Part VI: Summary of the Risk Management Plan

This is a summary of the RMP for SUBUTEX. The RMP details important risks of SUBUTEX, how these risks can be minimised, and how more information will be obtained about the SUBUTEX risks and uncertainties (missing information).

The product information for SUBUTEX provides essential information to healthcare professionals and patients on how SUBUTEX must be used.

Important new concerns or changes to the current concerns will be included in updates of the SUBUTEX RMP.

I. The Medicine and What it is Used For

SUBUTEX is indicated for the treatment of opioid dependence.

It is recommended that SUBUTEX treatment be prescribed as part of comprehensive management for opioid drug dependence.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of SUBUTEX, with measures to minimise such risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the product label addressed to patients and healthcare professionals.
- It can include important advice on the medicine's packaging.
- The authorised pack size and the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status, the way a medicine is supplied to the patient (e.g. with or without prescription), can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine PhV activities.

If important information that may affect the safe use of SUBUTEX is not yet available, it is listed under missing information below.

II.A List of important risks and missing information

Important risks of SUBUTEX are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SUBUTEX. Potential risks are

concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 15: List of Important Risks and Missing Information for SUBUTEX

Important identified risks	• Fatal overdose (including severe respiratory failure [mechanism for death by overdose]) • Respiratory depression/respiratory failure • Misuse and/or abuse (injection/intranasal) • Paediatric intoxication • Hepatitis, hepatic events, use in patients with hepatic impairment • Use during Pregnancy, and lactation (effects on newborn and infant) • CNS depression
Important potential risks	• Medication errors when switching between SUBUTEX/SUBOXONE and new buprenorphine-containing products (BCP) which are not interchangeable with SUBUTEX/SUBOXONE
Missing information	• Use in children/adolescents < 15 years old • Use in elderly patients (≥ 65 years old)

II.B Summary of Important Risks

Table 16: Summary of Important Risks

Fatal Overdose (including severe respiratory failure [mechanism for death by overdose])	
Evidence for linking the risk to the medicine	Section 4.4 of the SUBUTEX CCDS states that a number of cases of death due to respiratory depression have been reported, particularly when SUBUTEX was used in combination with benzodiazepines, when high dose buprenorphine was administered to non-opioid dependent individuals who had not developed a tolerance to the effects of opioids, or when buprenorphine was otherwise not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and other CNS depressants. Section 4.5 of the SUBUTEX CCDS states that a combination with benzodiazepines may result in death due to respiratory depression of central origin; which could lead to respiratory arrest and death. From the overdose study (PE-US003), recent figures at the EMCDDA recorded no buprenorphine-associated deaths in Denmark in their 2008-2011 reports. In Sweden, the fatal cases related to buprenorphine 15% had a filled prescription with SUBUTEX or SUBOXONE, 22% of the fatal methadone cases had filled prescription with methadone. The correlation between a fatal case related to buprenorphine and a filled prescription with SUBUTEX and SUBOXONE was hence relatively low and most of the

	subjects who died from a fatal overdose death by buprenorphine had obviously obtained the drug illegally.
Risk factors and risk groups	Patients abusing buprenorphine, especially IV abusers, polysubstance abusers, combining the use of buprenorphine with alcohol, benzodiazepines, and other drugs, are at high risk for overdose and associated respiratory depression. In substance-abuse treatment, SUBUTEX should be used with caution in patients with compromised respiratory function (e.g. chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis). Severe alcohol intoxication, alcohol withdrawal syndrome, and *delirium tremens* are associated with the risk of respiratory depression.
Risk minimisation measures	Routine risk minimisation measures: Supervised substance-abuse treatment on risk of death from SUBUTEX overdose is a major tool preventing overdose in SUBUTEX abusers. To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing buprenorphine, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability. Buprenorphine should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis). Patients with the physical and/or pharmacological risk factors above should be monitored, and dose reduction may be considered. Additional risk minimisation measures: None
Respiratory Depression/Respiratory Failure	
Evidence for linking the risk to the medicine	Section 4.4 of the SUBUTEX CCDS states that a number of cases of death due to respiratory depression have been reported, particularly when SUBUTEX was used in combination with benzodiazepines, when high dose buprenorphine was administered to opioid non-dependent individuals who had not developed tolerance to the effects of opioids, or when buprenorphine was otherwise not used according to prescribing information. Section 4.5 of the SUBUTEX CCDS states that a combination with benzodiazepines may result in death due to respiratory depression of central origin; which could lead to respiratory arrest and death. A case of respiratory arrest occurred during a clinical study (CR96/005) in which the patient severely overdosed on heroin and oxazepam that lead to the event of respiratory arrest. This case was considered possibly related to SUBUTEX.
Risk factors and risk groups	The risk for CNS depression is increased in patients who are on prescription medications for anxiety/depression and those with habitual alcohol intake. Risk factors for developing respiratory failure includes smoking tobacco products, excessive alcohol intake, a family history of

