**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Zubsolv 0.7 mg/0.18 mg sublingual tablets
Zubsolv 1.4 mg/0.36 mg sublingual tablets
Zubsolv 2.9 mg/0.71 mg sublingual tablets
Zubsolv 5.7 mg/1.4 mg sublingual tablets
Zubsolv 8.6 mg/2.1 mg sublingual tablets
Zubsolv 11.4 mg/2.9 mg sublingual tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zubsolv 0.7 mg/0.18 mg sublingual tablets

Each 0.7 mg/0.18 mg sublingual tablet contains 0.7 mg buprenorphine (as hydrochloride) and 0.18 mg naloxone (as hydrochloride dihydrate).

Zubsolv 1.4 mg/0.36 mg sublingual tablets

Each 1.4 mg/0.36 mg sublingual tablet contains 1.4 mg buprenorphine (as hydrochloride) and 0.36 mg naloxone (as hydrochloride dihydrate).

Zubsolv 2.9 mg/0.71 mg sublingual tablets

Each 2.9 mg/0.71 mg sublingual tablet contains 2.9 mg buprenorphine (as hydrochloride) and 0.71 mg naloxone (as hydrochloride dihydrate).

Zubsolv 5.7 mg/1.4 mg sublingual tablets

Each 5.7 mg/1.4 mg sublingual tablet contains 5.7 mg buprenorphine (as hydrochloride) and 1.4 mg naloxone (as hydrochloride dihydrate).

Zubsolv 8.6 mg/2.1 mg sublingual tablets

Each 8.6 mg/2.1 mg sublingual tablet contains 8.6 mg buprenorphine (as hydrochloride) and 2.1 mg naloxone (as hydrochloride dihydrate).

Zubsolv 11.4 mg/2.9 mg sublingual tablets

Each 11.4 mg/2.9 mg sublingual tablet contains 11.4 mg buprenorphine (as hydrochloride) and 2.9 mg naloxone (as hydrochloride dihydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Sublingual tablet

Zubsolv 0.7 mg/0.18 mg sublingual tablets

A white to off-white, oval tablet, length 6.8 mm and width 4.0 mm, debossed with ".7" on one side.

Zubsolv 1.4 mg/0.36 mg sublingual tablets

A white to off-white, triangular tablet, base 7.2 mm and height 6.9 mm, debossed with "1.4" on one

side.

Zubsolv 2.9 mg/0.71 mg sublingual tablets

A white to off-white, D-shaped tablet, height 7.3 mm and width 5.65 mm, debossed with “2.9” on one side.

Zubsolv 5.7 mg/1.4 mg sublingual tablets

A white to off-white, round tablet, 7 mm in diameter, debossed with “5.7” on one side.

Zubsolv 8.6 mg/2.1 mg sublingual tablets

A white to off-white, diamond shaped tablet, length 9.5 mm and width 8.2 mm, debossed with “8.6” on one side.

Zubsolv 11.4 mg/2.9 mg sublingual tablets

A white to off-white, capsule shaped tablet, length 10.3 mm and width 8.2 mm, debossed with “11.4” on one side.

## 4. CLINICAL PARTICULARS

### 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. Zubsolv 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

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

Zubsolv is not interchangeable with other buprenorphine products, as different buprenorphine products have different bioavailability. Therefore, the dose in mg can differ between products. Once the appropriate dose has been identified for a patient with a specific buprenorphine product, that product should not be exchanged with another product.

If a patient is changed between buprenorphine or buprenorphine and naloxone containing products, dose adjustments may be necessary due to the potential differences in bioavailability (see sections 4.4 and 5.2).

Use of multiples of the three lower dose presentations of Zubsolv to substitute for any of the three higher dose presentations (in for example cases where the higher dose presentations are temporarily not available) is not recommended (see section 5.2).

Precautions to be taken before induction

Prior to treatment initiation, consideration should be given to the type of opioid dependence (i.e. long- or short-acting opioid), the time since last opioid use and the degree of opioid dependence. To avoid precipitating withdrawal, induction with buprenorphine/naloxone or buprenorphine only should be undertaken when objective and clear signs of withdrawal are evident (demonstrated e.g. by

a score indicating mild to moderate withdrawal on the validated Clinical Opioid Withdrawal Scale, COWS).

- For patients dependent upon heroin or short-acting opioids, the first dose of buprenorphine/naloxone must be taken when signs of withdrawal appear, but not less than 6 hours after the patient last used opioids.
- For patients receiving methadone, the dose of methadone must be reduced to a maximum of 30 mg/day before beginning buprenorphine/naloxone therapy. The long half-life of methadone should be considered when starting buprenorphine/naloxone. The first dose of buprenorphine/naloxone should be taken only when 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 upon methadone.

Posology

*Initiation therapy (induction)*
The recommended starting dose in adults and adolescents over 15 years of age is 1.4 mg/0.36 mg or 2.9 mg/0.71 mg a day. An additional Zubsolv 1.4 mg/0.36 mg or 2.9 mg/0.71 mg may be administered on day one depending on the individual patient's requirement.
During the initiation of treatment, daily supervision of dosing is recommended to ensure proper sublingual placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

*Dosage stabilisation and maintenance therapy*
Following treatment induction on day 1, the patient must be rapidly stabilised on an adequate maintenance dose by titrating to achieve a dose that holds the patient in treatment and suppresses opioid withdrawal effects and is guided by reassessment of the clinical and psychological status of the patient. The maximum single daily dose should not exceed 17.2 mg buprenorphine (e.g. given as 11.4 + 5.7 mg, 2 x 8.6 mg or 3 x 5.7 mg).

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

The 0.7 mg/0.18 mg strength is intended to be used to fine tune the dose for patients especially during tapering of treatment or in case of tolerability issues during titration.

Physicians are encouraged to prescribe a single tablet once daily regimen where possible to minimise risk of diversion.

*Less than daily dosing*
After a satisfactory stabilisation has been achieved the frequency of Zubsolv dosing may be decreased to dosing every other day at twice the individually titrated daily dose. In some patients, after a satisfactory stabilisation has been achieved, the frequency of 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.) However, the dose given on any one day should not exceed 17.2 mg buprenorphine. Patients requiring a titrated daily dose > 5.7 mg buprenorphine /day may not find this regimen adequate.

*Medical withdrawal*
After a satisfactory stabilisation has been achieved, if the patient agrees, the dose may be reduced gradually to a lower maintenance dose; in some favourable cases, treatment may be discontinued. The availability of six different tablet strengths supports individual dose titration and tapering. Patients should be monitored following medical withdrawal because of the potential for relapse.

Special populations

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

*Hepatic impairment*
As buprenorphine/naloxone pharmacokinetics may be altered in patients with hepatic impairment, lower initial doses and careful dose titration in patients with mild to moderate hepatic impairment are recommended (see section 5.2). Buprenorphine/naloxone is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2).

