex prolonged-release injection and sedative medicines such as benzodiazepines or related drugs 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 Subutex prolonged-release injection 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).

Seizures
Buprenorphine may lower the seizure threshold in patients with a history of seizure disorder.

Use in adolescents
Due to lack of data in adolescents (age 16 to 18), patients in this age group should be more closely monitored during treatment.

General warnings related to the administration of opioids
Opioids may cause 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.
Opioids should be used with caution in patients with hypotension, prostatic hypertrophy 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.

## 4.5 Interaction with other medicinal products and other forms of interaction

The below guidance should also be considered for any patient who has discontinued Subutex prolonged-release injection within the last 6 months.
No interaction studies have been performed with Subutex prolonged-release injection.
Subutex should not be taken with alcoholic beverages or medicinal products containing alcohol, as alcohol enhances the sedative effect of buprenorphine and increases the risk of respiratory depression, severe sedation, coma and death (see section 4.7).
Subutex prolonged-release injection should be used cautiously together with:

- Sedative medicines such as benzodiazepines or related medicinal products: this combination may result in death due to respiratory depression of central origin; therefore, patients must be closely monitored and this combination should be avoided in cases where there is risk of misuse. An appropriate medical assessment of the benefit/risk ratio should be initiated before this combination is prescribed. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines whilst taking this product and should also be cautioned to use benzodiazepines concurrently with this product only as prescribed (see section 4.4). Before co□prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non□pharmacologic treatments.
- Gabapentinoids: The concomitant use of Subutex with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death. Therefore, dosages must be closely monitored and this combination must be avoided in cases where there is a risk of misuse. Patients should be cautioned to use gabapentinoids concurrently with this product only as directed by their physician (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, antipsychotics, clonidine and related substances. These combinations increase central nervous system depression. The reduced level of alertness can make driving and using machinery hazardous (see section 4.7).

- Anticholinergics: Concomitant administration of Subutex with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.
- Opioid analgesics: Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine. The potential for overdose also exists with a full agonist, especially when attempting to overcome buprenorphine partial agonist effects, or when plasma buprenorphine levels are declining (see section 4.4 “Pain Management”).
- Naltrexone and nalmefene: These are opioid antagonists that can block the pharmacological effects of buprenorphine. For opioid-dependent patients currently receiving buprenorphine treatment, naltrexone and nalmefene may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms. For patients currently receiving naltrexone or nalmefene treatment, the intended therapeutic effects of buprenorphine administration may be blocked by naltrexone or nalmefene.
- 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).
- Monoamine oxidase inhibitors (MAO inhibitors) may increase the effect of opioids.
- CYP3A4 inhibitors: The effects of co□administered CYP3A4 inhibitors on buprenorphine exposure in subjects treated with Subutex prolonged-release injection have not been studied and the effects may be dependent on the route of administration. CYP3A4 inhibitors may inhibit the metabolism of buprenorphine resulting in increased exposure of buprenorphine and norbuprenorphine.
  An interaction study of sublingual buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased $C_{max}$ and AUC of buprenorphine (approximately 50% and 70% respectively) and, to a lesser extent, of the metabolite, norbuprenorphine. Subutex prolonged-release injection avoids first-pass effects, and CYP3A4 inhibitors (e.g. protease inhibitors like ritonavir, nelfinavir or indinavir; azole antifungals such as ketoconazole, fluconazole or itraconazole; macrolide antibiotics; or grapefruit juice) are therefore expected to have less effect on the buprenorphine metabolism when they are administered together with Subutex prolonged-release injection than when they are administered together with sublingual buprenorphine. When being switched from sublingual buprenorphine to Subutex prolonged-release injection, patients receiving continuous treatment with a CYP 3A4 inhibitor may need to be monitored to ensure that buprenorphine levels in plasma are adequate. Patients who are already on Subutex prolonged-release injection and who start treatment with a CYP3A4 inhibitor should be monitored for signs and symptoms of overdosage. If a patient is being treated concomitantly with Subutex prolonged-release injection and a CYP3A4 inhibitor, and stops taking the CYP3A4 inhibitor, the patient must be monitored for withdrawal symptoms.

