EU RISK MANAGEMENT PLAN FOR SUBOXONE® SUBLINGUAL TABLET AND SUBOXONE SUBLINGUAL FILM

RMP version to be assessed as part of this application:

RMP Version number: 14.3

Data lock point for this RMP: 26 September 2018[a]

Date of final sign off: 08 April 2020

Rationale for submitting an updated RMP: Submission of application for SUBOXONE sublingual film.

Summary of significant changes in this RMP: Update to the list of safety concerns

Other RMP versions under evaluation

RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable

Details of the currently approved RMP

Version number:	Version 13.0
Approved with procedure:	Centralised Procedure
Date of approval (opinion date):	17 May 2018

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[a] Unless otherwise stated, the cut-off date for data provided in this document is 26 September 2018

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List of Abbreviations

Abbreviation	Term
ADMET	Absorption, Distribution, Metabolism, Excretion and Toxicology
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ASI	Addiction-Severity Index
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-time Curve
BCP	Buprenorphine-Containing Product(s)
CCI	Charlson Comorbidity Index
CCSA	Canadian Centre on Substance Use and Addiction
CDC	Centers for Disease Control
CDR	Cause of Death Register
CI	Confidence Interval
CNS	Central Nervous System
COWS	Clinical Opiate Withdrawal Scale
CPRD	Clinical Practice Research Datalink
CYP	Cytochrome P450
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EEA	European Economic Area
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EPAR	European Public Assessment Report
EU	European Union
GPRD	General Practice Research Database
GVP	Good Pharmacovigilance Practices
HBV	Hepatitis B Virus
HCl	Hydrochloride
HCV	Hepatitis C Virus
HCP	Healthcare Professional
HIV	Human Immunodeficiency Virus
HOI	Health Outcomes of Interest
HR	Hazard Ratio
IB	Investigator's Brochure
ICD	International Statistical Classification of Diseases and Related Health Problems
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IDU	Injection Drug User
IM	Intramuscular(ly)
INDV	Indivior Europe Limited / Indivior, Inc.
ITT	Intention-To-Treat
IV	Intravenously
LBW	Low Birth Weight
LPD	Longitudinal Patient Database(s)
MAH	Marketing Authorisation Holder
MAOI	Monoamine Oxidase Inhibitor(s)

MAT	Medication-Assisted Treatment
MBR	Medical Birth Register
MHRA	Medicines and Healthcare Products Regulatory Agency
MOTHER	Maternal Opioid Treatment: Human Experimental Research
NAS	Neonatal Abstinence Syndrome
NIDA	National Institute on Drug Abuse
OAMT	Opioid Agonist Maintenance Treatment
OR	Odds Ratio
OUD	Opioid Use Disorder
PAR	National Patient Register
PASS	Post-Authorisation Safety Study
PDR	Prescribed Drug Register
PhV	Pharmacovigilance
PIN	Personal Identification Number
PK	Pharmacokinetic(s)
PL	Package Leaflet
PTD	Patient Treatment Days
PTY	Patient Treatment Years
QPPV	Qualified Person for Pharmacovigilance
RHDSD	Recommended Human Daily Sublingual Dose
RMP	Risk Management Plan
SAE	Serious Adverse Event
SC	Subcutaneous(ly)
SFPT	Swedish Forensic Pathology and Forensic Toxicology
SmPC	Summary of Product Characteristics
SOWS	Subjective Opiate Withdrawal Scale
THIN	The Health Improvement Network
TME	Targeted Medical Event
UAE	United Arab Emirates
UK	United Kingdom
UNODC	United Nations Office on Drugs and Crime
US/USA	United States of America
WHO	World Health Organization
κ	kappa
mg	milligram(s)
µ	mu

Part I: Product(s) Overview

Table Part I.1: Products Overview

Active substance(s) **(INN or common name)**	Buprenorphine hydrochloride (HCl)/naloxone HCl dihydrate
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical (ATC) Code)	Group: Other nervous-system drugs, drugs used in addictive disorders (N07BC01 and N07BC51 - buprenorphine)
Marketing Authorisation Holder (MAH)	Indivior (INDV) Europe Limited
Medicinal products to which this RMP refers[b]	SUBOXONE® (buprenorphine HCl[c]/naloxone HCl dihydrate[d]) sublingual tablet SUBOXONE (buprenorphine HCl/naloxone HCl dihydrate) sublingual film
Invented name(s) in the European Economic Area (EEA)	SUBOXONE sublingual tablet SUBOXONE sublingual film
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	Chemical class: Chemically, buprenorphine HCl is (2S)-2-[17-cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol HCl; naloxone HCl dihydrate is 17-allyl-4,5 α -epoxy-3, 14-dihydroxy-morphinan-6-one HCl dihydrate.
	Summary of mode of action: Buprenorphine is an opioid partial agonist/antagonist which binds to the μ (mu) 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 persons. 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 (IV) to opioid-dependent persons, the presence of naloxone in SUBOXONE produces marked opioid antagonist effects and opioid withdrawal, thereby deterring IV abuse.

[b] Unless otherwise stated, SUBOXONE will refer to both SUBOXONE sublingual tablet and sublingual film.
[c] Buprenorphine HCl will be referred to as "buprenorphine" for the remainder of the document.
[d] Naloxone HCl dihydrate will be referred to as "naloxone" for the remainder of the document.

	Important information about its composition: SUBOXONE is a combination of buprenorphine and naloxone at a ratio of 4:1 buprenorphine:naloxone (ratio of free bases). SUBOXONE sublingual tablet excipients are lactose monohydrate, mannitol, maize starch, povidone K 30, citric acid anhydrous, sodium citrate, magnesium stearate, acesulfame potassium, and natural lemon and lime flavour. SUBOXONE sublingual film excipients are polyethylene oxide, maltitol liquid (hydrogenated glucose syrup), natural lime flavour, hypromellose, citric acid, acesulfame potassium, sodium citrate, Sunset Yellow [E110], white ink.
Hyperlink to the Product Information	Refer to Module 1.3.1
Indication(s) in the EEA[e]	Current (if applicable): SUBOXONE sublingual tablet Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter parenteral misuse. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction. SUBOXONE sublingual film N/A
	Proposed (if applicable): SUBOXONE sublingual tablet N/A SUBOXONE sublingual film Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter IV misuse. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.
Dosage in the EEA[e]	Current (if applicable): SUBOXONE sublingual tablet Treatment must be under the supervision of a physician experienced in the management of opiate dependence/addiction. 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

[e] This information is based on the current SUBOXONE sublingual tablet SmPC and proposed SUBOXONE sublingual film SmPC

	objective and clear signs of withdrawal are evident (demonstrated e.g. by a score indicating mild to moderate withdrawal on the validated Clinical Opiate Withdrawal Scale [COWS]). *Initiation therapy (induction)* The recommended starting dose in adults and adolescents over 15 years of age is one to two SUBOXONE 2 mg/0.5 mg. An additional one to two SUBOXONE 2 mg/0.5 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 adjustment and maintenance therapy* Following treatment induction on day one, the patient should be stabilised to a maintenance dose during the next few days by progressively adjusting the dose according to the clinical effect of the individual patient. Dose titration in steps of 2-8 mg buprenorphine is guided by reassessment of the clinical and psychological status of the patient and should not exceed a maximum single daily dose of 24 mg buprenorphine. SUBOXONE sublingual film N/A
	Proposed (if applicable): SUBOXONE sublingual tablet N/A SUBOXONE sublingual film *Initiation therapy (induction)* The recommended starting dose in adults and adolescents over 15 years of age is two SUBOXONE 2 mg/0.5 mg sublingual films or one SUBOXONE 4 mg/1 mg sublingual film. This may be achieved using two SUBOXONE 2 mg/0.5 mg sublingual films as a single dose or one SUBOXONE 4 mg/1 mg sublingual film, which can be repeated up to twice on day 1, to minimise undue withdrawal symptoms and retain the patient in treatment. Due to naloxone exposure being somewhat higher following buccal administration than sublingual administration, it is recommended that the sublingual site of administration be used during induction to minimise naloxone exposure and to reduce the risk of precipitated withdrawal. 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. *Dose 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 24 mg buprenorphine. During maintenance therapy, it may be necessary to periodically stabilise the patient to a new maintenance dose in response to changing patient needs.
Pharmaceutical form(s) and strengths	Current (if applicable): SUBOXONE sublingual tablet SUBOXONE sublingual tablet is currently available in three dosage strengths, 2 mg buprenorphine with 0.5 mg naloxone, 8 mg buprenorphine with 2 mg naloxone and 16 mg buprenorphine with 4 mg naloxone. **2 mg:** white hexagonal biconvex tablets of 6.5 mm with "N2" debossed on one side. **8 mg:** white hexagonal biconvex tablets of 11 mm with "N8" debossed on one side. **16 mg:** white round biconvex tablets of 10.5 mm with "N16" debossed on one side. SUBOXONE sublingual film NA
	Proposed (if applicable): SUBOXONE sublingual tablet N/A SUBOXONE sublingual film SUBOXONE 2 mg/0.5 mg sublingual film is an orange rectangular soluble film, nominal dimensions 22.0 mm x 12.8 mm, with "N2" imprinted in white ink. SUBOXONE 4 mg/1 mg sublingual film is an orange rectangular soluble film, nominal dimensions 22.0 mm x 25.6 mm, with "N4" imprinted in white ink. SUBOXONE 8 mg/2 mg sublingual film is an orange rectangular soluble film, nominal dimensions 22.0 mm x 12.8 mm, with "N8" imprinted in white ink. SUBOXONE 12 mg/3 mg sublingual film is an orange rectangular soluble film, nominal dimensions 22.0 mm x 19.2 mm, with "N12" imprinted in white ink.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Indication: Treatment of Opioid Dependence

Incidence and Prevalence

Opioid dependence is characterised by a cluster of cognitive, behavioural and physiological features. The International Classification of Diseases, 10th edition (ICD-10) identifies six such features which include:

- a strong desire or sense of compulsion to take opioids
- difficulties in controlling opioid use
- a physiological withdrawal state
- tolerance
- progressive neglect of alternative pleasures or interests because of opioid use
- persisting with opioid use despite clear evidence of overtly harmful consequences

ICD-10 defines opioid dependence as the presence of three or more of the above features present simultaneously at any one time in the preceding year (WHO 2009).