*Renal impairment*
Modification of the buprenorphine/naloxone dose is not required in 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*
The safety and efficacy of buprenorphine/naloxone in children below the age of 15 years have not been established. No data are available.

Method of administration

Physicians must warn patients that the sublingual route is the only effective and safe route of administration for this medicinal product (see section 4.4). The tablet is to be placed under the tongue until completely dissolved. Patients should not swallow or consume food or drink until the tablet is completely dissolved.

Zubsolv disintegrates usually within 40 seconds, however it may take 5 to 10 minutes for the patient to feel complete tablet disappearance from the mouth.

If more than one tablet is required, they may be taken all at the same time or in two divided portions; the second portion is to be taken directly after the first portion has dissolved.

## 4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
Severe respiratory insufficiency.
Severe hepatic impairment.
Acute alcoholism or delirium tremens.
Concomitant administration of opioid antagonists (naltrexone, nalmefene) for the treatment of alcohol or opioid dependence.

## 4.4 Special warnings and precautions for use

Misuse, abuse and diversion

Buprenorphine can be misused or abused in a manner similar to other opioids, legal or illicit. Some risks of misusers and abusers include overdose, spread of blood borne viral or localised and systemic 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 medicinal product is distributed for illicit use directly by the intended patient or if the medicinal product is not safeguarded against theft.

Sub-optimal treatment with buprenorphine/naloxone may prompt medicinal product misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with buprenorphine/naloxone may continue responding to uncontrolled withdrawal symptoms by self-

medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines.

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

Combining buprenorphine with naloxone in Zubsolv is intended to deter misuse and abuse of the buprenorphine. Intravenous or intranasal misuse of Zubsolv is expected to be less likely than with buprenorphine alone since the naloxone in Zubsolv can precipitate withdrawal in individual's dependent on heroin, methadone, or other opioid agonists.

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 buprenorphine was used in combination with benzodiazepines (see section 4.5) or when buprenorphine was not used according to the prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and other depressants such as alcohol or other opioids. If buprenorphine is administered to some non-opioid dependent individuals, who are not tolerant to the effects of opioids, potentially fatal respiratory depression may occur.

This medicinal product should be used with care in patients with asthma or respiratory insufficiency (e.g. chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis (curvature of spine leading to potential shortness of breath)).

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

Central Nervous System (CNS) depression

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

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products

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

Dependence

Buprenorphine is a partial agonist at the μ (mu)-opiate receptor and chronic administration produces dependence of the opioid type. Studies in animals, as well as clinical experience, have demonstrated that buprenorphine may produce dependence, but at a lower level than a full agonist e.g. morphine.

Abrupt discontinuation of treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset.

Hepatitis and hepatic events

Cases of acute hepatic injury have been reported in opioid-dependent addicts both in clinical trials and in post marketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases the presence of pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicinal products) and ongoing injecting drug use may have a causative or contributory role. These underlying factors must be taken into consideration before prescribing buprenorphine/naloxone and during treatment.

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

Precipitation of opioid withdrawal syndrome

When initiating treatment with buprenorphine/naloxone, the physician must be aware of the partial agonist profile of buprenorphine and that it can precipitate withdrawal in opioid-dependent patients, particularly if administered less than 6 hours after the last use of heroin or other short-acting opioid, or if administered less than 24 hours after the last dose of methadone. Patients should be clearly monitored during the switching period from buprenorphine or methadone to buprenorphine/naloxone since withdrawal symptoms have been reported.
To avoid precipitating withdrawal, induction with buprenorphine/naloxone should be undertaken when objective signs of withdrawal are evident (see section 4.2).

Withdrawal symptoms may also be associated with sub-optimal 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 in liver, plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment compared with healthy subjects. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and/or buprenorphine.

Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medicinal products (see section 4.5) and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended (see section 4.4).

Zubsolv sublingual tablets should be used with caution in patients with moderate hepatic impairment (see sections 4.2 and 5.2). In patients with severe hepatic insufficiency the use of buprenorphine/naloxone is contraindicated (see section 4.3).

Renal impairment

Renal elimination may be prolonged since 30% of the administered dose is eliminated by the renal route. 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 sections 4.2 and 5.2).

CYP 3A4 inhibitors

Medicinal products that inhibit the enzyme CYP3A4 may give rise to increased concentrations of buprenorphine. A reduction of the buprenorphine/naloxone dose may be needed. Patients already treated with CYP3A4 inhibitors should have their dose of buprenorphine/naloxone titrated carefully since a reduced dose may be sufficient in these patients (see section 4.5).

Class effects
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.

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.

The concomitant use of monoamine oxidase inhibitors (MAOI) might produce an exaggeration of the effects of opioids, based on experience with morphine (see section 4.5).

Changing between buprenorphine containing products

The dose in mg can differ between buprenorphine products and products are not directly interchangeable. Therefore, patients should be monitored when changing between different buprenorphine containing products as differences in bioavailability (see section 5.2) may be noticeable in some individual cases. Dose adjustments may therefore be necessary.

Paediatric population

Use in adolescents (age 15 - <18 years)

Due to the lack of data in adolescents (age 15 - <18 years), patients in this age group should be more closely monitored during treatment.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

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

Zubsolv must not be taken together with:

Zubsolv should not be taken together with:

- Alcoholic drinks or medicinal products containing alcohol, as alcohol increases the sedative effect of buprenorphine (see section 4.7).

Zubsolv should be used cautiously when co-administered with:

- Sedatives such as benzodiazepines or related medicinal products
  The concomitant use of opioids with sedative medicinal products such as benzodiazepines or related medicinal products increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use of sedative medicinal products should be limited (see section 4.4). Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking this medicinal product and should also be cautioned to use benzodiazepines concurrently with this medicinal product only as directed by their physician (see section 4.4).
- The concomitant use of Zubsolv with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).
- Other central nervous system depressants, other opioid derivatives (e.g. methadone, analgesics and antitussives), certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances: these combinations increase central nervous system depression. The reduced level of alertness can make driving and using machines hazardous.
- Furthermore, adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine/naloxone. Therefore the potential to overdose with a full agonist exists, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining
- 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 and nalmefene are opioid antagonists that can block the pharmacological effects of buprenorphine. Co-administration during buprenorphine/naloxone treatment is

contraindicated due to the potentially dangerous interaction that may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms (see section 4.3).

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of buprenorphine/naloxone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Towards the end of pregnancy buprenorphine may induce respiratory depression in the newborn infant even after a short period of administration. Long-term administration of buprenorphine during the last three months of pregnancy may cause a withdrawal syndrome in the neonate (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus or convulsions). The syndrome is generally delayed for several hours to several days after birth.

Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy, to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Furthermore, the use of buprenorphine/naloxone during pregnancy should be assessed by the physician. Buprenorphine/naloxone should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Breast-feeding

It is unknown whether naloxone/metabolites are excreted in human milk. Buprenorphine and its metabolites are excreted in human milk. In rat's buprenorphine has been found to inhibit lactation. Therefore, breastfeeding should be discontinued during treatment with Zubsolv.