- CYP3A4 inducers: The effects of co□administered CYP3A4 inducers on buprenorphine exposure in subjects treated with Subutex prolonged-release injection have not been studied. CYP3A4 inducers may increase the metabolism of buprenorphine resulting in decreased plasma buprenorphine levels. As Subutex prolonged-release injection avoids first-pass effects, CYP3A4 inducers (e.g. phenobarbital, carbamazepine, phenytoin or rifampicin) are therefore expected to have less effect on the buprenorphine metabolism when they are co-administered with Subutex prolonged-release injection than when they are co-administered with sublingual buprenorphine. When being switched from sublingual buprenorphine to Subutex prolonged-release injection, patients receiving continuous treatment with a CYP3A4 inducer should be monitored to ensure that the plasma buprenorphine levels are adequate. Patients who are already on Subutex prolonged-release injection and begin treatment with a CYP3A4 inducer should be monitored for signs and symptoms of withdrawal. If a patient is being treated concomitantly with Subutex prolonged-release injection and a CYP3A4 inducer, and stops taking the CYP3A4 inducer, the patient must be monitored for symptoms of overdose.
- The co-administration of Subutex prolonged-release injection with UGT inhibitors may have an impact on the systemic exposure of buprenorphine.

Note**

** Buprenorphine does not undergo first-pass metabolism following subcutaneous injection of Subutex prolonged-release injection, resulting in a much lower norbuprenorphine-to-buprenorphine AUC ratio (0.20 to 0.40) compared to sublingual buprenorphine (0.70 to 2.11). A clinically meaningful increase or decrease in plasma buprenorphine concentration is not expected with the concomitant use of Subutex prolonged-release injection and CYP3A4 inhibitors/inducers. The dose of the CYP3A4 inhibitors/inducers may need to be adjusted accordingly.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

No studies in pregnant women have been conducted with Subutex prolonged-release injection. Animal studies do not indicate human reproductive toxicity concern (see section 5.3).

Subutex prolonged-release injection should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Buprenorphine readily crosses the placental barrier and may cause respiratory depression in neonates. Exposure to buprenorphine following injection of Subutex prolonged-release during pregnancy or prior to conception may be responsible for a withdrawal syndrome in neonates (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.

Opioid-dependent women on buprenorphine maintenance therapy may require additional analgesia during labour. As with all opioids, use of buprenorphine prior to delivery may result in respiratory depression in the new-born. Closely monitor neonates for signs of respiratory depression.

Breast-feeding

Buprenorphine and its metabolites are excreted in human breast milk.

Caution should be exercised when Subutex prolonged-release injection is administered to a nursing woman or if it has been administered during pregnancy. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Subutex prolonged-release injection and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Advise breastfeeding women taking buprenorphine products to monitor the infant for increased drowsiness and breathing difficulties.

Fertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible. Male fertility may be reduced based on animal data demonstrating adverse effects of Subutex prolonged-release injection on sperm parameters (see Section 5.3).

## 4.7 Effects on ability to drive and use machines

Buprenorphine has moderate influence on the ability to drive and use machines when administered to opioid-dependent patients. Subutex prolonged-release injection may cause drowsiness, dizziness or impaired thinking, especially during treatment induction and dose adjustment. If taken together with alcohol or central nervous system depressants, the effect is likely to be more pronounced (see section 4.4. and 4.5). Patients should be cautioned about operating hazardous machinery in case buprenorphine may affect their ability to engage in such activities.

This medicine can impair cognitive function and can affect a patient's ability to drive safely.

This class of medicine is in the list of drugs included in regulations under 5a of the Road

Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

## 4.8 Undesirable effects

Summary of safety profile

The most commonly reported adverse drug reactions reported during the pivotal clinical trials with Subutex sublingual tablets were those related to withdrawal symptoms (e.g., insomnia, headache, nausea and hyperhidrosis) and pain. The frequency of adverse reactions observed during the pivotal clinical studies on Subutex prolonged-release injection were consistent with those reported with Subutex sublingual tablets with the exception of injection site reactions (e.g., erythema, induration, pain and pruritus).