As stated in the 2018 World Drug Report by United Nations Office on Drugs and Crime (UNODC), the number of past-year users of opioids and persons who use prescription opioids for non-medical purposes was estimated at 34.3 million people, of whom 19.4 million were estimated to have used opioids (heroin and opium) (UNODC 2018). WHO estimates that there were 450 000 deaths attributed to drug use worldwide, of which 167 750 of these deaths were associated with drug use disorders, with 76% of deaths of these deaths related to the use of opioids (UNODC 2018).

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) 2018 report, an estimated 1.3 million people received treatment for illicit drug use in the European Union (EU) during 2016 (1.5 million including Norway and Turkey) (EMCDDA 2018). Opioid users represent the largest group undergoing specialised treatment and consume the greatest share of available treatment resources, mainly in the form of substitution treatment. Differences between countries can be very large, however, with opioid users accounting for more than 90% of treatment entrants in Estonia and less than 5% in Hungary. The latest data show that heroin use accounts for the majority, around 80%, of new opioid-related treatment demands in Europe. In addition, the overall decline in treatment demand related to heroin, observed since 2007, is no longer evident. Of particular concern is the increasing European estimate for drug overdose deaths, which has now risen for the third consecutive year; heroin is implicated in many of these deaths. Also in Europe, problems related to highly potent synthetic opioids appear to be growing, as indicated by increasing reports of non-fatal intoxications and deaths received by the Early Warning System (EMCDDA 2017).

While heroin still remains the most commonly used opioid in Europe, and using heroin is still the reason why most people seek treatment, there has been an increase in treatment demand related to prescription opioids (UNODC 2017). In 2016, 18 European countries reported that more than 10 percent of all opioid treatment admissions were for problems related to opioids other than heroin. The most common opioids reported by treatment entrants include misused methadone, buprenorphine, fentanyl, codeine, morphine, tramadol and oxycodone. In some countries, non-heroin opioids represent the most common form of opioid use among treatment entrants (EMCDDA 2018).

Other countries are also experiencing an increase in opioid use and opioid related harms. In September 2017, the Canadian Centre on Substance Use and Addiction (CCSA) released a report stating that in 2016, there were at least 2 816 opioid-related deaths in Canada, at a rate of 7.8 deaths per 100 000 (CCSA 2017).

Australia had an opioid-related death rate of 0.78 to 1.19 deaths/100 000 population over 10 years (Blanch 2014). In the United States of America (USA), from 2000 to 2013, the age-adjusted rate for overdose deaths involving heroin nearly quadrupled from 0.7 deaths per 100 000 in 2000 to 2.7 deaths per 100 000 in 2013 (Hedegaard 2015).

Demographics of the target population and risk factors for the disease

In the global burden of disease study, the prevalence of opioid dependence is higher among males than females, 0.30% and 0.14%, respectively (Degenhardt 2014).

Male opioid users were more likely to also use other illicit drugs; female opioid users were more likely to also abuse other prescription drugs (Wu 2010). While there was a 265% increase in prescription overdoses for men between 1999 and 2010, women had a 400% increase (Campbell 2018).

In 2016, the average prevalence of high-risk opioid use among adults (15–64) was estimated at 0.4% of the EU population, the equivalent of 1.3 million high-risk opioid users in Europe (EMCDDA 2018). Five countries account for three quarters (76%) of the estimated high-risk opioid users in the EU (Germany, Spain, France, Italy, United Kingdom [UK]). About 177 000 patients who entered specialised treatment in Europe reported opioids as their primary drug, 35 000 of whom were first-time entrants. Primary heroin users accounted for 82% of first-time primary opioid users entering treatment. Among heroin users in EU, the mean age at first use is 23 years, while the mean age at first treatment is 34 years (EMCDDA 2018). Among first-time patients entering drug treatment in 2015 with heroin as their primary drug, the male to female ratio was approximately 4:1 (EMCDDA 2017).

Risk factors for opioid dependence include: a personal history of substance abuse, family history of substance abuse, young age, a history of preadolescent sexual abuse, psychological stress, polysubstance abuse, poor social support, non-functional status caused by pain, exaggeration of pain, and unclear cause of pain (NIDA 2007).

It has been estimated that genetic factors account for between 40 and 60 percent of a person's vulnerability to addiction; this includes the effects of environmental factors on the function and expression of a person's genes. A person's stage of development and other medical conditions they may have are also factors. Adolescents and people with psychiatric illnesses are at greater risk of drug abuse and addiction than the general population (NIDA 2014).

Predictors of dependence on opioid medications among pain patients include substance abuse-related diagnoses, positive toxicology for opioids, and other medical diagnoses. Other patients at risk include those with idiopathic pain (no clear etiology) or high levels of psychological distress or disability (Miller 2004).

The main existing treatment options

The existing literature supports that the most effective treatment for opioid use disorder (OUD) is medication assisted therapy (MAT) plus psychosocial treatment which is any psychological or social treatment provided to the patient in support of medical care (WHO 2009).

Methadone and buprenorphine are effective evidence-based medications currently used in the treatment of opioid dependence and have been placed on the WHO model list of essential medicines (WHO 2009).

The primary aim of OAMT is to reduce the use of illicit opioids and manage abstinence by preventing withdrawal symptoms, reducing drug craving, and decreasing the drug-liking effects of additional opioids if they are consumed (UNODC-WHO 2017).

Methadone is currently the most common treatment in Europe (Segrec 2017). Methadone reduces the symptoms and signs of opioid withdrawal, reduces craving, and may mitigate euphoria (Dematteis 2017). In Europe, methadone is received by around two-thirds (63%) of substitution clients (EMCDDA 2017). A further 35% of clients are treated with buprenorphine-based medications. These products reduce the symptoms and signs of opioid withdrawal and reduce craving. Buprenorphine containing products are the principal substitution drug in 8 countries (EMCDDA 2017). Other substances, such as slow-release morphine or diacetylmorphine (heroin), are more rarely prescribed, being received by an estimated 2% of substitution clients in Europe (EMCDDA 2017).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Long-term studies show that opioid dependence is a chronic relapsing illness. Estimates suggest a 2-5% annual remission rate, for example, 2 to 5% will stop using opioids in any one year (Lintzeris 2015).

The natural history of opioid dependence, if untreated, is morbidity and mortality. The main causes of death in this population are overdose and/or suicide, trauma, and infectious diseases (such as hepatitis C-related liver disease, human immunodeficiency virus (HIV) infection and endocarditis). Much of the overdose-related mortality associated with dependence on opioids is linked to use of other sedative drugs such as benzodiazepines and antidepressants and the use of alcohol which is a sedative as well. Effective treatment is associated with a 3-5-fold reduction in mortality (Lintzeris 2015).

Important co-morbidities

Hepatitis

People who inject drugs are at a risk for hepatitis B virus (HBV) and hepatitis C virus (HCV) infections through the sharing of needles and drug preparation equipment (CDC 2012).

Current research shows that the prevalence of HCV is high among opioid dependent individuals. Prior research showed that 80% of a sample of opioid dependent patients were positive for HCV antibody, and almost 67% were chronically infected (Murphy 2015). Chronic HCV infection can lead to long-term consequences including deaths and cases of severe liver disease, including cirrhosis and cancer, in an aging population of high-risk drug users (EMCDDA 2017).

Across Europe, HCV is highly prevalent among injection drug users (IDUs). For every 100 people infected with HCV, 75-80 will develop chronic infection (EMCDDA 2017). A study was conducted in Spain which showed the incidence of HCV infection among IDUs was found to be 39.8/100 person-years and was 52.9/100 person-years among those who continued injecting during the follow up period. Thus, the anti-HCV prevalence among the sample of IDUs was close to the highest reported in the world (Vallejo 2015).

Recent data show that the number of deaths is more than 3.5 times higher for hepatitis C and the number of years of "healthy" life lost (as measured by disability-adjusted life year [DALY]) is approximately 2.5 times higher. Hepatitis C is highly prevalent among IDUs, with the joint UNODC/WHO/United Nations AIDS (UNAIDS)/World Bank estimate of 51.5 per cent for 2015, suggesting that 6.1 million IDUs are infected with hepatitis C. For IDUs living with HIV, co-infection with hepatitis C is highly prevalent, at 82.4%, with hepatitis C among those living with HIV becoming a major cause of morbidity and mortality (UNODC 2017).

HIV/AIDS

The currently available data show that, globally, new HIV infections among IDUs climbed from an estimated 114 000 in 2011 to 152 000 in 2015. The joint UNODC/WHO/ UNAIDS/World Bank estimate for the prevalence of HIV among IDUs in 2015 is 13.1%. This suggests that roughly one in eight people who injected drugs in 2015 were living with HIV, which equates to 1.55 million IDUs infected with HIV worldwide (UNODC 2017).

Although the 1 233 new HIV infections reported in 2016 in the EU were the lowest for more than two decades, this still represents a significant public health problem. New HIV infections among people who inject drugs have declined in most European countries, with an overall decrease of 41% between 2007 and 2015. However, injecting drug use remains an important mode of transmission in some countries: in 2015, a quarter or more of newly diagnosed HIV cases were attributed to injecting drug use in Lithuania (34%), Latvia (32%), Luxembourg (27%) and Estonia (25%) (EMCDDA 2017).

Recent data show that HIV was reported in 21.5% of IDUs in Europe (11.4% in Western and Central Europe and 24% in Eastern and South-Eastern), 1.4% in Oceania, 4.7% in North America (population age 15-64 years) (UNODC 2017).

In 2010, approximately 1 700 people died of HIV/AIDS attributable to injection drug use in Europe (EMCDDA 2015).

Psychiatric disorders

A high prevalence of psychiatric comorbidities, especially depressive, anxiety, and personality disorders, in opioid dependent patients, is well established (Roncero 2016).

A study to determine the prevalence of psychiatric disorders among young IDUs outside of a treatment setting found that major depression was the most prevalent disorder with an estimated lifetime rate of 25% (95% confidence interval (CI): 16.9-34.9) for men and 31% (95% CI: 21.2-42.1%) for women (Mackesy-Amiti 2012). A recent study showed a very high prevalence of psychiatric disorders (comorbidities anxiety disorder, mood disorder, non-opioid substance use disorder, or personality disorder) among patients seeking treatment for co-occurring OUD and chronic pain. Most participants in this study (81%) met the criteria for at least 1 psychiatric comorbidity, and the majority of participants (59%) met the criteria for at least 2 (Barry 2016).