Fertility

Animal studies have shown a reduction in female fertility at high doses (systemic exposure > 2.4 times the human exposure at the maximum recommended dose of 17.2 mg buprenorphine, based on AUC) (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Buprenorphine/naloxone has minor to moderate influence on the ability to drive and use machines when administered to opioid dependent patients. This medicinal product 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 sections 4.4 and 4.5).

Patients should be cautioned about driving or operating hazardous machinery in case buprenorphine/naloxone may adversely affect their ability to engage in such activities.

## 4.8 Undesirable effects

Summary of the safety profile

The most commonly reported treatment related adverse reactions reported during the pivotal clinical trials were constipation and symptoms commonly associated with drug withdrawal (i.e. insomnia, headache, nausea, hyperhidrosis and pain). Some reports of seizure, vomiting, diarrhoea, and elevated liver function tests were considered serious.

Tabulated list of adverse reactions

Table 1 summarises adverse reactions reported from pivotal clinical trials in which, 342 of 472 patients (72.5%) reported adverse reactions and adverse reactions reported during post-marketing surveillance.

The frequency of possible adverse reactions listed below is defined using the following convention: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1 000 to <1/100), Rare (≥/10 000 to <1/1 000), Very rare (<1/10 000), Not known (cannot be estimated from available data).

**Table 1: Treatment-related adverse reactions reported in clinical trials and post-marketing surveillance of buprenorphine/naloxone**

| System Organ Class | Very common | Common | Uncommon | Not known |
|---|---|---|---|---|
| *Infections and infestations* | | Influenza<br>Infection<br>Pharyngitis<br>Rhinitis | Urinary tract infection<br>Vaginal infection | |
| *Blood and lymphatic system disorders* | | | Anaemia<br>Leukocytosis<br>Leukopenia<br>Lymphadenopathy<br>Thrombocytopenia | |
| *Immune system disorders* | | | Hypersensitivity | Anaphylactic shock |
| *Metabolism and nutrition disorders* | | | Decreased appetite<br>Hyperglycaemia<br>Hyperlipidaemia<br>Hypoglycaemia | |
| *Psychiatric disorders* | Insomnia | Anxiety<br>Depression<br>Libido decreased<br>Nervousness<br>Thinking abnormal | Abnormal dreams<br>Agitation<br>Apathy<br>Depersonalisation<br>Drug dependence<br>Euphoric mood<br>Hostility | Hallucination |
| *Nervous system disorders* | Headache | Migraine<br>Dizziness<br>Hypertonia | Amnesia<br>Hyperkinesia<br>Seizure | Hepatic encephalopathy<br>Syncope |

| System Organ Class | Very common | Common | Uncommon | Not known |
|---|---|---|---|---|
| | | Paraesthesia<br>Somnolence | Speech disorder<br>Tremor | |
| *Eye disorders* | | Amblyopia<br>Lacrimal disorder | Conjunctivitis Miosis | |
| *Ear and labyrinth disorders* | | | | Vertigo |
| *Cardiac disorders* | | | Angina pectoris<br>Bradycardia<br>Myocardial infarction<br>Palpitations<br>Tachycardia | |
| *Vascular disorders* | | Hypertension<br>Vasodilatation | Hypotension | Orthostatic hypotension |
| *Respiratory, thoracic and mediastinal disorders* | | Cough | Asthma Dyspnoea<br>Yawning | Bronchospasm<br>Respiratory depression |
| *Gastrointestinal disorders* | Constipation<br>Nausea | Abdominal pain Diarrhoea<br>Dyspepsia<br>Flatulence<br>Vomiting | Mouth ulceration<br>Tongue discolouration | Dental caries |
| *Hepatobiliary disorders* | | | | Hepatitis<br>Hepatitis acute<br>Jaundice<br>Hepatic necrosis<br>Hepatorenal syndrome |
| *Skin and subcutaneous tissue disorders* | Hyperhidrosis | Pruritus Rash<br>Urticaria | Acne Alopecia<br>Dermatitis exfoliative<br>Dry skin<br>Skin mass | Angioedema |
| *Musculoskeletal and connective tissue disorders* | | Back pain<br>Arthralgia<br>Muscle spasms<br>Myalgia | Arthritis | |
| *Renal and urinary disorders* | | Urine abnormality | Albuminuria<br>Dysuria<br>Haematuria<br>Nephrolithiasis<br>Urinary retention | |
| *Reproductive system and breast disorders* | | Erectile dysfunction | Amenorrhoea<br>Ejaculation disorder<br>Menorrhagia<br>Metrorrhagia | |
| *General disorders and administration site conditions* | Drug withdrawal syndrome | Asthenia<br>Chest pain<br>Chills<br>Pyrexia<br>Malaise pain | Hypothermia | Drug withdrawal syndrome neonatal |

| System Organ Class | Very common | Common | Uncommon | Not known |
|---|---|---|---|---|
| | | Oedema peripheral | | |
| *Investigations* | | Liver function test abnormal Weight decreased | Blood creatinine increased | Transaminases increased |
| *Injury, poisoning and procedural complications* | | Injury | Heat stroke | |

Description of selected adverse reactions

In cases of intravenous drug misuse, some adverse reactions are attributed to the act of misuse rather than the medicinal product and include 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 drug withdrawal syndrome similar to that associated with naloxone (see sections 4.2 and 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 national reporting system listed in Appendix V.

## 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. Signs of overdose may also include somnolence, amblyopia, miosis, hypotension, nausea, vomiting and/or speech disorders.

Management

General supportive measures should be initiated, including close monitoring of respiratory and cardiac status of the patient. 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.

If the patient vomits, care 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.

If naloxone is used, the long duration of action of buprenorphine should be taken into consideration when determining the length of treatment and medical surveillance needed to reverse the effects of an

overdose. Naloxone can be eliminated more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms, so a continuing infusion may be necessary.

If infusion is not possible, repeated dosing with naloxone may be required. Ongoing intravenous infusion rates should be titrated to patient response.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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

Mechanism of action

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

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

Naloxone is an antagonist at μ-opioid receptors. When administered orally or sublingually in usual doses to patients experiencing opioid withdrawal, naloxone exhibits little or no pharmacological effect because of its almost complete first pass metabolism. However, when administered intravenously to opioid-dependent patients the presence of naloxone in Zubsolv produces marked opioid antagonist effects and opioid withdrawal, thereby deterring intravenous abuse.