Tabulated list of adverse reactions

- adverse reactions reported from pivotal clinical studies on Subutex sublingual tablets with additional adverse reactions observed during pivotal clinical studies on Subutex prolonged-release injection. The frequency of possible side effects listed below is defined using the following convention: Very common (≥ 1/10), common (≥ 1/100 to < 1/10) and not known (cannot be estimated from the available data).
- the most commonly reported adverse drug reactions during post-marketing surveillance of Subutex sublingual tablets. Events occurring in at least 1 % of reports by healthcare professionals and considered expected are included. Frequency of events not reported in pivotal studies cannot be estimated and is given as not known.

**Table 1 Adverse effects observed in pivotal clinical studies and / or post-marketing surveillance listed by system organ class**

| ***System organ class*** | **Very common (≥ 1/10)** | **Common (≥ 1/100 to < 1/10)** | **Not known (cannot be estimated from the available data)** |
|---|---|---|---|
| *Infections and infestations* | | Bronchitis<br>Infection<br>Influenza<br>Pharyngitis<br>Rhinitis | Injection site infection* |
| *Blood and lymphatic system disorders* | | Lymphadenopathy | |
| *Immune system disorders* | | | Anaphylactic shock<br>Hypersensitivity |
| *Metabolism and nutrition disorders* | | Decreased appetite | |

| ***System organ class*** | **Very common (≥ 1/10)** | **Common (≥ 1/100 to < 1/10)** | **Not known (cannot be estimated from the available data)** |
|---|---|---|---|
| *Psychiatric disorders* | Insomnia | Agitation<br>Anxiety<br>Depression<br>Hostility<br>Nervousness<br>Paranoia<br>Thinking abnormal | Drug dependence (see section 4.4)<br>Hallucination |
| *Nervous system disorders* | Headache | Dizziness<br>Hypertonia<br>Lethargy*<br>Migraine<br>Paraesthesia<br>Sedation*<br>Somnolence<br>Syncope<br>Tremor | Hepatic encephalopathy<br>Seizures |
| *Eye disorders* | | Lacrimal disorder<br>Mydriasis | |
| *Ear and labyrinth disorders* | | | Vertigo |
| *Cardiac disorders* | | Palpitations | |
| *Vascular disorders* | | Vasodilatation | Orthostatic hypotension |
| *Respiratory, thoracic and mediastinal disorders* | | Cough<br>Dyspnoea<br>Yawning | Bronchospasm |
| *Gastrointestinal disorders* | Nausea | Abdominal pain<br>Constipation<br>Diarrhoea<br>Dry mouth<br>Dyspepsia<br>Gastrointestinal disorder<br>Flatulence<br>Tooth disorder<br>Vomiting | |
| *Hepatobiliary disorders* | | | Hepatitis<br>Hepatitis acute<br>Hepatic cytolysis<br>Hepatic necrosis<br>Hepatorenal syndrome<br>Jaundice |

| ***System organ class*** | **Very common (≥ 1/10)** | **Common (≥ 1/100 to < 1/10)** | **Not known (cannot be estimated from the available data)** |
|---|---|---|---|
| *Skin and subcutaneous tissue disorders* | Hyperhidrosis | Rash | Angioedema |
| *Musculoskeletal and connective tissue disorders* | | Arthralgia<br>Back pain<br>Bone pain<br>Muscle spasms<br>Myalgia<br>Neck pain | |
| *Renal and urinary disorders* | | | Urinary retention |
| *Reproductive system and breast disorders* | | Dysmenorrhoea | |
| *General disorders and administration site conditions* | Drug withdrawal syndrome<br>Pain | Asthenia<br>Chest pain<br>Chills<br>Fatigue*<br>Injection site erythema*<br>Injection site induration*<br>Injection site pain*<br>Injection site pruritus*<br>Malaise<br>Oedema peripheral<br>Pyrexia | Drug withdrawal syndrome neonatal |
| *Investigations* | | Hepatic enzyme increased*† | |

*Additional adverse reactions observed during pivotal clinical studies on Subutex prolonged-release injection

†The term hepatic enzyme increased includes elevations of ALT, AST, GGT, alkaline phosphatase, and/or bilirubin. There were no cases of severe drug-induced liver injury.