	respiratory disease or conditions, injury to the spine, brain, or chest, and immunocompromised patients (Macon 2017). Other risk factors include concomitant use of CNS depressants and respiratory illness.
Risk minimisation measures	Routine risk minimisation measures: SUBUTEX should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis). SUBUTEX should not be used together with alcoholic drinks and must be used cautiously with medicines containing alcohol. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBUTEX and should also be cautioned to use benzodiazepines concurrently with SUBUTEX only as prescribed. Additional risk minimisation measures: None
Misuse and/or abuse (injection/intranasal)	
Evidence for linking the risk to the medicine	Opioids are the most commonly abused type of prescription drug and appear to be the largest contributor of increases in the prevalence of prescription drug abuse in the USA (McHugh 2015). Buprenorphine has been associated with life-threatening respiratory depression and death. Many, but not all, postmarketing reports regarding coma and death involved misuse by self-injection by the IV route or were associated with the concomitant use of buprenorphine and benzodiazepines or other CNS depressants, including alcohol. In cases of IV misuse, local reactions, systemic viral (HIV, HCV and HBV), microbial (endocarditis) [Cooper 2007, Chong 2009, Lee 2009], and fungal (*Candida endophthalmitis*) [Hirsbein 2008, Cazorla 2005, Aboltins 2005, Aguilar 1979, Cassoux 2002] infections, and sometimes septic reactions have been reported. Many of the histories provided from postmarketing data in France indicated that some or all of the drugs detected at post-mortem had probably been injected. The majority of the non-fatal cases of misuse, which came to medical attention (n=72) also included histories of injection misuse. Buprenorphine is relatively well absorbed by a nasal route (Lindhardt 2000), and intranasal buprenorphine abuse has been reported (Simojoki 2008). The most frequently reported postmarketing adverse event observed with buprenorphine sublingual tablets was drug misuse or abuse.
Risk factors and risk groups	Risk factors associated with opioid abusers include 18-25-year olds, the male gender, patients with psychiatric disorders (including depression and bipolar disorder), exposure to violence and sexual abuse, a patient with a history of substance abuse, and a family history of substance abuse (Brady 2016).

	Opioid and polysubstance abusers are at risk of IV and intranasal abuse of SUBUTEX. Sub-optimal treatment with SUBUTEX may prompt medication misuse by the patient, leading to overdose or treatment dropout.
Risk minimisation measures	Routine risk minimisation measures: To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing SUBUTEX, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBUTEX and should also be cautioned to use benzodiazepines concurrently with SUBUTEX only as prescribed. Additional risk minimisation measures: None
Paediatric Intoxication	
Evidence for linking the risk to the medicine	Due to limited amount of available data, patients below the age 15 should be closely monitored during treatment. A retrospective study reported 86 cases of buprenorphine overdose in children; 54 developed toxicity (UNECE 2007). Children who ingested >2 mg buprenorphine were more likely to experience a clinical effect; all who ingested >4 mg experienced some effect. In 54 children who developed toxicity, the clinical effects included drowsiness or lethargy (55%), miosis (21%), vomiting (21%), respiratory depression (7%), agitation or irritability (5%), pallor (3%), and coma (2%). No fatality was reported.
Risk factors and risk groups	Paediatric patients exposed to buprenorphine are likely to have a household member who is using buprenorphine, and in most cases, may be inadvertently (accidentally) exposed to it. Children who are exposed will exhibit signs and symptoms of opioid toxicity, including respiratory depression, altered mental status, miosis within 8 hours of reported exposure (Toce 2017). In older paediatric patients who may be opioid abusers and abusing buprenorphine, especially IV abusers, polysubstance abusers, combining the use of buprenorphine with alcohol, benzodiazepines, and other drugs, are at high risk for overdose and associated respiratory depression. In substance-abuse treatment, SUBUTEX should be used with caution in patients with compromised respiratory function (e.g. chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis)
Risk minimisation measures	Routine risk minimisation measures: SUBUTEX is only available in child-proof blister packs and the labelling clearly instructs to keep out of reach and sight of children. Buprenorphine may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. Use of SUBUTEX is contraindicated in children under 15 years (French SUBUTEX SmPC). Additional risk minimisation measures: None
Hepatitis, Hepatic Events, Use in Patients with Hepatic Impairment	