Chronic pain

The use of opioid analgesics to treat chronic non-cancer pain, which is defined as pain lasting a least 3 months, has increased 3-fold since the early 1990s and has brought with it an epidemic of nonmedical opioid use, opioid overdose, and OUD (Barry 2016).

Part II: Module SII - Nonclinical Part of the Safety Specification

The toxicity of buprenorphine/naloxone and the single entity drugs has been evaluated in single and repeat dose studies employing various routes of administration and treatment durations that support both the tablet and film formulations. These nonclinical studies support both formulations unless specifically noted that a study was conducted with film formulations. The reproductive and genetic toxicity and carcinogenicity of buprenorphine/naloxone has also been investigated.

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 HCl and naloxone HCl 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 IV micronucleus test in the rat. Test article film identical to SUBOXONE sublingual film was tested in a Green Screen Human Cell Assay (GADD45α–GFP) with and without metabolic activation. The test article film was shown to be non-genotoxic with or without metabolic activation, but was cytotoxic at the lowest effective concentrations of 15.63 µg/mL in 1% dimethylsulfoxide (DMSO) and 0.04 mg/mL (in sterile water) in the absence of metabolic activation.

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 5x 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 (possibly due to 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 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 2.4x for buprenorphine at a human dose of 24 mg buprenorphine/naloxone based on area under the concentration-time curve (AUC), plasma levels of naloxone were below the limit of detection in rats) had no adverse effect on fertility in females. No reproduction differences are expected between the two dosage forms.

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 to 75 times, based on a human daily sublingual dose of 16 mg calculated on a mg/m² basis. Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dosage groups (SUBOXONE Sublingual Tablet SmPC 2015).

A summary of key safety findings from nonclinical studies are provided below.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Single and repeat dose toxicity	
• Single-dose toxicity Acute toxicity profiles for both buprenorphine and naloxone administered alone reflect the low oral bioavailability of buprenorphine and very low bioavailability of naloxone. The toxicity of co-administered mixtures of buprenorphine and naloxone was less than that of the more toxic of the active ingredients for a given route and species (SUBOXONE Sublingual Tablet Investigator's Brochure (IB), 2016). • Repeat-dose toxicity Data on the toxicity of development formulations containing ratios (in terms of bases) of buprenorphine and naloxone from 1:1 to 3:2 for periods of up to 28 days in both the rat and the dog by a variety of enteral and parenteral routes of administration were evaluated. No clear evidence of specific target organ toxicity was identified in rats exposed to substantial multiples of the proposed human dose except possibly for the adrenal gland (SUBOXONE Sublingual Tablet IB 2016). Beagle dogs were given six 8 mg/2 mg SUBOXONE sublingual film strips daily for 28 days sublingually and evaluated for effects. Primary effects were typical of the pharmacological effects of buprenorphine at high doses: few or absent faeces, hard faeces, vomitus/emesis, decreased activity, discoloured faeces (black), salivation, and tremors. One group had exaggerated effects including ataxia or gait abnormalities. Electrocardiogram (ECG) findings were noted on Day 1, but not at Week 4, after daily dosing a > 10% lengthening of mean QT and QTc intervals (pooled for both sexes, Group 2: +14.35%; Group 3: +13.48%; Group 4: +15.22%). As there was no QTc prolongation at Week 4, it is unlikely that the QTc prolongation noted at Day 1 was related to hERG blockade. It is postulated that the QTc interval prolongation in this study reflects acute test article-related effects on autonomic tone as reflected by associated neurological and gastrointestinal signs. Reduced activity, tremors and vocalisation were noted in all test article administered groups on Day 1. With the exception of discoloured faeces and few or absent faeces, the clinical signs (ataxia, emesis, watery faeces) and QT/QTc changes were not present at the subsequent ECG collection at Week 4, lending further support to that transient changes in autonomic tone secondary to the acute administration of SUBOXONE accounted for the QT/QTc prolongation at Day 1. The transient change in QT prolongation was not considered adverse and the results of this study demonstrated no evidence of toxicological concern.	The relevance to human usage is not expected based on the high exposure multiples at which effects occurred in the single-dose studies. The data indicate that acute co-administration of buprenorphine and naloxone is unlikely to present any significant risk to humans. Repeated-dose toxicology studies in rats and dogs utilising a variety of routes of administration both alone and in combination with naloxone indicate low general toxicity of buprenorphine. The data indicate that repeated-dose co-administration of buprenorphine and naloxone is unlikely to present any significant risk to humans.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Reproductive Findings	
• **Infertility Findings** *Buprenorphine/naloxone* Dietary administration of buprenorphine/naloxone (4:1) to rats at concentrations of 500 ppm or greater (~47 mg/kg/day or greater; exposure 28 times the recommended human daily sublingual dose (RHDSD) resulted in a reduction in fertility, as seen in reduced female conception rates. No adverse effects on fertility were seen with the 100 ppm diet (~10 mg/kg/day; exposure 6 times the RHDSD) (SUBOXONE Sublingual Tablet IB 2016). *Buprenorphine* 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 24 mg buprenorphine, based on AUC). Dietary administration of buprenorphine 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 times for buprenorphine at a human dose of 24 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 (SUBOXONE Sublingual Tablet SmPC 2015). *Naloxone* Published data indicate that administration of naloxone at doses of up to 500 mg/kg/day in mice and rats did not impair fertility or harm the foetus (Medicines and Healthcare Products Regulatory Agency (MHRA) 2011).	Based on the results from a rat fertility toxicity study, SUBOXONE should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus (SUBOXONE Sublingual Tablet SmPC 2015). Because animal reproductive toxicity studies are not always predictive, the potential risk for humans is unknown.
Embryofoetal Development	
Embryofoetal development studies in rats and rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of buprenorphine/naloxone suggest a wide safety margin. Following oral administration to rats and rabbits, no teratogenic effects were observed at doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (150 times and 50 times the RHDSD, respectively). No definitive drug related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (20 times and 35 times the RHDSD, respectively). Acephalous was observed in one rabbit foetus from the low-dose group and omphalocele was observed in two rabbit foetuses from the same litter in the mid-dose group; no findings were observed in foetuses from the high-dose group (SUBOXONE Sublingual Tablet IB 2016).	Pregnancy outcome post authorisation safety study (PASS) (Indivior (PE-US001) 2014) was conducted in Sweden and Denmark between 2005-2011. Data were collected from the Swedish Medical Birth Register (MBR). Out of 37 *in utero* SUBOXONE-exposed infants, 7 (18.9%) were with neonatal abstinence syndrome (NAS). There was also one infant with major congenital malformations who may also have been exposed *in utero* to methylphenidate, ketoconazole, and amoxicillin during the first trimester and clavulanic acid during the second trimester. Some of these concomitant drugs can cause malformations which is an important confounding factor when assessing causality. SUBOXONE-exposed

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
	women had significantly lower rates of pre-term birth than methadone and SUBUTEX. Data from Denmark included one pregnant woman exposed to SUBOXONE giving preterm birth to twins. Both infants had congenital malformations but no NAS. This single case is not valid to draw any conclusion. For generalisable estimations more exposures are needed. No adequate and well controlled studies have been conducted with SUBOXONE in pregnant women that can be used to establish safety. Published data on human clinical experience with buprenorphine use during pregnancy suggest that a supervised therapeutic regimen is unlikely to pose a substantial teratogenic risk. Pregnant women involved in buprenorphine maintenance programs are reported to have significantly improved prenatal care leading to improved neonatal outcomes when compared with women using illicit drugs. Because animal reproductive toxicity studies are not always predictive, the potential risk for humans is unknown. 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 (SUBOXONE Sublingual Tablet SmPC 2015).
Peri-and Postnatal Development	
No peri- or postnatal studies have been conducted with the buprenorphine/naloxone drug combination. Dystocia was noted in pregnant rats treated IM with buprenorphine 5 mg/kg/day (3 times the RHDSD). Studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (0.5 times the RHDSD), after IM doses of 0.5 mg/kg/day and up (0.3 times the RHDSD) and after subcutaneous (SC) doses of 0.1 mg/kg/day and up (0.06 times the RHDSD). Delays in development of righting reflex and startle response were noted in rat pups at oral dose of 80 mg/kg/day (50 times the RHDSD) (SUBOXONE Sublingual Tablet IB 2016).	These results in rats correspond with reports of neonatal withdrawal in infants of women treated with buprenorphine during pregnancy. Because animal reproductive toxicity studies are not always predictive, the potential risk for humans is unknown. 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 justifies the potential risk to the foetus (SUBOXONE Sublingual Tablet SmPC 2015).
Breast-feeding	
It is unknown whether naloxone is excreted in human breast milk. Buprenorphine and its metabolites are excreted in human breast milk. In rats, buprenorphine has been found to inhibit lactation (SUBOXONE Sublingual Tablet SmPC 2015).	Therefore, breast-feeding should be discontinued during treatment with SUBOXONE (SUBOXONE Sublingual Tablet SmPC 2015).

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Kidney Toxicity	
In the 4-week intramuscular rat study, visual inspection of the mean relative organ weights suggested that kidney and adrenal weights increased in males and females receiving 90mg/kg/day (buprenorphine and naloxone [ratio 3:2]) (SUBOXONE Sublingual Tablet IB 2016).	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) (SUBOXONE Sublingual Tablet SmPC 2015).
Liver Toxicity	
Buprenorphine undergoes hepatic first pass metabolism following oral administration via *O*-glucuronidation and cytochrome P450 (CYP) 3A (CYP3A)-mediated *N*-dealkylation into norbuprenorphine and cyclopropanecarboxaldehyde. The results of an *in vivo* study in mice suggested that the hepatotoxicity of buprenorphine is mainly due to its mitochondrial effects (SUBOXONE Sublingual Tablet IB 2016). Mitochondrial and metabolic activation of buprenorphine effects were investigated (Berson 2001) in isolated rat liver mitochondria and microsomes, its toxicity in isolated rat hepatocytes and its *in vivo* toxicity in mice. Effects on liver were identified in studies in rats and dogs consistent with the results in other species.	Hepatic Impairment Both buprenorphine and naloxone are extensively metabolised in the liver. The effects of hepatic impairment on the pharmacokinetics (PK) of buprenorphine and naloxone were evaluated in a post-marketing study (Nasser 2015). No clinically significant changes were observed in subjects with mild hepatic impairment. Plasma levels were shown to be higher and half-life values were shown to be longer for both buprenorphine and naloxone in subjects with moderate and severe hepatic impairment. The magnitude of the effects on naloxone were greater than that on buprenorphine in both moderately and severely impaired subjects. The difference in magnitude of the effects on naloxone and buprenorphine were greater in subjects with severe hepatic impairment than in subjects with moderate hepatic impairment. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and/or buprenorphine. As buprenorphine/naloxone PK 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 (SUBOXONE Sublingual Tablet SmPC 2015).

