Prescribing Information

Please refer to the Summary of Product Characteristics (SmPC) before prescribing **Zubsolv (buprenorphine, naloxone) 0.7 mg/0.18 mg; 1.4 mg/0.36 mg; 2.9 mg/0.71 mg; 5.7 mg/1.4 mg; 8.6 mg/2.1 mg; 11.4 mg/2.9 mg Sublingual Tablets.**

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Presentation: Each sublingual tablet contains 0.7 mg/0.18 mg, 1.4 mg/0.36 mg, 2.9 mg/0.71 mg, 5.7 mg/1.4 mg, 8.6 mg/2.1 mg, 11.4 mg/2.9 mg buprenorphine (as hydrochloride)/naloxone (as hydrochloride dihydrate) respectively. **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. **Dosage and 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. 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. 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 preparations are temporarily not available) is not recommended. *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. 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. *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 supresses 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. 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, see SmPC. 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 dosage 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. *Elderly & paediatric population:* The safety and efficacy of buprenorphine/naloxone in elderly patients over 65 years of age, and in children below the age of 15 years, 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. Buprenorphine/naloxone is contraindicated in patients with severe hepatic impairment. *Renal impairment:* Modification of 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). *Method of administration:* Physicians must warn patients that the sublingual route is the only effective and safe route of administration for this medicinal product. 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. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. 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. **Warnings and Precautions:** 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 it 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 underdosed 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 avoiding prescribing multiple refills early in treatment, and conducting patient follow-up visits with clinical monitoring that is appropriate for 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 this medicinal product 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 deaths due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines 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. 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. *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. 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. *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. 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-opiate receptor and chronic administration produces dependence of the opioid type. Studies in animals, as well as clinical experience has 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 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. *Hepatic impairment:* Both buprenorphine and naloxone are extensively metabolised in the liver, and 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 and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended. Zubsolv sublingual tablets should be used with caution in patients with moderate hepatic impairment. In patients with severe hepatic insufficiency the use of buprenorphine/naloxone is contraindicated. *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). *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. *CYP3A4 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. *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. *Changing between buprenorphine containing products:* The dose in mg can differ between buprenorphine products and products are not directly interchangeable. Patients should be monitored when changing between different buprenorphine containing products as differences in bioavailability may be noticeable in some individual cases. Dose adjustments may therefore be necessary. Contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'. *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 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. Patients should be cautioned about driving or operating hazardous machinery. **Pregnancy & Lactation:** *Pregnancy:* There are no or limited amount of data from the use of buprenorphine/naloxone in pregnant women. 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 withdrawal syndrome in the neonate (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 and used only if the potential benefit outweighs the potential risk to the foetus. *Breast-feeding:* Buprenorphine and its metabolites are excreted in human milk. In rats, buprenorphine has been found to inhibit lactation. Therefore, breastfeeding should be discontinued during treatment with Zubsolv. **Adverse Events include:** ***Adverse events which could be considered serious include:*** *Common:* Diarrhoea, vomiting, erectile dysfunction. *Uncommon:* Leukopenia, thrombocytopenia, drug dependence, seizure, angina pectoris, bradycardia, myocardial infarction, dermatitis exfoliative, nephrolithiasis, urinary retention, hypothermia. *Not known:* Anaphylactic shock, hallucination, hepatic encephalopathy, syncope, respiratory depression, hepatitis, hepatitis acute, hepatic necrosis, hepatorenal syndrome, angioedema, elevated liver function tests, local reactions -sometimes septic (abscess, cellulitis), infections (such as pneumonia, endocarditis). *Other Very Common adverse events:* Insomnia, headache, constipation, nausea, hyperhidrosis, drug withdrawal syndrome. *Other Common adverse events:* Influenza, amblyopia, pharyngitis, rhinitis, anxiety, depression, libido decreased, nervousness, thinking abnormal, migraine, dizziness, hypertonia, paraesthesia, somnolence, lacrimal disorder, hypertension, vasodilation, cough, abdominal pain, dyspepsia, flatulence, pruritus, rash, urticaria, back pain, arthralgia, muscle spasms, myalgia, urine abnormality, asthenia, chest pain, chills, pyrexia, malaise pain, oedema peripheral, liver function test abnormal, weight decreased, injury. *Other Uncommon adverse events:* Urinary tract infection, vaginal infection, anaemia, leukocytosis, lymphadenopathy, hypersensitivity, decreased appetite, hyperglycaemia, hyperlipidaemia, hypoglycaemia, abnormal dreams, agitation, apathy, depersonalisation, euphoric mood, hostility, amnesia, hyperkinesia, speech disorder, tremor, conjunctivitis miosis, palpitations, tachycardia, hypotension, asthma, dyspnoea, yawning, mouth ulceration, tongue discolouration, acne, alopecia, dry skin, skin mass, arthritis, albuminuria, dysuria, haematuria, amenorrhoea, ejaculation disorder, menorrhagia, metrorrhagia, blood creatinine increased, heat stroke. See SmPC for details of other adverse events. **Shelf life:** 0.7 mg / 0.18 mg - 2 years, 2.9 mg / 0.71 mg -3 years, 1.4 mg / 0.36 mg; 5.7 mg / 1.4 mg; 8.6 mg / 2.1 mg; 11.4 mg / 2.9 mg – 4 years. Store below 25°C. **Pack sizes:** 28

tablets. **Marketing Authorisation Holder:** Accord Healthcare S.L.U., World Trade Center Moll de Barcelona, s/n, Edifici Est 6ª planta, 08039 Barcelona, Spain. **Marketing Authorisation Numbers:** EU/1/17/1233/001-018. **Legal Category:** POM. Full prescribing information including the SmPC is available on request from Accord Healthcare Ltd, Euro House, Little Island, Co. Cork. Tel: 021-4619040 or www.accord-healthcare.com/ie/products. Adverse events should be reported directly to HPRA Pharmacovigilance, website: www.hpra.ie, e-mail: medsafety@hpra.ie. Adverse reactions can also be reported to **Medical Information at Accord Healthcare Ltd. via e-mail:** medinfo@accord-healthcare.com **or Tel:** +44(0)1271385257.

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