Description of selected adverse reactions

The following is a summary of other post-marketing adverse event reports involving other buprenorphine-containing products that are considered serious or otherwise noteworthy:

- In cases of intravenous misuse, local reactions, sometimes septic (abscess, cellulitis), and potentially serious acute hepatitis and other infections such as pneumonia, endocarditis 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.

Drug dependence
Repeated use of buprenorphine can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

Symptoms

Respiratory depression, as a result of central nervous system depression, is the primary symptom requiring intervention in the case of overdose because it may lead to respiratory arrest and death. Preliminary symptoms of overdose may also include somnolence, amblyopia, miosis, hypotension, nausea, vomiting and / or speech disorders.

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Treatment

General supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. Symptomatic treatment of respiratory depression, following standard intensive care measures, should be instituted. 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. If the patient vomits, precautions must be taken to prevent aspiration of the vomitus. 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 buprenorphine and the extended release characteristics of Subutex prolonged-release injection formulation 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. Ongoing IV infusion rates should be titrated to patient response. If infusion is not possible, repeated dosing with naloxone may be required.

Clinicians should consider the potential role and contribution of buprenorphine, other opioids, and other CNS depressant drugs in a patient's clinical presentation.

In the event the depot must be removed, it can be surgically excised under local anesthesia. Due to the expected polymer degradation, this can be done most easily within about 14 days of injection. Patients who have the depot removed should be monitored for signs and symptoms of withdrawal.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, drugs used in opioid dependence, ATC code: N07BC01

Mechanism of action

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Its activity in opioid maintenance treatment is attributed to its slowly reversible properties with the mu-opioid receptors which, over a prolonged period, might minimise the need of opioids for patients with opioid dependence.

Clinical efficacy and safety

The efficacy and safety of Subutex prolonged-release injection in the treatment of opioid dependence was evaluated in a pivotal Phase 3, 24 weeks, randomized, double-blind, placebo-controlled, multi-center trial in treatment-seeking patients with moderate to severe opioid dependence. In this study, 504 patients were randomized to one of the following dosing regimens: 6 once-monthly 300 mg doses (300/300 mg; 201 subjects), 2 once-monthly 300 mg doses followed by 4 once-monthly 100 mg doses (300/100 mg; 203 subjects), or 6 once-monthly subcutaneous injections of volume-matched placebo (100 subjects). All patients received manual guided psychosocial support at least once a week. Prior to the first dose, subjects were inducted and dose-stabilized on 8/2 to 24/6 mg per day of buprenorphine/naloxone sublingual film for a minimum of 7 days. After randomisation, supplemental dosing with sublingual buprenorphine was not permitted. Of the 504 randomised patients, 64 % (129/201) of subjects in the 300/300 mg group and 62 % (125/203) of the subjects in the 300/100 mg group completed the study compared to 34 % (34/100) subjects in the placebo group. Efficacy and safety outcome measures were assessed at weekly visits. Abstinence was assessed based on urine drug screens for opioids combined with self-reports of illicit opioid use. Missing urine sample results and/or self-reports were counted as positive for illicit opioids.

The study met the primary endpoint of superiority to placebo regarding patients' percentage abstinence from opioid use, defined as the percentage of each patient's negative urine samples and self-reports of illicit opioid use from Week 5 to Week 24 (Table 3). The proportion of patients achieving treatment success (defined as patients with ≥80% opioid-free weeks) was statistically significantly higher in both groups receiving Subutex prolonged-release injection compared to the placebo group. Withdrawal and craving were suppressed over the study period

**Table 3 Primary and key secondary endpoints for efficacy in a pivotal Phase 3, randomised, double-blind, placebo-controlled study in patients with moderate-to-severe opioid dependence**

| | **Subutex prolonged-release injection 300/100 mg (n = 194)** | **Subutex prolonged-release injection 300/300 mg (n = 196)** | **Placebo (n = 99)** |
|---|---|---|---|
| **Percentage Abstinence (Opioid-free Weeks)** | | | |
| Mean (SD) | 42.7 % (38.50 %) | 41.3 % (39.66 %) | 5.0 % (16.98 %) |
| p-value | < 0.0001 | < 0.0001 | - |
| **≥80% Abstinence (Opioid-free Weeks) (Responder)** | | | |
| Treatment Success* | 28.4 % | 29.1 % | 2.0 % |
| p-value | < 0.0001 | < 0.0001 | - |

*Treatment success was defined as any subject with ≥80 % of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 5 and Week 24. A "grace period" was applied for Weeks 1 through 4 to allow patients to stabilise in treatment.