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Genotoxicity	
The combination (4:1) of buprenorphine HCl and naloxone HCl 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 IV micronucleus test in the rat (SUBOXONE Sublingual Tablet SmPC 2015). Buprenorphine was studied in a broad series of tests utilising gene, chromosome, and deoxyribonucleic acid (DNA) interactions in both prokaryotic and eukaryotic systems. Results were negative in the majority of these assays but were equivocal in one (of several) Ames test and were positive in a few DNA synthesis assays using testicular cells from mice (SUBOXONE Sublingual Tablet IB 2016). An Ames study with naloxone alone resulted in a weak positive response in one bacterial tester strain. An Ames test with a naloxone drug substance impurity was negative, though the *in vitro* cytogenetic assay in human peripheral lymphocytes was mildly positive at high concentrations with and without metabolic activation. Exposure to this impurity is controlled to levels below the International Council for Harmonisation (ICH)-recommended acceptable daily intake limits by drug substance specifications (SUBOXONE Sublingual Tablet IB 2016).	Study results did not demonstrate buprenorphine, naloxone, or buprenorphine/naloxone to be genotoxic.
Carcinogenicity	
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 to 75 times, based on a human daily sublingual dose of 16 mg calculated on a mg/m^2 basis. Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dosage groups (SUBOXONE Sublingual Tablet SmPC 2015).	The clinical relevance of the Leydig cell tumour findings noted in rats to humans is limited based on the estimated exposure. No increased risk of carcinogenicity is expected for buprenorphine as a result of SUBOXONE use.
Mechanisms for drug interactions	
Inhibition studies *in vitro* suggested that buprenorphine would not be expected to interact with drugs metabolised by CYP1A2, 2A6, 2B6, 2C9, 2C19 or 2E1. Since buprenorphine and many benzodiazepines are CYP3A substrates, the possibility of PK interaction was investigated. Buprenorphine was found to be a weak inhibitor of CYP3A *in vitro*; however, human PK studies indicated that co-administration of ketoconazole with SUBUTEX resulted in clinically significant increases in exposure to both buprenorphine and the metabolite norbuprenorphine, suggesting an increase in the bioavailability of buprenorphine. Available data indicate that co-administration of buprenorphine should not induce zidovudine toxicity;	SUBOXONE should be used cautiously when co-administered with CYP3A4 inhibitors. An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C_{max} and AUC of buprenorphine (approximately 70 % and 50 % respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving SUBOXONE should be closely monitored and may require dose-reduction if combined with potent CYP3A4 inhibitors (e.g. protease inhibitors like ritonavir, nelfinavir or indinavir or azole antifungals such as ketoconazole, macrolide antibiotics or itraconazole) (SUBOXONE Sublingual Tablet SmPC 2015).

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
this is of importance since many IDUs are HIV positive (SUBOXONE Sublingual Tablet IB 2016).	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 (SUBOXONE Sublingual Tablet SmPC 2015).
Receptor binding studies indicated that there was no evidence of inhibition at peripheral or central benzodiazepine receptors with either buprenorphine or norbuprenorphine. The receptor binding studies suggest that clinical central nervous system (CNS) depressant effects reported following concomitant use of benzodiazepines and buprenorphine are not due to interactions at the receptor level (SUBOXONE Sublingual Tablet IB 2016).	Using SUBOXONE sublingual tablet concomitantly with benzodiazepines may result in death due to respiratory depression of central origin. Therefore, dosages must be limited and this combination must be avoided in cases where there is a risk of misuse. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBOXONE and should also be cautioned to use benzodiazepines concurrently with SUBOXONE only as directed by their physician (SUBOXONE Sublingual Tablet SmPC 2015).
No pharmacodynamic drug interactions have been identified between buprenorphine and naloxone (SUBOXONE Sublingual Tablet IB 2016). There was no indication of an undesirable pharmacological interaction between buprenorphine and naloxone; both drugs have a long history of safe use. For this reason, classical safety pharmacology studies in animals have not been conducted on the combination product and this omission is considered to be fully justified. No pharmacodynamic drug interactions have been identified (SUBOXONE Sublingual Tablet IB 2016).	Nonclinical safety studies conducted with buprenorphine/naloxone or as single entities suggest that human risk is likely to be minimal.
Other toxicity-related information or data	
• **Alcohol**	SUBOXONE should not be taken together with alcoholic drinks or medicines containing alcohol, as alcohol increases the sedative effect of buprenorphine (SUBOXONE Sublingual Tablet SmPC 2015).
• **Analgesics**	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 (SUBOXONE Sublingual Tablet SmPC 2015).
• **MAOI**	SUBOXONE should be used cautiously when co-administered with monoamine oxidase inhibitors (MAOI), as the concomitant use of MAOI might

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
	produce exaggeration of the effects of opioids, based on experience with morphine (SUBOXONE Sublingual Tablet SmPC 2015).
• **Other drugs**	SUBOXONE should be used cautiously when co-administered with other CNS 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 CNS depression. The reduced level of alertness can make driving and using machines hazardous (SUBOXONE Sublingual Tablet SmPC 2015).
• **Opioid antagonists**	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 (SUBOXONE Sublingual Tablet SmPC 2015).

Based on the results of the above nonclinical data accumulated over the course of the SUBOXONE clinical development programme, no additional nonclinical data are required.

Both buprenorphine and naloxone have been used individually in humans in the EU. The pharmacology, pharmacodynamics, absorption, distribution, metabolism, excretion and toxicology (ADMET) of each molecule has been characterised sufficiently (in both animals and humans) to the extent that it can now be predicted that neither would interfere with the ADMET of the other molecule.

SUBOXONE contains naloxone which is intended to deter misuse and abuse of the buprenorphine. Intravenous or intranasal misuse of SUBOXONE is expected to be less likely than buprenorphine alone since the naloxone in SUBOXONE can precipitate withdrawal in individuals dependent on heroin, methadone, or other opioid agonists.
As there was no potential for toxicological interactions/potentiating effect and the PK profile and clinical data on the combination was compelling (with a clinical safety profile of the combination therapy similar to that of the individual components), the decision was made not to assess the nonclinical safety pharmacology or toxicology of the fixed-dose combination of buprenorphine and naloxone formulation in animals, in line with EMEA/CHMP/SWP/258498/2005 guideline on the nonclinical development of fixed combinations of medicinal products.

There is a wealth of existing public domain nonclinical data that has provided a scientific foundation from which to assess the safety of buprenorphine and naloxone and in a fixed-dose combination tablet.

Part II: Module SIII - Clinical Trial Exposure[f]

Table SIII.1: Completed and Ongoing Clinical Trials with Exposure to SUBOXONE Sublingual Tablet

Phase Count	Phase of Study	Protocol Number	Number of Subjects Enrolled	Number of Subjects Treated
Phase I: 30	Phase I	CR95/001	8	8
	Phase I	CR97/007	16	16
	Phase I	CR96/023	9	9
	Phase I	0600154	14	14
	Phase I	0600163	36	36
	Phase I	RB-UK-12-0007[g]	41	40
	Phase I	RB-UK-12-0008[g]	52	52
	Phase I	20-197-SA	15	15
	Phase I	20-A70-AU	15	15
	Phase I	20-A71-AU	16	15
	Phase I	20-A72-AU	15	14
	Phase I	20-B20-AU	48	45
	Phase I	20-273-SA	47	44
	Phase I	20-272-SA	48	41
	Phase I	20-A90-AU	48	48
	Phase I	20-250-SA	45	41
	Phase I	1003395	47	47
	Phase I	BU0805	38	36
	Phase I	BU0820	6	6
	Phase I	BU0806	38	36
	Phase I	BU0823	6	6
	Phase I	BU0914	8	8
	Phase I	RB-UK-10-0014	15	15
	Phase I	RB-US-11-0020	15	12
	Phase I	RB-US-12-0002	48	48
	Phase I	RB-US-12-0001	52	52
	Phase I	RB-UK-12-0007[h]	50	50

[f] The exposure is derived from studies where datasets are available to INDV only, studies include CR88/130, CR92/102, CR95/002, CR96/013, CR96/014, 0600163, NIDA1018, RB-UK-12-0007, RB-UK-12-0008, 20-197-SA, 20-A70-AU, 20-A71-AU, 20-A72-AU, 20-B20-AU, 20-273-SA, 20-272-SA, 20-A90-AU, 20-250-SA, 1003395, BU0805, BU0820, BU0806, BU0823, P05042, BU0914, RB-UK-10-0014, BU0902, RB-UK-11-0017, RB-US-11-0020, RB-US-08-0003, RB-US-12-0002, RB-US-12-0001, RB-UK-11-0018, RB-UK-12-0007, RB-UK-12-0008 , RB-CN-10-0012, RB-CN-10-0013 and RB-CN-10-0015. The total number of persons (2 573) will not equal the number of subjects treated (3 595) represented in SIII.1 as that table included additional exposure (taken from clinical study reports) from studies where datasets are not available.