Evidence for linking the risk to the medicine	Section 4.4 of the SUBUTEX CCDS states that cases of acute hepatic injury have been reported in opioid dependent patients, both in clinical trials and in postmarketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases, the presence of pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, viral infection such as hepatitis B and chronic hepatitis C, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicines, or ongoing drug use by injection) may have a causative or contributory role. The effect of hepatic impairment on the PK of sublingual buprenorphine has been evaluated in a PK study. While no clinically significant changes have been observed in subjects with mild hepatic impairment, the plasma levels have been shown to be higher and half-life values have been shown to be longer for buprenorphine in subjects with moderate to severe hepatic impairment.
Risk factors and risk groups	Patients who are positive for viral hepatitis or having existing liver dysfunction are at greater risk of liver injury. Injection drug users are at risk of contracting infectious diseases (EMCDDA 2017).
Risk minimisation measures	Routine risk minimisation measures: Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. SUBUTEX should be used with caution in patients with moderate to severe hepatic impairment. Baseline liver function tests and documentation of viral hepatitis status are 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. When a hepatic event is suspected, further biological and etiological evaluation is required. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If the treatment is continued, hepatic function should be monitored closely. Additional risk minimisation measures: None
Use during pregnancy/lactation (effects on newborn and infant)	
Evidence for linking the risk to the medicine	Section 4.8 of the SUBUTEX CCDS states that neonatal drug withdrawal syndrome has been reported among newborns of women who have received buprenorphine products during pregnancy. The syndrome may be milder and more protracted than that from short acting full μ-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history. A PASS (PE-US001) was conducted to monitor pregnancy outcomes associated with exposure to SUBOXONE, SUBUTEX and methadone among pregnant opioid dependent women using medical registries in Sweden and Denmark from 2005 to 2011. In Sweden, in general, women exposed to SUBUTEX or methadone more often delivered preterm and C-sections were more common, when compared to the total population. There were 34 infants with NAS exposed to SUBUTEX. In Denmark, among the 571 823 mothers who gave birth during the study period; 564 exposed infants in 557 pregnancies were identified. Compared with the nonexposed, all recorded opioid use was associated with greater prevalence of preterm birth prevalence ratios were 3.5 (95% CI: 0.6<20.1) in SUBUTEX exposed

	and low birth weight (LBW) prevalence ratios 4.6 (95% CI: 0.8<26.7) in SUBUTEX exposed. No stillbirths occurred in SUBUTEX only exposed pregnancies. A pregnancy assessment report was completed in 2013 that summarised all adverse event cases among women exposed to any buprenorphine product during pregnancy (SUBOXONE, SUBUTEX, TEMGESIC, LEPETAN, BUPRENEX or buprenorphine not otherwise specified) that were reported to INDV through 31 December 2012. A total of 7 268 ICSRs from INDV's safety database, reported through 31 December 2012, were reviewed. The majority of these cases involved exposure to pregnancy without development of any adverse events. A total of 1 789 cases involved a pregnant woman/foetus or infant reported a TME of interest in pregnancy which were classified into the following categories: pregnancy loss; prematurity; other complications of pregnancy, labour/delivery and postpartum; congenital/foetal anomalies; NAS/neonatal drug withdrawal syndrome; other neonatal, infant and child conditions; developmental delay; and designated medical events. A comprehensive review of the TME case safety data from all sources, including postmarketing surveillance of PhV reports and the scientific literature, did not identify any new or emerging safety concerns in relation to the use of buprenorphine or buprenorphine-naloxone combination medicinal products during pregnancy. Additionally, the MOTHER study was a double-blind, double-dummy, flexible dosing, parallel-group randomised clinical trial of the relative maternal and neonatal safety and efficacy of buprenorphine monotherapy (SUBUTEX) versus methadone for the treatment of opioid dependence during pregnancy. The primary outcomes included the number of neonates requiring treatment for NAS, the peak NAS score, the total amount of morphine needed to treat NAS, the length of hospital stay for neonates, and neonatal head circumference among the two groups. The results showed that neonates exposed to buprenorphine *in utero* required significantly less morphine than did neonates exposed to methadone (mean total doses of 1.1 mg and 10.4 mg, respectively; P < 0.0091), and also had a significantly shorter hospital stay (10.0 vs. 17.5 days, respectively; P < 0.0091). The percentage of neonates requiring NAS treatment did not differ significantly between groups (P=0.26), nor did the groups differ significantly with respect to the peak NAS score (P=0.04) or head circumference (P=0.04) (Jones 2010).
Risk factors and risk groups	Women with opioid use disorder may be affected by psychosocial and environmental factors including a history of sexual abuse and/or interpersonal violence, inadequate social supports, poor nutrition, unstable housing, and co-occurring psychiatric conditions (SAMHSA 2016).
Risk minimisation measures	Routine risk minimisation measures: *Pregnancy*: Buprenorphine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Chronic use of SUBUTEX by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions) in the neonate. The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