In this 24-week trial, administration of Subutex prolonged-release injection compared to placebo was associated with improved health status, increased employment, decreased health care utilization and increased medication satisfaction (88 % versus 46 % for placebo at Week 25).

A long-term, open-label, multi-center, Phase 3 safety study was conducted in treatment-seeking patients to assess the long-term safety and tolerability of Subutex prolonged-release injection. The study enrolled 669 patients with moderate-to-severe opioid dependence: 412 *de novo* subjects (not previously treated with Subutex prolonged-release injection) and 257 roll-over subjects from the previous study (300/100 mg group: 112 subjects; 300/300 mg group: 113 subjects; placebo group: 32 subjects). All subjects received at least 1 dose of 300 mg of Subutex prolonged-release injection followed by flexible monthly dosing with 100 mg or 300 mg for a total of 12 injections (de novo) or 6 injections (roll-overs); 406 subjects completed the study. Few subjects (2.2 % overall) were withdrawn because of an adverse event. Retention rates after 48 weeks were 50.5% for participants treated with Subutex prolonged-release injection in the randomized, double-blind and the open-label studies combined. In this subgroup retained in the study for 48 weeks, 69.3% were abstinent at the 48-week assessment based on urine sample and self-report of illicit opioid use.

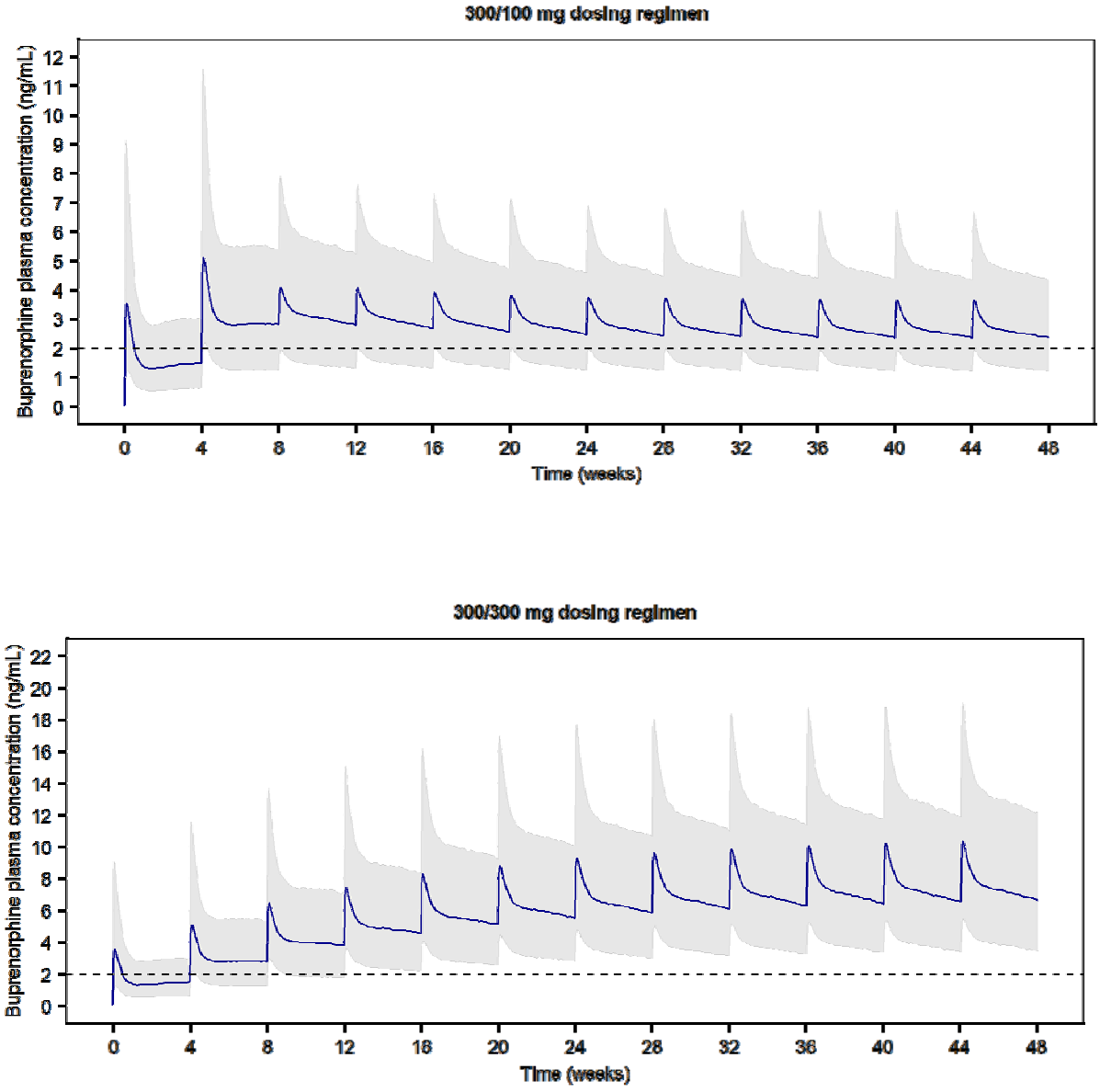
## 5.2 Pharmacokinetic properties

Absorption

After administration of Subutex prolonged-release injection, an initial buprenorphine peak was observed and the median $T_{max}$ occurred at 24 hours after injection. After the initial buprenorphine peak, the plasma buprenorphine concentrations decreased slowly to a plateau.

Steady-state is achieved at 9 months after repeated administrations of 300 mg. When 100 mg is administered after 2 initial doses of 300 mg, steady-state is reached at approximately 4 months and levels close to steady-state are achieved after the second 300-mg dose. Plasma buprenorphine concentration-time profiles after repeated administration are illustrated in figure 1 for each dosing regimen.

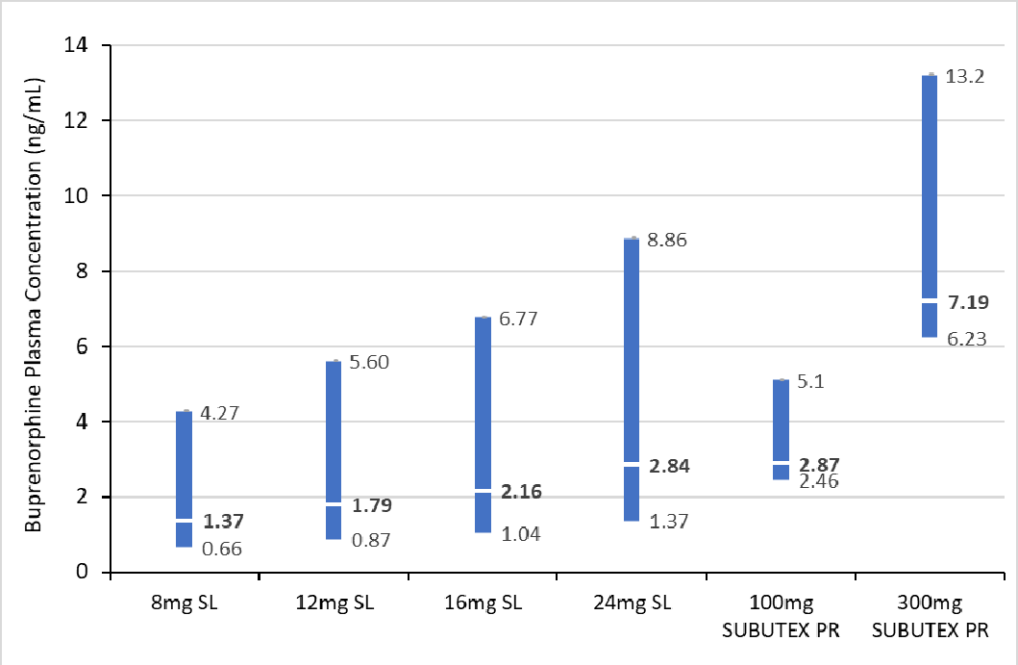
**Figure 1 Plasma buprenorphine concentration-time profiles over the first 12 months of treatment**




Plasma concentrations were derived by pharmacokinetic simulation and summarised at each time point using the median (bold curve) and 90% prediction interval (delineated by the 5th and 95th percentiles). The horizontal dashed line indicates the 2 ng/mL threshold at which opioid drug liking effects are likely to be fully suppressed.