[g] Study conducted at Icon

[h] Study conducted at Celerion

Phase Count	Phase of Study	Protocol Number	Number of Subjects Enrolled	Number of Subjects Treated
	Phase I	RB-UK-12-0008[h]	48	48
	Phase I	RB-CN-10-0012	82	82
	Phase I	RB-US-14-0002	48	48
	Phase I	RB-CN-10-0015	32	32
	Phase II	CR92/102[i]	150	132
Phase II: 7	Phase II	CR88/130[i]	53	53
	Phase II	CR92/111[i]	9	9
	Phase II	CR95/002	25	25
	Phase II	CR97/003	47	29
	Phase II	CR97/004	46	22
	Phase II	RB-UK-11-0017	80	80
	Phase II	RB-UK-11-0018	36	36
Phase III: 8	Phase III	CR96/013	110	109
	Phase III	CR96/014	472	472
	Phase III	0600201	40	40
	Phase III	US08	103	103
	Phase III	0600123 (NIDA1018)	582	582
	Phase III	RB-CN-10-0013	329	329
Phase IV: 5	Phase IV	P05094	60	53
	Phase IV	P04843	240	240
	Phase IV	P05042	188	187
	Phase IV	BU0902	79	72
	Phase IV	RB-US-08-0003	43	43
Total: 50			**3 698**	**3 595**
Note: Studies 20-250-SA, 20-272-SA, 20-273-SA, RB-US-12-0001, RB-US-12-0002, RB-US-14-0002, 20-A71-AU, 20-A72-AU, and 20-A90-AU are included in both SUBOXONE tablet and film exposure tables.				

Table SIII.2: Completed and Ongoing Clinical Trials with Exposure to SUBOXONE Sublingual Film

Phase Count	Phase of Study	Protocol Number	Number of Subjects Enrolled	Number of Subjects Treated
Phase I: 14	Phase I	1003395	47	47
	Phase I	20-250-SA	45	41
	Phase I	20-272-SA	48	48
	Phase I	20-273-SA	47	47

[i] Studies CR88/130, CR92/111 and CR92/102, utilised a buprenorphine sublingual solution administered sublingually that was never submitted for marketing authorisation approval.

Phase Count	Phase of Study	Protocol Number	Number of Subjects Enrolled	Number of Subjects Treated
	Phase I	20-291-SA	60	60
	Phase I	20-293-SA	60	60
	Phase I	20-B20-AU	48	48
	Phase I	RB-US-12-0001	52	52
	Phase I	RB-US-12-0002	48	48
	Phase I	RB-US-13-0006	66	66
	Phase I	RB-US-14-0002	48	48
	Phase I	20-A71-AU	16	16
	Phase I	20-A72-AU	15	15
	Phase I	20-A90-AU[j]	48	48
Phase II: 3	Phase II	RB-US-07-0001	382	382
	Phase II	RB-US-07-0002	18	18
	Phase II	RB-US-13-0002	39	39
Phase III: 2	Phase III	RB-US-13-0001	1 187	665
	Phase III	RB-US-13-0003	994	775
Phase IV: 1	Phase IV	RBP-OSZ1	33	32
Total			**3 301**	**2 555**

Table SIII.3: Duration of Exposure - Completed Clinical Trial Exposure for SUBOXONE Sublingual Tablet

Indication: Opioid dependence			
	(n=2 573)		
Duration of exposure (at least)	**Persons**	**Patient treatment days (PTD)**	**Patient treatment Years (PTY)**
< 1 m (1- 30 days)	1 376	9 849	27.0
1 m (31-90 days)	286	15 950	43.7
3 m (91-180 days)	250	31 677	86.7
6 m (181-360 days)	287	87 520	239.6
12 m (361-540 days)	116	43 571	119.3
>18 m (>541 days)	0	0	0
Total	**2 315**	**188 567**	**516.3**

For 54 subjects in the Studies 20-250-SA, 20-272-SA, 20-273-SA, 20-A72-AU, 20-A90-AU, 20-B20-AU, BU0805, BU0806, BU0902, P05042, RB-UK-12-0007, RB-US-12-0001, there was no exposure duration data available. Additionally, due to variable dosing, subjects who received SUBOXONE tablet only during induction and stabilisation have not been included (RB-CN-10-0013 [199] and RB-CN-10-0015 [5]). Total including these subjects equals 2 573.

[j] In study 20-A90-AU, the 16/4 mg dosage strength evaluated was never submitted for the marketing authorisation approval.

Table SIII.4: Duration of Exposure - Completed Clinical Trial Exposure for SUBOXONE Sublingual Film

Indication: Opioid Dependence			
Duration of exposure (at least)	**Persons**	**Patient treatment days (PTD)**	**Patient treatment years (PTY)**
1-30 days	279	1 246	3.41
1-30 days*	1 044	11 244	30.78
31-90 days*	14	536	1.47
91-180 days*	3	452	1.24
181-360 days*	103	23 841	65.27
361-540 days*	9	3 377	9.25
Total	**1 452**	**40 696**	**111.42**

* Includes the number of subjects in RB-US-13-0001 and RB-US-13-0003 who received SUBOXONE and their corresponding exposure duration, which only includes information collected for in-clinic dosing during the run-in period and taper periods (RB-US-13-0001 only); taking home (i.e. non-clinic) dosing data is excluded as the daily doses actually taken could not be confirmed.

1003395, 20-250-SA, 20-272-SA, 20-273-SA, 20-291-SA, 20-293-SA, 20-A71-AU, 20-A72-AU, 20-A90-AU, 20-B20-AU, RB-US-07-0001 and RBP-OSZ1 are not included in this table due to insufficient data. Studies 20-197-SA and 20-A70-AU have been previously included in this report but have now been removed because the buprenorphine/naloxone formulation used in these studies is not the formulation that became approved as SUBOXONE sublingual film.

Table SIII.5: Cumulative Exposure to SUBOXONE Sublingual Tablet by Dose

Dose of exposure (Daily dosage of buprenorphine in SUBOXONE)	Persons (n=2 573)	Patient treatment days (PTD)	Patient treatment Years (PTY)
2 mg	235	1 743	4.8
4 mg	74	182	0.5
6 mg	2	2	<0.1
8 mg	478	22 775	62.4
8-24 mg	188	4 148	11.4
10 mg	5	5	<0.1
12 mg	194	510	1.4
14 mg	5	5	<0.1
16 mg	516	45 487	124.5
18 mg	13	13	<0.1
20 mg	16	710	1.9
22 mg	4	4	<0.1
24 mg	25	136	0.4
Total	**1 755**	**75 720**	**207.3**

614 subjects had unknown dosage exposure in Studies NIDA1018, 20-250-SA, 20-272-SA, 20-273-SA, 20-A72-AU, 20-A90-AU, 20-B20-AU, and RB-UK-12-0007. Additionally, due to variable dosing, subjects who received SUBOXONE tablet only during induction and stabilisation have not been included (RB-CN-10-0013 [199] and RB-CN-10-0015 [5]). Total including these subjects equals 2 573. Dose as "8 mg-24 mg", indicates dose escalation within a study after randomisation. The dose presented is the dose level of buprenorphine in SUBOXONE (buprenorphine/naloxone).

Table SIII.6: Cumulative Exposure to SUBOXONE Sublingual Film by Dose

Indication: Opioid Dependence			
Duration of exposure (by daily dosage)	**Persons**	**Patient treatment days (PTD)**	**Patient treatment years (PTY)**
2 mg/0.5 mg	565	4 138	11.33
4 mg/1 mg	1 461	18 433	50.47

Indication: Opioid Dependence			
Duration of exposure (by daily dosage)	**Persons**	**Patient treatment days (PTD)**	**Patient treatment years (PTY)**
8 mg/2 mg	1 276	22 447	61.46
12 mg/3 mg	1 028	13 484	36.92
4 mg	41	60	0.16
8 mg	17	66	0.18
12 mg	44	173	0.47
16 mg	40	192	053
20 mg	16	127	0.35
24 mg	5	53	0.15
Total	**4 493**	**59 173**	**162.01**

1003395, 20-250-SA, 20-272-SA, 20-273-SA, 20-291-SA, 20-293-SA, 20-A71-AU, 20-A72-AU, 20-A90-AU, 20-B20-AU, and RB-US-07-0001 are not included in this table due to insufficient data. Studies 20-197-SA and 20-A70-AU have been previously included in this report but have now been removed because the buprenorphine/naloxone formulation used in these studies is not the formulation that became approved as SUBOXONE sublingual film.
Subjects could have been counted more than once if the subject took more than one dose. For example, a subject who took both 4 mg and 12 mg doses would be counted in 4 mg as well as in 12 mg.
Dosage are displayed as collected in study data.

Table SIII.7: Cumulative Exposure to SUBOXONE Sublingual Tablet by Age Group and Gender

Indication: Opioid dependence						
Age group (years of age)	**Persons Male**	**Persons Female**	**Patient treatment days (PTD) Male**	**Patient treatment days (PTD) Female**	**Patient treatment Years (PTY) Male**	**Patient treatment Years (PTY) Female**
	(n=2 573)					
<25	322	168	11 465	9 259	31.4	25.3
25-<30	261	103	10 744	4 442	29.4	12.2
30-<35	229	85	15 371	5 512	42.1	15.1
35-<40	237	98	16 094	11 057	44.1	30.3
40-<45	247	78	22 376	6 492	61.3	17.8
45-<50	129	36	13 228	4 370	36.2	12.0
>=50	120	30	9 624	523	26.3	1.4
Total	1 545	598	98 902	41 655	270.8	114.0

226 subjects had no gender assigned in the dataset for NIDA 1018. Additionally, due to variable dosing, subjects who received SUBOXONE tablet only during induction and stabilisation have not been included (RB-CN-10-0013 [199] and RB-CN-10-0015 [5]). Total including these subjects equals 2 573.

Table SIII.8: Cumulative Exposure to SUBOXONE Sublingual Film by Age Group and Gender

Indication: Opioid Dependence						
Age group (years of age)	**Persons**		**Patient treatment days (PTD)**		**Patient treatment years (PTY)**	
	M	F	M	F	M	F
< 25	108	61	2 421	1 485	6.63	4.07
25 - < 30	164	93	3 619	2 032	9.91	5.56
30 - < 35	147	76	3 764	1 732	10.31	4.74

Indication: Opioid Dependence						
Age group (years of age)	**Persons**		**Patient treatment days (PTD)**		**Patient treatment years (PTY)**	
35 - < 40	134	78	3 174	1 159	8.69	3.17
40 - < 45	115	47	2 387	2 239	6.54	6.13
45 - < 50	93	46	4 646	937	12.72	2.57
≥50	209	81	7 647	3 454	20.94	9.46
Total	**970**	**482**	**27 658**	**13 038**	**75.72**	**35.70**

1003395, 20-250-SA, 20-272-SA, 20-273-SA, 20-291-SA, 20-293-SA, 20-A71-AU, 20-A72-AU, 20-A90-AU, 20-B20-AU, and RB-US-07-0001 are not included in this table due to insufficient data.