Clinical efficacy and safety

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

In a double-blind, double-dummy, parallel-group study comparing buprenorphine ethanolic solution versus a full agonist active control, 162 subjects were randomised to receive the ethanolic sublingual solution of buprenorphine at 8 mg/day (a dose which is roughly comparable to a dose of 12 mg/day of buprenorphine/naloxone), or two relatively low doses of active control, one of which was low enough to serve as an alternative to placebo, during a 3 to10 day induction phase, a 16-week maintenance phase and a 7-week detoxification phase. Buprenorphine was titrated to maintenance dose by Day 3; active control doses were titrated more gradually. Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, buprenorphine was more effective than the low dose of the control, in keeping heroin addicts in treatment and in reducing their use of opioids while in treatment. The effectiveness of buprenorphine, 8 mg per day

was similar to that of the moderate active control dose, but equivalence was not demonstrated.

## 5.2 Pharmacokinetic properties

Zubsolv disintegrates usually within 40 seconds, however it may take 5 to 10 minutes for the patient to feel complete tablet disappearance from the mouth.

Zubsolv sublingual tablets have a higher bioavailability than conventional sublingual tablets. Therefore the dose in mg can differ between products. Zubsolv is not interchangeable with other buprenorphine products.

In comparative bioavailability studies Zubsolv 11.4/2.9 mg displayed equivalent buprenorphine exposure to 16/4mg (2 x 8/2mg) buprenorphine/naloxone administered as conventional sublingual tablets however Zubsolv 2 x 1.4/0.36 mg displayed 20% lower buprenorphine exposure to 2 x 2/0.5 mg buprenorphine/naloxone administered as conventional sublingual tablets. Naloxone exposure was not higher from Zubsolv at any of the tested dose levels.

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.

There are small deviations in buprenorphine dose proportionality exposure parameters as well as deviations from strict compositional proportionality for the three lower strengths (2.9/0.71, 1.4/0.36, and 0.7/0.18 mg) compared to the three higher dose presentations. Therefore, multiples of the three lower dose presentations of Zubsolv should not be used to substitute for any of the three higher dose Zubsolv presentations.

Peak plasma concentrations are achieved approximately 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, although the increase was less than dose-proportional.

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

Buprenorphine is highly lipophilic, which leads to rapid penetration of the blood-brain barrier. Buprenorphine is approximately 96 % protein bound, primarily to alpha and beta globulin.

*Biotransformation*
Buprenorphine is primarily metabolised through -N-dealkylation by liver microsomal CYP3A4. the parent molecule and the primary dealkylated metabolite, norbuprenorphine, undergo subsequent glucuronidation. Norbuprenorphine binds to opioid receptors in vitro; however, it is not known whether norbuprenorphine contributes to the overall effect of buprenorphine/naloxone.

*Elimination*
Elimination of buprenorphine is bi- or tri-exponential, and the a mean terminal elimination half-life from plasma of 32 hours.

Buprenorphine is excreted in the faeces (~70 %) by biliary excretion of the glucuroconjugated metabolites, the rest (~30 %) being eliminated in the urine.

Naloxone

*Absorption*
Following sublingual administration of buprenorphine/naloxone, plasma naloxone concentrations are low and decline rapidly. Naloxone mean peak plasma concentrations were too low to assess dose-proportionality. Naloxone has not been found to affect the pharmacokinetics of buprenorphine.

*Distribution*
Naloxone is approximately 45 % protein bound, primarily to albumin.

*Biotransformation*
Naloxone is metabolised in the liver, primarily by glucuronide conjugation, and excreted in the urine. Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide, as well as N-dealkylation and reduction of the 6-oxo group.

*Elimination*
Naloxone is excreted in the urine, with a mean half-life of elimination from plasma ranging from 0.9 to 9 hours.

Special populations

*Elderly*
No pharmacokinetic data in elderly patients are available.

*Renal impairment*
Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine/naloxone. No dose modification based on renal function is required but caution is recommended when dosing subjects with severe renal impairment (see section 4.4).

*Hepatic impairment*
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study.

Table 2 summarizes the results from a clinical trial in which the exposure after single-dose administration of buprenorphine/naloxone sublingual tablet was determined in healthy subjects, and in subjects with varied degree of hepatic impairment.

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

| PK parameter | Mild hepatic impairment (Child-Pugh Class A) (n=9) | Moderate hepatic impairment (Child-Pugh Class B) (n=8) | Severe hepatic impairment (Child-Pugh Class C) (n=8) |
|---|---|---|---|
| **Buprenorphine** | | | |
| $C_{max}$ | 1.2-fold increase | 1.1-fold increase | 1.7-fold increase |
| $AUC_{last}$ | Similar to control | 1.6-fold increase | 2.8-fold increase |
| | | | |
| **Naloxone** | | | |
| $C_{max}$ | Similar to control | 2.7-fold increase | 11.3-fold increase |

| | | | |
|---|---|---|---|
| $AUC_{last}$ | 0.2-fold decrease | 3.2-fold increase | 14.0-fold increase |

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

### 5.3 Preclinical safety data

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

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

Reproduction studies by oral administration of buprenorphine: naloxone (ratio 1:1) indicated that embryolethality occurred in rats in the presence of maternal toxicity at all doses. The lowest dose studied represented exposure multiples of 1x for buprenorphine and 5 x for naloxone at the maximum human therapeutic dose calculated on a mg/m² basis. No developmental toxicity was observed in rabbits at maternally toxic doses. Further, no teratogenicity has been observed in either rats or rabbits. A peri-postnatal study has not been conducted with buprenorphine/naloxone; however, maternal oral administration of buprenorphine at high doses during gestation and lactation resulted in difficult parturition (possible as a result of the sedative effect of buprenorphine), high neonatal mortality and a slight delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats.

Dietary administration of buprenorphine/naloxone in the rat at dose levels of 500 ppm or greater produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (estimated exposure approximately 2.4 x for buprenorphine at a human dose of 17.2 mg buprenorphine/naloxone based on AUC, plasma levels of naloxone were below the limit of detection in rats) had no adverse effect on fertility in females.

A carcinogenicity study with buprenorphine/naloxone was conducted in rats at doses of 7, 30 and 120 mg/kg/day, with estimated exposure multiples of 3 to75 times, based on a Zubsolv equivalent human daily sublingual dose of 11.4 mg of buprenorphine calculated on a mg/m² basis. Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dose groups.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Mannitol (E 421)
Citric acid (E 330)
Sodium citrate (E 331)
Microcrystalline cellulose
Croscarmellose sodium
Sucralose
Levomenthol
Colloidal anhydrous silica
Sodium stearyl fumarate

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

0.7 mg/0.18 mg

2 years

1.4 mg/0.36 mg

4 years

2.9 mg/0.71 mg

3 years

5.7 mg/1.4 mg

4 years

8.6 mg/2.1 mg

4 years

11.4 mg/2.9 mg

4 years

## 6.4 Special precautions for storage

Store below 25 °C.
Store in the original package in order to protect from moisture.