Mean plasma buprenorphine concentrations levels for $C_{avg}$, $C_{max}$ and $C_{trough}$ at steady-state are presented in figure 2 in comparison to transmucosal buprenorphine.

**Figure 2 Comparison of steady-state plasma buprenorphine exposure between transmucosal buprenorphine and Subutex prolonged-release injection at trough ($C_{trough}$), average ($C_{avg}$) and peak ($C_{max}$) levels**




SL: sublingual; PR: prolonged release

Each bar shows the geometric mean for buprenorphine trough concentration (bottom), average plasma concentration (white mark), and peak plasma concentration (top).

Distribution

Buprenorphine is approximately 96 % protein bound, primarily to alpha and beta globulin. The peripheral volume of distribution (Vd/F) has been estimated as 1110 L using population pharmacokinetic modelling.

Biotransformation

Buprenorphine is metabolized to its major metabolite, norbuprenorphine, primarily via cytochrome P450 CYP3A4 and to a lesser extent by CYP2C8. Both buprenorphine and norbuprenorphine are glucuronidated by UGT isoforms. Norbuprenorphine has been found to bind to opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity.

Buprenorphine does not undergo first-pass metabolism following subcutaneous injection of Subutex prolonged-release injection, resulting in a much lower norbuprenorphine-to-buprenorphine AUC ratio (0.20 to 0.40) compared to sublingual buprenorphine (0.70 to 2.11).

Elimination

The apparent terminal plasma half-life of buprenorphine following single-ascending doses (50 to 200 mg) of subcutaneous injection of Subutex prolonged-release

injection ranged between 43 to 60 days as a result of the slow release of buprenorphine from the subcutaneous depot.

Based on population pharmacokinetic modelling, the apparent terminal plasma half-life of buprenorphine following repeated monthly administration in patients (n=570) at clinically-relevant doses (100 and 300 mg) was estimated to be 57 days.

A mass balance study of buprenorphine administered by IV infusion in humans showed complete recovery of radiolabel in urine (30 %) and faeces (69 %) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine were conjugated (buprenorphine: 1 % free and 8.4 % conjugated; norbuprenorphine: 2.7 % free and 8.8 % conjugated). In faeces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine: 33 % free and 4.8 % conjugated; norbuprenorphine: 21 % free and 2.1 % conjugated).

Pharmacokinetics in special patient groups

Based on population pharmacokinetic analyses, age, sex and race did not have a clinically meaningful effect on the pharmacokinetics of Subutex prolonged-release injection

*Elderly*

No pharmacokinetic data in elderly patients (>65 years) are available.

*Paediatric population*

No pharmacokinetic clinical data in paediatrics (<18 years) are available. Simulated buprenorphine exposure data in adolescents aged 16 and 17 years show slightly higher exposure in adolescent than adults after multiple dose administration of both dosing regimens.

*Hepatic Impairment*

Buprenorphine does not undergo first-pass metabolism following subcutaneous injection of Subutex prolonged-release injection.

The effect of hepatic impairment on the pharmacokinetics of Subutex prolonged release injection has not been studied. Based on a study using sublingual tablets (2 mg/0.5 mg buprenorphine/naloxone), plasma buprenorphine exposure was found to be increased by 64% and 181% in subjects with moderate and severe hepatic impairment, respectively, compared to healthy matched subjects.

Subutex prolonged-release injection can be administered to patients with mild or moderate hepatic impairment. Because buprenorphine levels cannot be rapidly lowered following Subutex prolonged-release injection, caution should be exercised in treating patients with pre-existing moderate hepatic impairment. Subutex prolonged-release injection should not be given to patients with pre-existing severe hepatic impairment (see section 4.2 and section 4.3). Patients who develop moderate-to-severe hepatic impairment while being treated with Subutex prolonged-release injection should be monitored for signs and symptoms of toxicity or overdose caused by the increased levels of buprenorphine (see section 4.4).