Table SIII.9: Cumulative Exposure to SUBOXONE Sublingual Tablet by Ethnic or Racial Origin

Indication: Opioid Dependence			
Ethnic/racial origin	**Persons (n=2 573*)**	**Patient treatment days (PTD)**	**Patient treatment Years (PTY)**
American Indian or Alaska Native	24	1 652	4.5
Asian	213	1 283	3.5
Black or African American	361	30 240	82.8
Caucasian	1 300	76 435	209.3
Native Hawaiian or Other Pacific Islander	2	2	<0.1
White	29	918	2.5
Other	440	78 037	213.7
Total	**2 369***	**188 567**	**516.3**

*Due to variable dosing, subjects who received SUBOXONE tablet only during induction and stabilisation have not been included for Studies RB-CN-10-0013 (199) and RB-CN-10-0015 (5). Total including these subjects equals 2 573.

Table SIII.10: Cumulative Exposure to SUBOXONE Sublingual Film by Ethnic or Racial Origin

Indication: Opioid Dependence			
Ethnic/racial origin	**Persons**	**Patient treatment days (PTD)**	**Patient treatment years (PTY)**
American Indian or Alaskan Native	13	208	0.57
Asian	11	436	1.19
Black or African-American	394	13 687	37.47
Multiple	10	301	0.82
Native Hawaiian or Other Pacific Islander	3	29	0.08
White	1 016	25 973	71.11
Other	5	62	0.17
Total	**1 452**	**40 696**	**111.42**

1003395, 20-250-SA, 20-272-SA, 20-273-SA, 20-291-SA, 20-293-SA, 20-A71-AU, 20-A72-AU, 20-A90-AU, 20-B20-AU, and RB-US-07-0001 are not included in this table due to insufficient data.

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Use in Children/Adolescents Less Than 15 Years Old

Reason for exclusion: The safety and efficacy of buprenorphine/naloxone in children below the age of 15 years have not been established. SUBOXONE 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 [sachet] safely, to never open the blister [sachet] in advance, to keep the medication out of the reach of children and other household members, and not to take this medicine in front of children (SUBOXONE Sublingual Tablet SmPC 2015).

Is it considered to be included as missing information? No

Rationale: Use in children/adolescents < 15 years old is not considered missing information as it has not been demonstrated that the safety profile is likely to differ in this patient population. Though the safety and efficacy of buprenorphine/naloxone in children below the age of 15 years have not been established, this is adequately stated in the product information.

Geriatric Use (Elderly Patients Greater Than 65 years old)

Reason for exclusion: The safety and efficacy of SUBOXONE in patients over 65 years of age have not been established. No pharmacokinetic data in elderly patients are available. The SmPC provide no recommendation on the posology of elderly patients. Opioids should be administered with caution to elderly or debilitated patients.

Is it considered to be included as missing information? No

Rationale: Use in elderly patients (> 65 years old) is not considered missing information as it has not been demonstrated that the safety profile is likely to differ in this patient population. Though the safety and efficacy of buprenorphine/naloxone in patients over 65 years of age have not been established, this is adequately stated in the product information.

Pregnant or Breastfeeding Women

Reason for exclusion:
SUBOXONE should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Toward the end of pregnancy, buprenorphine may induce respiratory depression in the new-born 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 onset of the syndrome is generally delayed from 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.

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

Is it considered to be included as missing information? No; however, drug use during pregnancy and lactation is considered an identified risk.

Rationale: A PASS (Indivior (PE-US001) 2014) 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 *in utero* 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 individual case safety reports (ICSRs) from INDV's safety database, reported through 31 December 2012, were reviewed. The majority of these cases involved exposure during pregnancy without development of any adverse events. A total of 1 789 cases involved a pregnant woman/foetus or infant with targeted medical events (TMEs) of interest in pregnancy reported 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 post marketing surveillance of pharmacovigilance (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 Maternal Opioid Treatment: Human Experimental Research (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).

Patients Who Have Been Shown to be Hypersensitive to SUBOXONE

Reason for exclusion: A history of hypersensitivity to buprenorphine, naloxone or to any other component of the product is a contraindication to SUBOXONE use.

Is it considered to be included as missing information? No

Rationale: Although uncommon (≥1/1000 to <1/100), there have been treatment-related adverse reactions of hypersensitivity reported in clinical trials and post-marketing surveillance of SUBOXONE.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. However, given the extended post-marketing experience of the component products, for example, over 30 years for buprenorphine, the detection of signals for uncommon, rare or very rare adverse events would be less of a concern for SUBOXONE.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table SIV.1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Use in children/adolescents < 15 years old	Individuals < 15 years old were excluded from the clinical development programme for SUBOXONE.
Use in elderly patients (≥ 65 years old)	The clinical development programme for SUBOXONE did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects.
Pregnant women	Pregnant women were excluded from the SUBOXONE clinical development programme; however, there were 7 pregnant women exposed during SUBOXONE clinical trials. A PASS (Indivior (PE-US001) 2014) 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. 1. Sweden. SUBOXONE was approved in EEA on 26 September 2006. Although the number of pregnant women on SUBOXONE during pregnancy has increased compared to the earlier study

Type of Special Population	Exposure
	periods the number is still too small to draw any conclusions on use during pregnancy or its consequences. To perform estimations more exposures are needed. Among the SUBOXONE-exposed pregnant women in Sweden, there were 7 infants with NAS and one congenital malformation case. 2. [redacted] There was only one pregnant woman exposed to SUBOXONE giving preterm birth to twins. Both infants had congenital malformations but no NAS. This single case is not valid to draw any conclusion. For generalisable estimations more exposures are needed. 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 with TMEs of interest in pregnancy reported 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 post-marketing 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).
Breastfeeding women	Breastfeeding women were not included in the clinical development programme for SUBOXONE.

Type of Special Population	**Exposure**
Patients with hepatic impairment	There were 173 patients (27.7 PTD) with hepatic impairment exposed during SUBOXONE clinical trials. In 2013, INDV completed the PASS Study RB-US-08-0003 (PK of Buprenorphine and Naloxone in Subjects with Mild to Severe Hepatic Impairment (Child-Pugh Classes A, B, and C), in HCV-Seropositive, and in Healthy Volunteers). The objective was to quantify the impact of hepatic impairment or HCV infection on the PK of buprenorphine or naloxone and their major metabolites. PK parameters were derived from 33 subjects. Compared with healthy subjects, for patients with severe hepatic impairment, total and peak exposures increased to 281.4 % [90 % confidence interval 187.1-423.3] and 171.8 % [117.9-250.2] for buprenorphine, 1401.9 % [707.6-2777.5] and 1129.8 % [577.2-2211.4] for naloxone. For moderate hepatic impaired subjects, naloxone total and peak exposure increased to 317.6 % [164.9-611.5] and 270.0 % [141.9-513.9]. For buprenorphine, only total exposure increased to 163.9 % [110.8-242.3]. Changes in maximum observed plasma concentration, area under the plasma concentration-time curve from time zero to time of the last quantifiable concentration, and area under the plasma concentration-time curve from time zero to infinity of buprenorphine or naloxone in subjects with mild hepatic impairment or with hepatitis C virus infection were within twofold of those of healthy subjects. Serious adverse events were not observed (Nasser 2015).
Patients with renal impairment	There were 22 patients (7.0 PTD) with renal impairment exposed to SUBOXONE during clinical trials.
Patients with cardiovascular impairment	Patients with cardiovascular impairment were not included in the clinical development programme for SUBOXONE; 1 patient with cardiovascular impairment (0.003 PTD) was exposed to SUBOXONE during clinical trials.
Immunocompromised patients	There were 9 patients with HIV who were exposed to SUBOXONE during clinical trials.
Patients with a disease severity different from inclusion criteria in clinical trials	Patients with a disease severity different from inclusion criteria in clinical trials were not included in the clinical development programme for SUBOXONE.

<table>
<tr><th>Type of Special Population</th><th>Exposure</th></tr>
<tr><td>Population with relevant different ethnic origin for SUBOXONE</td><td>

Cumulative Exposure to SUBOXONE Sublingual Tablet by Ethnic or Racial Origin

<table>
<tr><th colspan="4">Indication: Opioid Dependence</th></tr>
<tr><th>Ethnic/racial origin</th><th>Persons</th><th>Patient treatment days (PTD)</th><th>Patient treatment years (PTY)</th></tr>
<tr><td></td><td>(n=2 573)*</td><td></td><td></td></tr>
<tr><td>American Indian or Alaska Native</td><td>24</td><td>1 652</td><td>4.5</td></tr>
<tr><td>Asian</td><td>213</td><td>1 283</td><td>3.5</td></tr>
<tr><td>Black or African American</td><td>361</td><td>30 240</td><td>82.8</td></tr>
<tr><td>Caucasian</td><td>1 300</td><td>76 435</td><td>209.3</td></tr>
<tr><td>Native Hawaiian or Other Pacific Islander</td><td>2</td><td>2</td><td><0.1</td></tr>
<tr><td>White</td><td>29</td><td>918</td><td>2.5</td></tr>
<tr><td>Other</td><td>440</td><td>78 037</td><td>213.7</td></tr>
<tr><td>Total</td><td>2 369</td><td>188 567</td><td>516.3</td></tr>
</table>

* Due to variable dosing, subjects who received SUBOXONE tablet only during induction and stabilisation have not been included for Studies RB-CN-10-0013 (199) and RB-CN-10-0015 (5). Total including these subjects equals 2 573.