	Breastfeeding: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBUTEX and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. Additional risk minimisation measures: None
CNS Depression	
Evidence for linking the risk to the medicine	Respiratory depression may occur as a result of CNS depression and may lead to respiratory arrest and death. Any drug that has CNS depressant activity can add to the CNS depressant activity of buprenorphine. There has been a report of respiratory arrest during a clinical study (CR96/005) that involved the concomitant administration of SUBUTEX and other CNS depressants. While taking SUBUTEX, this patient severely overdosed on heroin and oxazepam which lead to the event of respiratory arrest. This case was considered possibly related to SUBUTEX. Section 4.4 of the SUBUTEX CCDS states that a number of cases of death due to respiratory depression have been reported, particularly when SUBUTEX was used in combination with benzodiazepines, when HDB was administered to non-opioid dependent individuals who had not developed a tolerance to the effects of opioids, or when buprenorphine was otherwise not used according to prescribing information. Epidemiological studies on opioids show little evidence of association between opioid use and crash risk (impairment of operating motorised machinery), in opioid dependent patients, whereas benzodiazepines, even at concentrations within the therapeutic range, are associated with increased crash risk (Schindler 2004). However, opioids combined with benzodiazepines, a preferred combination among polysubstance abusers, can significantly impair driving ability.
Risk factors and risk groups	The risk for CNS depression is increased in patients who are on prescription medications for anxiety/depression and those with habitual alcohol intake. Risk factors for developing respiratory failure includes smoking tobacco products, excessive alcohol intake, a family history of respiratory disease or conditions, injury to the spine, brain, or chest, and immunocompromised patients (Macon 2017). Additionally, anyone driving under the influence of drugs, alcohol, or prescription or illicit CNS depressants are among the leading risk factors for traffic accidents. Young males are also at risk for substance abuse. Other risk factors include CNS depressants and respiratory illness.
Risk minimisation measures	Routine risk minimisation measures: SUBUTEX may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If used with alcohol or CNS depressants (such as benzodiazepines, tranquilisers, sedatives or hypnotics) the effect is likely to be more pronounced. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities. Additional risk minimisation measures: None