## 6.5 Nature and contents of container

PVC/oPA/Alu/PVC//Alu/PET/Paper child- resistant blister cards.
Pack size of 7, 28 or 30 sublingual tablets.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

# 7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n
Edifici Est 6ª planta
08039 Barcelona
Spain

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1233/001
EU/1/17/1233/002
EU/1/17/1233/003
EU/1/17/1233/004
EU/1/17/1233/005
EU/1/17/1233/006
EU/1/17/1233/007
EU/1/17/1233/008
EU/1/17/1233/009
EU/1/17/1233/010
EU/1/17/1233/011
EU/1/17/1233/012
EU/1/17/1233/013
EU/1/17/1233/014
EU/1/17/1233/015
EU/1/17/1233/016
EU/1/17/1233/017
EU/1/17/1233/018

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

Date of first authorisation: 10 November 2017
Date of latest renewal: 27 July 2022

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Orexo AB
Virdings allé 22
Uppsala
754 50
Sweden

Accord Healthcare Polska Sp.z o.o.
ul. Lutomierska 50,
95-200 Pabianice,
Poland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to special and restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**PACK OF 7, 28, and 30 TABLETS 0.7 mg / 0.18 mg STRENGTH**

## 1. NAME OF THE MEDICINAL PRODUCT

Zubsolv 0.7 mg/0.18 mg sublingual tablets
buprenorphine/naloxone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 0.7 mg buprenorphine (as hydrochloride) and 0.18 mg naloxone (as hydrochloride dihydrate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Sublingual tablet

7 sublingual tablets
28 sublingual tablets
30 sublingual tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use.
Do not swallow.
Keep the tablet under your tongue until it dissolves.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Zubsolv is not interchangeable with other buprenorphine products.

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
Store in the original package in order to protect from moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n
Edifici Est 6ª planta
08039 Barcelona
Spain

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1233/001 - 30 sublingual tablets
EU/1/17/1233/007 - 7 sublingual tablets
EU/1/17/1233/008 - 28 sublingual tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

ZUBSOLV 0.7 mg/0.18 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**PACK OF 7, 28, and 30 TABLETS 0.7 mg / 0.18 mg STRENGTH**

## 1. NAME OF THE MEDICINAL PRODUCT

Zubsolv 0.7 mg/0.18 mg sublingual tablets
buprenorphine/naloxone

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

Fold here
Tear here

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**PACK OF 7, 28, and 30 TABLETS 1.4 mg / 0.36 mg STRENGTH**

## 1. NAME OF THE MEDICINAL PRODUCT

Zubsolv 1.4 mg/0.36 mg sublingual tablets
buprenorphine/naloxone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 1.4 mg buprenorphine (as hydrochloride) and 0.36 mg naloxone (as hydrochloride dihydrate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Sublingual tablet

7 sublingual tablets
28 sublingual tablets
30 sublingual tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use.
Do not swallow.
Keep the tablet under your tongue until it dissolves.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Zubsolv is not interchangeable with other buprenorphine products.

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
Store in the original package in order to protect from moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n
Edifici Est 6ª planta
08039 Barcelona
Spain

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1233/002 - 30 sublingual tablets
EU/1/17/1233/009 - 7 sublingual tablets
EU/1/17/1233/010 - 28 sublingual tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

ZUBSOLV 1.4 mg/0.36 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**PACK OF 7, 28, and 30 TABLETS 1.4 mg / 0.36 mg STRENGTH**

## 1. NAME OF THE MEDICINAL PRODUCT

Zubsolv 1.4 mg/0.36 mg sublingual tablets
buprenorphine/naloxone

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

Fold here
Tear here

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**PACK OF 7, 28, and 30 TABLETS 2.9 mg / 0.71 mg STRENGTH**

## 1. NAME OF THE MEDICINAL PRODUCT

Zubsolv 2.9 mg/0.71 mg sublingual tablets
buprenorphine/naloxone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 2.9 mg buprenorphine (as hydrochloride) and 0.71 mg naloxone (as hydrochloride dihydrate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Sublingual tablet

7 sublingual tablets
28 sublingual tablets
30 sublingual tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use.
Do not swallow.
Keep the tablet under your tongue until it dissolves.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Zubsolv is not interchangeable with other buprenorphine products.

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
Store in the original package in order to protect from moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n
Edifici Est 6ª planta
08039 Barcelona
Spain

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1233/003 - 30 sublingual tablets
EU/1/17/1233/011 - 7 sublingual tablets
EU/1/17/1233/012 - 28 sublingual tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

ZUBSOLV 2.9 mg/0.71 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**PACK OF 7, 28, and 30 TABLETS 2.9 mg / 0.71 mg STRENGTH**

## 1. NAME OF THE MEDICINAL PRODUCT

Zubsolv 2.9 mg/0.71 mg sublingual tablets
buprenorphine/naloxone

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

Fold here
Tear here

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**PACK OF 7, 28, and 30 TABLETS 5.7 mg / 1.4 mg STRENGTH**

## 1. NAME OF THE MEDICINAL PRODUCT

Zubsolv 5.7 mg/1.4 mg sublingual tablets
buprenorphine/naloxone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 5.7 mg buprenorphine (as hydrochloride) and 1.4 mg naloxone (as hydrochloride dihydrate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Sublingual tablet

7 sublingual tablets
28 sublingual tablets
30 sublingual tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use.
Do not swallow.
Keep the tablet under your tongue until it dissolves.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Zubsolv is not interchangeable with other buprenorphine products.

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
Store in the original package in order to protect from moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n
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08039 Barcelona
Spain

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1233/004 - 30 sublingual tablets
EU/1/17/1233/013 - 7 sublingual tablets
EU/1/17/1233/014 - 28 sublingual tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

ZUBSOLV 5.7 mg/1.4 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**PACK OF 7, 28, and 30 TABLETS 5.7 mg / 1.4 mg STRENGTH**

## 1. NAME OF THE MEDICINAL PRODUCT

Zubsolv 5.7 mg/1.4 mg sublingual tablets
buprenorphine/naloxone

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

Fold here
Tear here

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**PACK OF 7, 28, and 30 TABLETS 8.6 mg / 2.1 mg STRENGTH**

## 1. NAME OF THE MEDICINAL PRODUCT

Zubsolv 8.6 mg/2.1 mg sublingual tablets
buprenorphine/naloxone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 8.6 mg buprenorphine (as hydrochloride) and 2.1 mg naloxone (as hydrochloride dihydrate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Sublingual tablet

7 sublingual tablets
28 sublingual tablets
30 sublingual tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use.
Do not swallow.
Keep the tablet under your tongue until it dissolves.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Zubsolv is not interchangeable with other buprenorphine products.