Cumulative Exposure to SUBOXONE Sublingual Film by Ethnic or Racial Origin

<table>
<tr><th colspan="4">Indication: Opioid Dependence</th></tr>
<tr><th>Ethnic/racial origin</th><th>Persons</th><th>Patient treatment days (PTD)</th><th>Patient treatment years (PTY)</th></tr>
<tr><td>American Indian or Alaskan Native</td><td>13</td><td>208</td><td>0.57</td></tr>
<tr><td>Asian</td><td>11</td><td>436</td><td>1.19</td></tr>
<tr><td>Black or African-American</td><td>394</td><td>13 687</td><td>37.47</td></tr>
<tr><td>Multiple</td><td>10</td><td>301</td><td>0.82</td></tr>
<tr><td>Native Hawaiian or Other Pacific Islander</td><td>3</td><td>29</td><td>0.08</td></tr>
<tr><td>White</td><td>1 016</td><td>25 973</td><td>71.11</td></tr>
<tr><td>Other</td><td>5</td><td>62</td><td>0.17</td></tr>
<tr><td>Total</td><td>1 452</td><td>40 696</td><td>111.42</td></tr>
</table>

</td></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Not included in the clinical development programme for SUBOXONE.</td></tr>
</table>

Part II: Module SV - Post-authorisation Experience

SV.1 Post-Authorisation Exposure for SUBOXONE

SV.1.1 Methods Used to Calculate Exposure

Marketing experience of SUBOXONE sublingual tablet/film has been determined by combining the numbers of dose units manufactured and released for sale by INDV to all countries. The recommended starting dose is 2 to 4 mg, an additional 2 to 4 mg may be administered on Day 1 depending on the individual patients' requirements. Doses are increased until the desired clinical effect is reached for each patient, subject to a maximum daily dose of 24 mg. The rare requirement for a highly tolerant patient to receive a dose between 24 mg/d and 32 mg/d should prompt a thorough review of the patient's progress toward meeting treatment goals. For the purpose of exposure estimation, it is assumed that the average daily dose is 8 mg (WHO 2017).

To estimate patient exposure, unit sales for the time period were converted from number of SUBOXONE sublingual tablet/film to the number of milligrams (mg) buprenorphine for each of the 2 mg, 4 mg, 8 mg, 12 mg and 16 mg sublingual tablet/film strengths. The number of mg for each SUBOXONE sublingual tablet/film strength was summed to give the total number of mg which was then divided by the average daily dose to estimate the number of PTD. The total number of PTD was then divided by 365.25 to estimate the total number of PTY.

Cumulatively, worldwide patient exposure was estimated to be 2 654 285 PTY for SUBOXONE sublingual tablet, see Table SV.1, and 4 122 306 for SUBOXONE sublingual film, see Table SV.2.

Table SV.1: SUBOXONE Sublingual Tablet Exposure Table for Indication: Opioid Dependence

Region*	Lifetime Exposure			
	2 mg Tablet	8 mg Tablet	12 mg Tablet	16 mg Tablet
Americas (mg)[k]	306 743 158	5 724 362 784	1 418 592	801 920
Americas (PTD)	38 342 895	715 545 348	177 324	100 240
Americas (PTY)	104 977	1 959 056	485	274
Europe (mg)	295 170 642	1 022 499 832	0	14 627 648
Europe (PTD)	405 398	127 812 479	0	1 828 456
Europe (PTY)	101 017	349 931	0	5 006
RoW (mg)[l]	82 621 638	307 384 936	0	192 640
RoW (PTD)	10 327 705	38 423 117	0	24 080
RoW (PTY)	28 276	105 197	0	66
Global exposure (mg)	**684 535 438**	**7 054 247 552**	**1 418 592**	**15 622 208**
Global exposure (PTD)	**85 566 930**	**881 780 944**	**177 324**	**1 952 776**
Global exposure (PTY)	**234 269**	**2 414 185**	**485**	**5 346**

*Regions are divided geographically.

[k] SUBOXONE sublingual tablet 12 mg and 16 mg are only available in Canada
[l] SUBOXONE sublingual tablet is provided as unlicensed medicinal product in Qatar and United Arab Emirates (UAE)

Table SV.2: SUBOXONE Sublingual Film Exposure Table for Indication: Opioid Dependence

Region*	Lifetime Exposure			
	2 mg Film	4 mg Film	8 mg Film	12 mg Film
Americas (mg)[m]	240 883 680	136 480 800	10 933 761 600	302 310 720
Americas (PTD)	30 110 460	17 060 100	1 366 720 200	37 788 840
Americas (PTY)	82 438	46 708	3 741 876	103 460
Europe (mg)[n]	3 672 060	0	27 875 280	12 663 360
Europe (PTD)	459 008	0	3 484 410	1 582 920
Europe (PTY)	1 257	0	9 540	4 334
RoW (mg)[o]	61 190 852	270 480	325 325 392	943 200
RoW (PTD)	7 648 857	33 810	40 665 674	117 900
RoW (PTY)	20 941	93	111 337	323
Global exposure (mg)	**305 746 592**	**136 751 280**	**11 286 962 272**	**315 917 280**
Global exposure (PTD)	**38 218 324**	**17 093 910**	**1 410 870 284**	**39 489 660**
Global exposure (PTY)	**104 636**	**46 801**	**3 862 752**	**108 117**

*Regions are divided geographically.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to diversion. As a partial agonist, buprenorphine abuse potential is less than that of heroin, morphine or methadone. As a consequence, buprenorphine is widely available for the treatment of opioid dependence. The overdose risk of buprenorphine is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

The results of a multicentre, randomised, open-label, active-controlled trial of the effectiveness of buprenorphine / naloxone in reducing IV buprenorphine misuse in France (Indivior (BU0902) 2013) concluded that the combination of naloxone and buprenorphine was substantially more effective than buprenorphine alone in reducing the IV misuse of buprenorphine in opioid dependent patients. This was evident from the high percentage of patients achieving a ≥ 30% reduction in the average weekly number of study treatment injections in the buprenorphine/naloxone group compared with the buprenorphine group (89.2% vs. 42.4%) between the treatment period (Day 1 to Day 84) and the pre-randomisation period (Day -1 to Day -7). These results were supported by the finding of substantially lower mean number of study drug injections in the buprenorphine/naloxone group compared with the buprenorphine group (3.16 vs. 16.09) during the treatment period; as well as by the finding that a substantially greater percentage of patients stopped injecting study drug in the buprenorphine/ naloxone group compared with the buprenorphine group (73.1% vs. 15.6%).

[m] SUBOXONE sublingual film is provided as unlicensed medicinal product in Canada
[n] SUBOXONE sublingual film is provided as unlicensed medicinal product in Denmark, Finland, Norway, and Sweden
[o] SUBOXONE sublingual film is provided as unlicensed medicinal product in Kuwait, Qatar and UAE

Severity of opiate withdrawal symptoms (assessed via COWS and subjective opiate withdrawal scale [SOWS]) and severity of SOWS (assessed via the addiction-severity index (ASI)) were generally improved or unchanged from Day -7 to Day 84 in both the buprenorphine/naloxone and buprenorphine groups indicating no adverse impact of the addition of naloxone on the severity of addiction or opiate withdrawal symptoms.

Safety findings indicated that the combination of naloxone with buprenorphine resulted in an overall increase in the number of adverse events (AE) and treatment-related AEs compared with buprenorphine alone; however, most AEs were mild or moderate and severe AEs and serious AEs (SAE) occurred to a similarly low extent in both treatment groups.

Indivior has undertaken a post-marketing study to determine effects of SUBOXONE overdose through a PASS (Indivior (PE-US003) 2013). Retrospective safety evaluation studies were conducted to investigate the drug's impact on total overdose death, in particular heroin-associated, and the relative contribution of buprenorphine to fatal overdose. Temporal trends in total drug-associated overdose deaths, as well as the proportion associated with buprenorphine, methadone, and heroin/morphine was examined. Further, the study investigated risk factors for fatal overdose associated with buprenorphine, in particular misuse by IV injection and concomitant intake of other CNS depressants. Trends in substitution treatment distribution, buprenorphine and methadone, were also assessed.

The results of the PASS (Indivior (PE-US003) 2013) for Sweden showed that of the fatal cases related to buprenorphine, 15% had a filled prescription with SUBUTEX or SUBOXONE, and 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 or SUBOXONE was hence relatively low. Presumably, most of the subjects who died from a fatal overdose death associated with buprenorphine had obtained their drug illegally. In Denmark, approximately 200 fatal poisoning of drug abusers are registered each year. About 0.5% of these cases have been buprenorphine related. However, in Denmark, SUBUTEX and SUBOXONE are not reimbursed and are, therefore, not systematically recorded in the regional prescription databases. Hence, it was not possible to obtain data to divide buprenorphine-related deaths into SUBUTEX or SUBOXONE treatment. There were no indications of an increase in buprenorphine-related deaths in Denmark.

Introduction of 16 mg SUBOXONE tablets
It is believed that with the introduction of the higher strength 16 mg tablets (MHRA 2011), treatment compliance will increase as less tablets need to be administered to achieve the same dosage, which accompanied by improved efficacy will reduce the risk of abuse, misuse and diversion.

As suboptimal treatment with buprenorphine/naloxone may prompt medication misuse by the patient, leading to overdose or treatment dropout, the higher dose tablets may reduce this risk.

Improved patient adherence and treatment compliance will improve clinical outcomes and benefit to patients. Supporting such approaches will minimise the risk of prescription opioid abuse, addiction, and diversion; reduce health services utilisation association with opioid abuse; improve patient outcomes; reduce overall costs; and reduce major public-health burdens.

The presence of naloxone in the SUBOXONE formulation is intended to deter misuse by injection. The extent to which SUBOXONE will be less likely to be misused by injection is not known and determining the relative extent of its misuse is one of the goals of the RMP through routine PhV.

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

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission for SUBOXONE

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The following risks are not considered important for SUBOXONE:

Fatal overdose (including severe respiratory failure [mechanism for death by overdose]) is not being considered an important identified risk. Cases of overdose and fatal overdose have been reported. There have been a number of post-marketing reports regarding death including cases with the concomitant use of other CNS depressants including opioids, benzodiazepines or alcohol. In many of these cases, buprenorphine was misused by self-injection of crushed buprenorphine tablets. Respiratory depression is considered the main mechanism of death in overdose and is described in the product information. Since no additional risk minimisation measures, additional PhV activities or product information advising on specific clinical actions to be taken to minimise this risk are proposed, fatal overdose is not included as an important identified risk.

Respiratory depression/respiratory failure is not being considered an important identified risk. A number of cases of death due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines, administered to individuals not tolerant to opioids, or when SUBOXONE was otherwise not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and other CNS depressants such as alcohol or other opioids, as described in the product information. No additional risk minimisation measures, additional PhV activities or product information advising on specific clinical actions to be taken to minimise this risk (other than caution in patients with respiratory insufficiency) are proposed, therefore respiratory depression/respiratory failure is not included as an important identified risk.

CNS depression (including effects on driving ability) is not an important identified risk as CNS depression is a well-known class effect of opioids and no additional measures addressing this risk are proposed. SUBOXONE may cause drowsiness, dizziness or impaired thinking, especially during treatment induction and dose adjustment or when used together with CNS depressants and a large number of reports of symptoms of CNS depression have been received. SUBOXONE may impair the ability to drive and use machines when administered to opioid-dependent patients.