Medication errors when switching between SUBUTEX/SUBOXONE and new buprenorphine-containing products (BCP) which are not interchangeable with SUBUTEX/SUBOXONE	
Evidence for linking the risk to the medicine	The switching between buprenorphine-containing products which are not interchangeable may be necessary (e.g., if a person moves between care settings from the community in to prison or between prisons and doesn't need restabilisation). In addition, the risk for inadvertent substitution (prescribing and dispensing errors) may occur in the event of HCPs not being aware that Espranor and Zubsolv are not interchangeable with SUBUTEX/SUBOXONE or their generics. Espranor (buprenorphine oral lyophilisate) is not interchangeable with other buprenorphine sublingual formulations at the same dose ("like for like" switch) as its bioavailability is 25-30% higher. The recommended starting dose of Espranor is 2 mg – 6 mg compared to 2 mg – 8 mg for other oral buprenorphine preparations and the maximum single daily dose for Espranor is 18 mg, not 24 mg as with SUBUTEX. There is no 0.4 mg strength of Espranor, the lowest strength is 2 mg. The Espranor SmPC suggests that patients may need to be switched to 0.4 mg sublingual buprenorphine tablets to enable dose reduction (Section 4.2 of Espranor SmPC). Section 4.2 of the Espranor SmPC includes a boxed warning stating that 'Espanor is not interchangeable with other buprenorphine products. 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 certain product (brand), the product cannot readily be exchanged with another product' (Espranor SmPC, July 2017). Patient's Brochure for use of BCP (distributed by pharmaceutical companies marketing BCP, under the authority of the ANSM) states that 'There are 2 presentations of buprenorphine: the sublingual tablet and the orodispersible lyophilisate. These 2 formulations are different and are not interchangeable. Always follow your doctor's prescription. Not to exchange the sublingual and orodispersible forms of buprenorphine'. Zubsolv is a rapidly disintegrating sublingual tablet containing 0.7 mg / 1.4 mg / 2.9 mg / 5.7 mg / 8.6 mg / 11.4 mg buprenorphine (as hydrochloride) and 0.18 mg / 0.36 mg / 0.71 mg / 1.4 mg / 2.1 mg / 2.9 mg naloxone (as hydrochloride dihydrate) as active substances. Development formulations were found to have improved absorption compared to the reference product SUBOXONE. The EPAR for Zubsolv states that 'the differences between SUBOXONE and Zubsolv formulations imply that switching between the two *(at the same dose in mg)* would not reproduce the same plasma concentrations of buprenorphine. A lower buprenorphine exposure from Zubsolv may potentially result in reduced opioid receptor stimulation leading to withdrawal symptoms when switching from another buprenorphine product at a dose level below 5.7 mg/1.4 mg. In addition, owing to the long terminal half-life of buprenorphine, it would take several days to reach a new steady state when switching between formulations. This uncertainty supports the recommendation that patients should not switch between products. In the context of switching between SUBOXONE and Zubsolv products, the risk of under-dosing with secondary withdrawal symptoms is mitigated with amended guidance for switching formulation in Section 4.2 and 5.2 of the [Zubsolv] SmPC. In addition, in the clinical context, buprenorphine is individually titrated to clinical effect, and if small exposure differences between products were to translate to differences in clinical effects, this would be addressed by dose adjustments in the

	standard care of the patient' (Espranor Public Assessment Report, July 2015). Section 4.2 of the Zubsolv SmPC includes a statement that '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'. 'In comparative bioavailability studies Zubsolv 11.4 mg/2.9 mg displayed equivalent buprenorphine exposure to 16 mg/4 mg (2 x 8 mg/2 mg) buprenorphine/naloxone administered as conventional sublingual tablets however Zubsolv 2 x 1.4 mg/0.36 mg displayed 20% lower buprenorphine exposure to 2 x 2 mg/0.5 mg buprenorphine/naloxone administered as conventional sublingual tablets' (Zubsolv SmPC, Section 5.2). Phase II clinical studies comparing safety and effectiveness of Espranor and SUBUTEX in opioid dependent patients suggest that administration of Espranor did not result in a higher risk of respiratory depression compared to SUBUTEX (Espranor Public Assessment Report, July 2015). Adverse events in both healthy subjects and patient clinical studies were comparable between Zubsolv and SUBOXONE. The SAEs were consistent with the known safety profile for the buprenorphine/naloxone combination product (Espranor Public Assessment Report, July 2015) . Although the products are not bioequivalent, they are similar enough that switching is unlikely to result in severe consequences.
Risk factors and risk groups	Patients switching from SUBUTEX/SUBOXONE to Espranor or Zubsolv.
Risk minimisation measures	Routine risk minimisation measures: The risk of inadvertent substitution due to prescribing and dispensing errors is mitigated through Espranor and Zubsolv labelling alerting HCPs and patients of the differences between the products. Based on existing Espranor and Zubsolv clinical studies, significant clinical concerns related to this transfer are not anticipated. Patients being switched between different formulations should be started on the corresponding dose compared to the previously administered product. Patients should be monitored for symptoms related to overdosing or under-dosing and dosing adjustments should be made as clinically indicated. Additional risk minimisation measures: None
Use in Children/Adolescents Less Than 15 Years Old	
Risk minimisation measures	Routine risk minimisation measures: Children must be protected against exposure. Keep out of reach and sight of children. Use of SUBUTEX is contraindicated in children under 15 years (French SUBUTEX SmPC).

	Additional risk minimisation measures: None
Use in Elderly (Patients Greater Than or Equal To 65 Years Old)	
Risk minimisation measures	Routine risk minimisation measures: Opioids should be administered with caution to elderly or debilitated patients. Additional risk minimisation measures: None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of SUBUTEX.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for SUBUTEX.