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
Store in the original package in order to protect from moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n
Edifici Est 6ª planta
08039 Barcelona
Spain

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1233/005 - 30 sublingual tablets
EU/1/17/1233/015 - 7 sublingual tablets
EU/1/17/1233/016 - 28 sublingual tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

ZUBSOLV 8.6 mg/2.1 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**PACK OF 7, 28, and 30 TABLETS 8.6 mg / 2.1 mg STRENGTH**

## 1. NAME OF THE MEDICINAL PRODUCT

Zubsolv 8.6 mg/2.1 mg sublingual tablets
buprenorphine/naloxone

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

Fold here
Tear here

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**PACK OF 7, 28, and 30 TABLETS 11.4 mg / 2.9 mg STRENGTH**

## 1. NAME OF THE MEDICINAL PRODUCT

Zubsolv 11.4 mg/2.9 mg sublingual tablets
buprenorphine/naloxone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 11.4 mg buprenorphine (as hydrochloride) and 2.9 mg naloxone (as hydrochloride dihydrate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Sublingual tablet

7 sublingual tablets
28 sublingual tablets
30 sublingual tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use.
Do not swallow.
Keep the tablet under your tongue until it dissolves.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Zubsolv is not interchangeable with other buprenorphine products.

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
Store in the original package in order to protect from moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n
Edifici Est 6ª planta
08039 Barcelona
Spain

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1233/006 - 30 sublingual tablets
EU/1/17/1233/017 - 7 sublingual tablets
EU/1/17/1233/018 - 28 sublingual tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

ZUBSOLV 11.4 mg/2.9 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**PACK OF 7, 28, and 30 TABLETS 11.4 mg / 2.9 mg STRENGTH**

## 1. NAME OF THE MEDICINAL PRODUCT

Zubsolv 11.4 mg/2.9 mg sublingual tablets
buprenorphine/naloxone

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

Fold here
Tear here

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Zubsolv 0.7 mg/0.18 mg sublingual tablets**
**Zubsolv 1.4 mg/0.36 mg sublingual tablets**
**Zubsolv 2.9 mg/0.71 mg sublingual tablets**
**Zubsolv 5.7 mg/1.4 mg sublingual tablets**
**Zubsolv 8.6 mg/2.1 mg sublingual tablets**
**Zubsolv 11.4 mg/2.9 mg sublingual tablets**
buprenorphine/naloxone

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


1. What Zubsolv is and what it is used for
2. What you need to know before you take Zubsolv
3. How to take Zubsolv
4. Possible side effects
5. How to store Zubsolv
6. Contents of the pack and other information


## 1. What Zubsolv is and what it is used for

Zubsolv contains the active substances buprenorphine and naloxone. Zubsolv is used to treat dependence on opioid (narcotic) drugs such as heroin or morphine in drug addicts who have agreed to be treated for their addiction. Zubsolv is used in adults and adolescents over 15 years of age, who are also receiving medical, social and psychological support.

**How Zubsolv works**
The tablet contains buprenorphine which is responsible for the treatment of opioid (narcotic) dependence. It also contains naloxone which is used to deter intravenous abuse of the product.

## 2. What you need to know before you take Zubsolv

**Do not take Zubsolv if you:**
- are allergic to buprenorphine, naloxone or any of the other ingredients of this medicine (listed in section 6)
- have **serious breathing problems**
- have **serious liver problems**
- are intoxicated due to alcohol or have trembling, sweating, anxiety, confusion, or hallucinations caused by alcohol
- are taking naltrexone or nalmefene for the treatment of alcohol or opioid dependence

**Warnings and precautions**

- **Misuse, abuse and diversion**

Serious cases of infections with potential fatal outcome may occur if Zubsolv is misused, by taking it intravenously.
This medicine can be a target for people who abuse prescription medicines, and should be kept in a safe place to protect it from theft (see section 5). Do not give this medicine to anyone else. It can cause death or otherwise harm them.

- **Breathing problems** (see also 'Do not take Zubsolv' above )

Some people have died from respiratory failure (inability to breathe) because they misused this medicine or took it in combination with other central nervous system depressants, such as alcohol, benzodiazepines (tranquilisers), or other opioids.

This medicine should be used with care in patients with pre-existing breathing problems

This medicine may cause severe, possibly fatal, respiratory depression (reduced ability to breathe) in children and non-opioid dependent people who accidentally or deliberately take it.

- **Drowsiness**

This medicine can cause drowsiness, particularly when taken together with alcohol or other central nervous system depressants (such as tranquilisers, sedatives or hypnotics).

- **Dependence**

This medicine can cause dependence.

- **Liver damage**

Liver damage has been reported after taking buprenorphine/naloxone, especially when the medicine is misused. This could also be due to viral infections (chronic hepatitis C), alcohol abuse, anorexia or use of other medicines that can harm your liver (see section 4). Regular blood tests may be conducted by your doctor to monitor the condition of your liver. **Tell your doctor if you have any liver problems before you start treatment with Zubsolv.**

- **Withdrawal symptoms**

This medicine can cause withdrawal symptoms if you take it less than six hours after you use a short-acting opioid (e.g. morphine, heroin) or less than 24 hours after you use a long-acting opioid such as methadone.

Zubsolv can also cause withdrawal symptoms if you stop taking it abruptly.

- **Blood pressure**

This medicine may cause your blood pressure to drop suddenly, causing you to feel dizzy if you get up too quickly from sitting or lying down.

- **Sleep-related breathing disorders**

Zubsolv can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

- **Children and adolescents**

You may be more closely monitored by your doctor if you are below the age of 18. This medicine should not be taken by those under 15 years of age.

- **Diagnosis of unrelated medical conditions**

This medicine may mask pain symptoms that could assist in the diagnosis of some diseases. Do not forget to advise your doctor if you take this medicine.

**Talk to your doctor before taking Zubsolv** if you:

- have a depression or other conditions that are treated with antidepressants. The use of these medicines together with Zubsolv can lead to serotonin syndrome, a potentially life-threatening condition (see "Other medicines and Zubsolv")
- have kidney problems
- have recently suffered a head injury or brain disease
- have low blood pressure, enlarged prostate gland or difficulties passing water because of narrowing of the urethra
- have under-active thyroid gland which can cause tiredness or weight gain
- have poor adrenal gland function (e.g. Addison's disease)
- have problems with the biliary tract (e.g. gall bladder, bile duct)
- are elderly
- are debilitated

**Other medicines and Zubsolv**

Tell your doctor if you are taking, have recently taken or might take any other medicines. Some medicines may increase the side effects of Zubsolv and may sometimes cause very serious reactions. Do not take any other medicines whilst taking Zubsolv without first talking to your doctor, especially:

- anti-depressants such as **moclobemide, tranylcypromine, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, amitriptyline, doxepine, or trimipramine**. These medicines may interact with Zubsolv and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, hallucinations, coma, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C. Contact your doctor when experiencing such symptoms.
- **Naltrexone and nalmefene** (drugs used to treat addictive disorders) as they may prevent the therapeutic effects of Zubsolv. They must not be taken at the same time as Zubsolv treatment because you may experience a sudden onset of prolonged and intense withdrawal.
- **Benzodiazepines** (used to treat anxiety or sleep disorders) such as diazepam, temazepam, alprazolam. Concomitant use of Zubsolv and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible. However if your doctor does prescribe Zubsolv together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor. Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.
- Gabapentin or pregabalin to treat epilepsy or pain due to nerve problems (neuropathic pain)
- **Other medicines that may make you feel sleepy** which are used to treat illnesses such as anxiety, sleeplessness, convulsions/seizures, pain and other mental disorders. These types of medicines will reduce your alertness levels making it dangerous for you to drive and use machines. They may also cause central nervous system depression, which is very serious. Below is a list of examples of these types of medicines:
  - other opioid containing medicines such as methadone, certain pain killers and cough suppressants
  - some anti-depressants (used to treat depression) such as isocarboxazid, phenelzine, selegiline, tranylcypromine, valproate and monoamine oxidase inhibitors (MAOIs) may increase the effects of this medicine
  - sedative $H_1$ receptor antagonists (used to treat allergic reactions) such as

diphenhydramine and chlorphenamine
  - barbiturates (used to cause sleep or sedation) such as phenobarbital, secobarbital
  - tranquilisers (used to cause sleep or sedation) such as chloral hydrate
  - clonidine (used to treat high blood pressure) and related medicines may extend the effects of this medicine
- anti-retrovirals (used to treat HIV) such as ritonavir, nelfinavir, indinavir may increase the effects of this medicine
- some antifungal agents (used to treat fungal infections) such as ketoconazole, itraconazole and certain antibiotics, may extend the effects of this medicine
- some medicines may decrease the effect of Zubsolv. These include medicines used to treat epilepsy (such as carbamazepine and phenytoin), and medicines used to treat tuberculosis (rifampicin)

**Zubsolv with food, drink and alcohol**
Alcohol may increase drowsiness and may increase the risk of respiratory failure if taken with Zubsolv. **Do not take Zubsolv together with alcohol.** Do not swallow or consume food or any drink until the tablet is completely dissolved.

**Pregnancy and breast-feeding**
The risks of using Zubsolv in pregnant women are not known. Tell your doctor if you are pregnant or intend to become pregnant. Your doctor will decide if your treatment should be continued with an alternative medicine.
When taken during pregnancy, particularly late pregnancy, medicines like Zubsolv may cause drug withdrawal symptoms including problems with breathing in your newborn baby. This may appear several days after birth.

Do not breast-feed whilst taking this medicine, since Zubsolv passes into breast milk. Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**
Zubsolv may cause drowsiness, dizziness or impair your thinking. This may happen more often in the first few weeks of treatment when your dose is being changed, but can also happen if you drink alcohol or take other sedative medicines when you take Zubsolv. Do not drive, use any tools or machines, or perform dangerous activities until you know how this medicine affects you.

**Zubsolv contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

## 3. How to take Zubsolv

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your treatment is prescribed and monitored by doctors who are experienced in the treatment of drug dependence.

Your doctor will determine the best dose for you. During your treatment, the doctor may adjust the dose, depending upon your response.

**Starting treatment**
The recommended starting dose for adults and adolescents over the age of 15 years is:

- one tablet of Zubsolv 1.4 mg/0.36 mg each day, or

- one tablet of Zubsolv 2.9 mg/0.71 mg each day

An additional tablet of the Zubsolv 1.4 mg/0.36 mg or 2.9 mg/0.71 mg may be administered on Day 1 depending on your needs.

There are other strengths that are available to be used by your doctor who will decide what is the best treatment for you. This may involve taking a combination of different strengths, but your daily dose should not exceed 17.2 mg of buprenorphine.

Clear signs of withdrawal should be evident before taking your first dose of Zubsolv. A doctor's assessment of your readiness for treatment will guide the timing of your first Zubsolv dose.

- Starting treatment of Zubsolv whilst dependent on heroin:

If you are dependent upon heroin or a short acting opioid, your first dose of Zubsolv should be taken when signs of withdrawal appear, but not less than 6 hours after you last used opioids

- Starting treatment of Zubsolv whilst dependent on methadone:

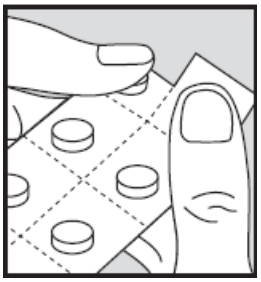
If you have been taking methadone or a long acting opioid, the dose of methadone should ideally be reduced to below 30 mg/day before beginning Zubsolv therapy. The first dose of Zubsolv should be taken when signs of withdrawal appear, but not less than 24 hours after you last used methadone

**Taking Zubsolv**

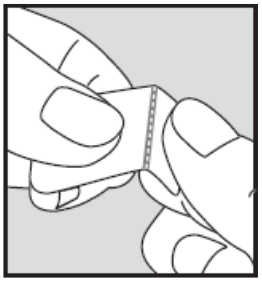
- Take the dose once a day or as advised by your doctor.
- Remove the tablet as described below. Only open the blister immediately before taking the dose. Never open in advance as the tablet is sensitive to moisture.
- Place the tablets under the tongue
- Keep the tablets in place under the tongue until they have completely dissolved
- Do not chew or swallow the tablets, as the medicine will not work and you may get withdrawal symptoms
- Do not consume any food or drink until the tablets have completely dissolved. Whilst you may notice that most of the table disintegrates within 40 seconds, it may take 5 to 10 minutes for the entire table to disappear from your mouth

**How to remove the tablet from the blister**

1. Do not push the tablet through the foil.



2. Remove just one section from the blister pack, tearing it along the perforated line.



3. Fold the packet along the dotted line.

4. Tear following the direction of the arrow. If the blister is damaged, discard the tablet.

**Dose adjustment and maintenance therapy**
Your doctor may increase the dose of Zubsolv you take according to your needs. If you feel that the effect of Zubsolv is too strong or too weak, talk to your doctor or pharmacist. The maximum daily dose is 17.2 mg.

After a period of successful treatment, you may agree with your doctor to reduce the dose gradually to a lower maintenance dose.

**Stopping treatment**
Do not change the treatment in any way or stop treatment without the agreement of the doctor who is treating you.

Depending on your condition, the dose of Zubsolv may continue to be reduced under careful medical supervision, until eventually it may be stopped.

**If you take more Zubsolv than you should**
If you or someone else takes too much of this medicine, you must go or be taken immediately to an emergency centre or hospital for treatment as **overdose** with Zubsolv may cause serious and life-threatening breathing problems.

Symptoms of overdose may include breathing more slowly and weakly than normal, feeling more sleepy than normal, reduction in the size of the pupils, low blood pressure, feeling sick, vomit and/or slurred speech.