*Renal Impairment*

Clinical studies of Subutex prolonged-release injection did not include subjects with severe renal impairment. Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine and metabolites. Therefore, no dose modification based on renal function is required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment ($CL_{cr}$ <30 mL/min).

### 5.3 Preclinical safety data

Non-clinical data for Subutex prolonged-release injection reveal no special hazard at human dose levels based on conventional studies of local tolerance, single dose toxicity, repeated dose toxicity, genotoxicity at clinically relevant dose levels of buprenorphine.

In a series of reproduction and developmental studies with Subutex prolonged-release injection administered in a clinically relevant dosing scheme or its excipient administered daily there were no adverse findings at clinically relevant dose levels. Findings at high dose levels were consistent with pharmacological activity of buprenorphine or the known effects of its excipient.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

ATRIGEL delivery system contains

- Poly(DL-lactide-co-glycolide) (50:50)
- *N*-methyl-2-pyrrolidone

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

2 years

## 6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Remove Subutex prolonged-release injection from the refrigerator prior to administration. The product requires at least 15 minutes to reach room temperature. Do not open the foil pouch until the patient has arrived for their injection. Once outside the refrigerator this product may be stored in its original packaging at room temperature (at or below 25°C) for up to 4 weeks prior to administration.

## 6.5 Nature and contents of container

Subutex 300 mg prolonged-release injection is supplied in a sterile 2.25 mL cyclicolefin copolymer syringe with rubber tip cap and stopper, together with a 19 G 16-mm safety needle in a single use pack.

Each assembled syringe with plastic plunger rod is supplied in an aluminium foil-laminate pouch containing an oxygen absorber. The pouch is in a labelled paperboard carton along with a sterile safety needle and labelling.

## 6.6 Special precautions for disposal

**Important Information**

- For abdominal subcutaneous injection only
- Intravascular (intravenous) and intramuscular administration must be avoided
- To be administered by a healthcare professional only
- Make sure that patient undergoes induction and stabilization by initiating a transmucosal buprenorphine-containing product, delivering the equivalent of 8 mg/day to 24 mg/day of buprenorphine for a minimum of 7 days prior to receiving Subutex prolonged-release injection
- Should not be given to patients with pre-existing severe hepatic impairment. Caution should be exercised in treating patient with pre-existing moderate hepatic impairment.
- Subutex prolonged-release injection is not interchangeable with other buprenorphine prolonged-release solutions for injection.
- Any attempts to remove the depot should be monitored throughout treatment.
- In the event the depot must be removed, it can be surgically excised under local anesthesia within 14 days of injection. Due to the expected polymer degradation, this can be done most easily within about 14 days of injection. Patients who have the depot removed should be monitored for signs and symptoms of withdrawal.
- In the event of overdose, consider the potential role and contribution of buprenorphine, other opioids, and other CNS depressant drugs in a patient’s clinical presentation

**Before Administration**

- Please read the instructions carefully before handling the product
- As a universal precaution, always wear gloves
- Remove Subutex prolonged-release injection from the refrigerator prior to administration.
- The product requires at least 15 minutes to reach room temperature. Do not open the foil pouch until the patient has arrived for his or her injection.
- Discard Subutex prolonged-release injection if left at room temperature for longer than 4 weeks.

**After Administration**

- After administration, lock the fold-down needle guard into place by pushing it against a hard surface such as a table.
- Also, a small amount of Subutex prolonged-release injection will remain in the needle and syringe after administration and should be properly disposed of.
- Dispose of all syringe components in a secure sharps disposal container. Any unused medicinal product or waste material should be disposed of in accordance with applicable instructions.

For detailed, stepwise instruction on preparation and administration of Subutex prolonged-release injection, see the document **INFORMATION FOR HEALTHCARE PROFESSIONALS ONLY.**

## 7 MARKETING AUTHORISATION HOLDER

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United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 36699/0009

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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## 10 DATE OF REVISION OF THE TEXT

06/01/2025