**If you forget to take Zubsolv**
Tell your doctor as soon as possible if you miss a dose.

**If you stop taking Zubsolv**
Do not change the treatment in any way or stop treatment without the agreement of the doctor who is treating you. **Stopping treatment suddenly may cause withdrawal symptoms.**

If you have any further questions on the use of this product, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Tell your doctor immediately or seek urgent medical attention** if you experience serious side effects, such as:

- swelling of the face, lips, tongue or throat which may cause difficulty in swallowing or breathing, severe hives/nettle rash. These may be signs of a life-threatening allergic reaction
- feeling sleepy and uncoordinated, have blurred vision, have slurred speech, cannot think well or clearly, or your breathing gets much slower than is normal for you
- severe tiredness, itching with yellowing of skin or eyes. These may be symptoms of liver damage
- seeing or hearing things that are not there (hallucinations)

**Other side effects**

**Very common side effects** (may affect more than one in 10 people):

- insomnia (inability to sleep)
- headache
- constipation, nausea
- excessive sweating
- drug withdrawal syndrome

**Common side effects** (may affect up to 1 in 10 people):

- flu-like symptoms, infection, sore throat and painful swallowing, runny nose
- anxiety, depression, decreased sexual drive, nervousness, abnormal thinking
- migraines, dizziness, fainting, increase in muscle tension, tingling, drowsiness
- increased tearing (watering eyes) or other tearing disorder, blurred vision
- increased blood pressure, flushing
- increased cough
- abdominal pain, upset stomach or other stomach discomfort, diarrhoea, flatulence, vomiting
- rash, itching, hives
- back pain, joint pain, muscle pain, leg cramps (muscle spasm)
- urine abnormality
- difficulty in getting or keeping an erection
- weakness, chest pain, chills, fever, feeling of general discomfort, pain, swelling (hands and feet)
- abnormal liver function, weight loss
- accidental injury caused by loss of alertness or co-ordination

**Uncommon side effects** (may affect up to 1 in 100 people):

- abnormal blood tests, swollen glands (lymph nodes)
- abnormal dreams, agitation, loss of interest, depersonalisation (not feeling like yourself), medicine dependence, exaggerated feeling of well-being, feelings of hostility
- amnesia (memory disturbance), convulsion (fits), speech disorder, tremor
- eye inflammation or infection, small pupil size
- rapid or slow heartbeat, myocardial infarction (heart attack), palpitations, chest tightness
- low blood pressure
- asthma, shortness of breath, yawning
- pain and sores in mouth, tongue discolouration
- acne, hair loss, dry or scaling skin, skin nodule
- inflammation of joints
- protein in your urine, urinary tract infection, difficulty urinating, painful or difficult

urination, blood in urine, kidney stone
- menstrual or vaginal problems, abnormal ejaculation
- sensitivity to heat or cold
- heat stroke
- excessive muscle activity
- loss of appetite

**Not known** (frequency cannot be estimated from the available data):
- slow or difficult breathing
- dental caries
- liver injury with or without jaundice
- hallucinations
- swelling of face and throat or life threatening allergic reactions
- drop in blood pressure on changing position from sitting or lying down to standing
- sudden withdrawal syndrome caused by taking product too soon after use of illicit opioids,
- drug withdrawal syndrome in newborn babies

Misusing this medicine by injecting it can cause withdrawal symptoms, infections, other skin reactions and potentially serious liver problems (see section 2, Warnings and precautions).

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Zubsolv

Keep this medicine out of the sight and reach of children. **It can cause serious harm and be fatal to people who may take this medicine by accident, or intentionally when it has not been prescribed for them.**

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Store below 25 °C.
Store in the original package in order to protect from moisture.

Zubsolv can be a target for people who abuse prescription medicine. Keep this medicine in a safe place to protect it from theft.

Store the blister safely.

Never open the blister in advance.

Do not take this medicine in front of children.

An emergency unit should be contacted immediately in case of accidental ingestion or suspicion of ingestion.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Zubsolv contains

The active substances are buprenorphine and naloxone.

Each 0.7 mg/0.18 mg sublingual tablet contains 0.7 mg buprenorphine (as hydrochloride) and 0.18 mg naloxone (as hydrochloride dihydrate).

Each 1.4 mg/0.36 mg sublingual tablet contains 1.4 mg buprenorphine (as hydrochloride) and 0.36 mg naloxone (as hydrochloride dihydrate).

Each 2.9 mg/0.71 mg sublingual tablet contains 2.9 mg buprenorphine (as hydrochloride) and 0.71 mg naloxone (as hydrochloride dihydrate).

Each 5.7 mg/1.4 mg sublingual tablet contains 5.7 mg buprenorphine (as hydrochloride) and 1.4 mg naloxone (as hydrochloride dihydrate).

Each 8.6 mg/2.1 mg sublingual tablet contains 8.6 mg buprenorphine (as hydrochloride) and 2.1 mg naloxone (as hydrochloride dihydrate).

Each 11.4 mg/2.9 mg sublingual tablet contains 11.4 mg buprenorphine (as hydrochloride) and 2.9 mg naloxone (as hydrochloride dihydrate).

The other ingredients are mannitol, citric acid, sodium citrate, microcrystalline cellulose, croscarmellose sodium, sucralose, levomenthol, colloidal anhydrous silica and sodium stearyl fumarate (see section 2 "Zubsolv contains sodium").

### What Zubsolv looks like and contents of the pack

Zubsolv is available in six different strengths, differentiated by shape and debossing:

| **Zubsolv tablet strength** (buprenorphine/naloxone) | **Zubsolv tablet description** | **Zubsolv tablet debossing** | **Appearance** |
|---|---|---|---|
| 0.7 mg/0.18 mg | A white to off-white, oval tablet, length 6.8 mm and width 4.0 mm | ".7" on one side |  |
| 1.4 mg/0.36 mg | A white to off-white, triangular tablet, base 7.2 mm and height 6.9 mm | "1.4" on one side |  |
| 2.9 mg/0.71 mg | A white to off-white, D-shaped tablet, height 7.3 mm and width 5.65 mm | "2.9" on one side |  |
| 5.7 mg/1.4 mg | A white to off-white, round tablet, 7 mm in diameter | "5.7" on one side |  |
| 8.6 mg/2.1 mg | A white to off-white, diamond shaped tablet, length 9.5 mm and width 8.2 mm | "8.6" on one side |  |

| | | | |
|---|---|---|---|
| 11.4 mg/2.9 mg | A white to off-white, capsule shaped tablet, length 10.3 mm and width 8.2 mm | "11.4" on one side |  |

Zubsolv is available in blisters of 7, 28 or 30 sublingual tablets.
Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n
Edifici Est 6ª planta
08039 Barcelona
Spain

**Manufacturer**
Orexo AB
Virdings allé 22
Uppsala 754 50
Sweden

Accord Healthcare Polska Sp.z o.o.
ul. Lutomierska 50,
95-200 Pabianice,
Poland

**This leaflet was last revised in MM/YYYY.**

Detailed information on this medicine is available on the European Medicines Agency web site:
https://www.ema.europa.eu.