Differences in bioavailability between SUBOXONE sublingual tablets and film in switching is not being considered an important identified risk. In PK studies, differences in bioavailability have been observed between sublingual tablets and film depending on dose administered and on type of administration (buccally versus sublingually) with a higher bioavailability observed for the film. The product information advises that patients being switched between SUBOXONE sublingual tablets and SUBOXONE sublingual film should be started on the same dose as the previously administered medicinal product. Patients should, however, be monitored for symptoms of overdose or withdrawal. Though the product information advises on specific clinical actions to be taken (monitoring for signs of overdose or withdrawal when switching patients from one pharmaceutical form to the other), considering that the difference in bioavailability observed is unlikely to cause severe overdose or withdrawal, differences in bioavailability between SUBOXONE sublingual tablets and film is not included as an important identified risk.

Oral reactions is not being included as an identified risk for SUBOXONE sublingual film, as it is not likely to have an impact on the benefit risk balance of the product. There have been numerous post marketing reports of, mostly non-serious, oral reactions in patients using SUBOXONE sublingual film. During clinical trials, the most commonly reported treatment related adverse reactions associated with the sublingual or buccal administration were oral hypoesthesia and oral mucosal erythema, respectively. In the proposed SmPC, several symptoms of administration site reactions have been listed as undesirable effects with frequency uncommon or not known; however, no additional risk minimisation measures, additional PhV activities or product information advising on specific clinical actions to be taken to minimise this risk are proposed.

Use in patients with a head injury and increase in intracranial pressure is not considered an important risk as it is already a well-known opioid class effect. Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure, which may cause seizures. Opioids should be used with caution in patients with head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased, or history of seizure.

Peripheral oedema is not considered an important risk. Peripheral oedema is considered a commonly reported adverse drug reaction during post-marketing surveillance and does not require additional PhV activities or additional risk minimisation measures. Additionally, peripheral oedema is considered a common treatment-related undesirable effect in clinical studies of SUBOXONE.

Drug dependence is not considered an important risk. The risk of drug dependence with use of opioids is well-known to healthcare professionals (HCP) and does not require additional PhV activities or additional risk minimisation measures. Buprenorphine is a partial agonist at the μ-opioid receptor and chronic administration may produce dependence of the opioid type. Drug dependence is listed as the most commonly reported adverse drug reaction during post-marketing surveillance. Appropriate precautions should be taken when prescribing and dispensing SUBOXONE, 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.

Allergic reaction(s) is not considered an important risk. The risk of allergic reactions with the use of opioids is well-known to HCPs and does not require additional PhV activities or

additional risk minimisation measures. As stated in the product information, cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in post-marketing experience. The most common signs and symptoms include rash, urticaria, and pruritus. Cases of bronchospasm, angioedema, angioneurotic oedema and anaphylactic shock have been reported. SUBOXONE is contraindicated in patients with hypersensitivity to buprenorphine or to any other component of the product.

Switching between SUBUTEX and SUBOXONE is not considered an important risk. Switching from SUBUTEX to SUBOXONE with equivalent doses of buprenorphine does not raise significant clinical concerns, although dose adjustments may be necessary in some cases, especially in the later phase of the treatment (Cassoux 2002). A PASS study (Indivior (PE-US004) 2015) was conducted that included monitoring patients switching from SUBOXONE to buprenorphine. The study concluded that none of the safety terms specially searched for and classified as adverse event/reaction reached the 5% threshold. Based on existing clinical studies, significant clinical concerns related to this transfer are not anticipated. SUBOXONE and SUBUTEX have similar clinical effects and are interchangeable; however, when switching between SUBOXONE and SUBUTEX, the prescriber, patient and treatment staff should agree to the change, and the patient should be monitored in case a need to readjust the dose occurs. In June 2018, the product information for SUBUTEX was updated to harmonise SUBUTEX posology with SUBOXONE with regard to the same maximum daily buprenorphine induction dose (i.e., 2 to 8 mg) and maximum recommended maintenance dose (i.e., 24 mg).

Medication errors when switching between SUBUTEX/SUBOXONE and new buprenorphine-containing products (BCP) which are not interchangeable with SUBUTEX/SUBOXONE is not considered an important potential risk. The bioavailability of SUBOXONE differs from other BCPs for transoromucosal administration (e.g. Zubsolv, Espranor). Additionally, the marketed dosage strengths differ between products. Consequently, products are not readily interchangeable. There is a limited number of post-marketing reports of patients switching between SUBOXONE tablet or film and Zubsolv. Based on the mostly non-serious though substantial number of withdrawal reactions, and the limited information provided, switching is unlikely to result in severe consequences. No additional risk minimisation measures, additional PhV activities or product information advising on specific clinical actions other than monitoring to be taken to minimise this risk are proposed.

Use in children/adolescents < 15 years old is not considered missing information as it has not been demonstrated that the safety profile is likely to differ in this patient population. Though the safety and efficacy of buprenorphine/naloxone in children below the age of 15 years have not been established, this is adequately stated in the product information.

Use in elderly patients (> 65 years old) is not considered missing information as it has not been demonstrated that the safety profile is likely to differ in this patient population. Though the safety and efficacy of buprenorphine/naloxone in patients over 65 years of age have not been established, this is adequately stated in the product information.

Reason for Not Including an Identified or Potential risk in the List of Safety Concerns in the RMP:

The following known risks require no further characterisation and are followed up via routine PhV; i.e., through signal detection and adverse reaction reporting, and a determination of

whether the risk minimisation messages in the product information are adhered to by prescribers:

- fatal overdose (including severe respiratory failure [mechanism for death by overdose])
- respiratory depression/respiratory failure
- CNS depression (including effects on driving ability)
- differences in bioavailability between SUBOXONE sublingual tablets and film in switching
- oral reactions (SUBOXONE sublingual film only)
- use in patients with head injury and increase in intracranial pressure
- peripheral oedema
- drug dependence
- allergic reaction(s)
- switching between SUBUTEX and SUBOXONE
- medication errors when switching between SUBUTEX/SUBOXONE and new BCPs which are not interchangeable with SUBUTEX/SUBOXONE
- use in children/adolescents < 15 years old
- use in elderly patients (> 65 years old)

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk 1: Abuse, misuse and diversion

Risk-benefit impact: SUBOXONE can be misused or abused in a manner similar to other opioids, legal or illicit. Some risks of misuse and abuse include overdose, spread of blood borne viral infections, respiratory depression and hepatic injury. SUBOXONE misuse by someone other than the intended patient poses the additional risk of new drug dependent individuals using buprenorphine as the primary drug of abuse and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicine is not safeguarded against theft. Intravenous misuse of buprenorphine has been documented and usually occurs when heroin or the opioid of choice is not readily available, is of poor quality, or not under control on prescribing.

In cases of drug abuse or intentional drug misuse, some adverse experiences attributed to the act of misuse rather than the medicine product have included: local reactions, such as cellulitis or abscess that are sometimes septic, potentially serious acute hepatitis, pneumonia, endocarditis and other serious infections.

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

Buprenorphine/naloxone may cause severe, possibly fatal, respiratory depression in children and nondependent persons in case of accidental or deliberate ingestion.

Thus, the risk of abuse, misuse and diversion is classified as an important identified risk.

Important Identified Risk 2: Use in patients with hepatic impairment

Risk-benefit impact: The effects of hepatic impairment on the PK of buprenorphine were evaluated in a post-marketing study. Since both buprenorphine and naloxone are extensively metabolised, and plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment; in these patients, dose adjustments may be required. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and/or buprenorphine. SUBOXONE should be used with caution in patients with moderate hepatic impairment. In patients with severe hepatic insufficiency, the use of buprenorphine/naloxone is contraindicated.

Thus, use in patients with hepatic impairment is classified as an important identified risk.

Important Identified Risk 3: Hepatic disorders

Risk-benefit impact: Cases of acute hepatic injury have been reported in opioid-dependent patients, 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 cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases, the presence of pre-existing conditions (genetic disease, liver enzyme abnormalities, viral infection such as hepatitis B and chronic hepatitis C, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicines, or ongoing drug use by injection) may have a causative or contributory role.

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

Thus, the risk of hepatic disorders is classified as an important identified risk.

Important Identified Risk 4: Drug withdrawal syndrome

Risk-benefit impact: When initiating treatment with SUBOXONE, it is important to be aware of buprenorphine's partial agonist profile. Buprenorphine can precipitate withdrawal signs and symptoms in opioid-dependent patients (i.e., physically dependent on an opioid other than buprenorphine). To avoid precipitating withdrawal upon induction from short-acting or long-acting opioids, the patient should show objective signs and symptoms of moderate withdrawal prior to induction dosing.

Since buprenorphine is a μ-opioid partial agonist, concomitantly administered opioid antagonists such as naltrexone can reduce or completely block the effects of SUBOXONE. Patients maintained on SUBOXONE may experience a sudden onset of intense and possibly prolonged opioid withdrawal signs and symptoms if administered an opioid antagonist.

In a multicentre clinical trial of SUBUTEX, SUBOXONE sublingual tablets, and placebo, the most frequently reported events for the buprenorphine products were those often associated with opioid withdrawal syndrome (headache, pain, abdominal pain, back pain, diarrhoea, nausea, insomnia, rhinitis, and sweating).

Thus, drug withdrawal syndrome is classified as an important identified risk.

Important Identified Risk 5: Use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child

Risk-benefit impact: SUBOXONE should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Chronic use of SUBOXONE 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 onset of 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. Additionally, use during pregnancy or lactation may lead to opioid toxicity or withdrawal signs and symptoms in the newborn.

Neonatal drug withdrawal syndrome has been reported among neonates of women who have received buprenorphine products during pregnancy. The syndrome may be milder and more protracted than that seen with short-acting full μ-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug-use history.

Thus, use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child is classified as an important identified risk.

Important Potential Risk: None

Missing Information: None

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

SVII.2.1. New Safety Concerns

No new safety concerns have been added to this RMP (version 14.2), with the addition of SUBOXONE sublingual film, compared with the previously approved SUBOXONE RMP (version 13.0).

SVII.2.2. Reclassified Safety Concerns

This RMP includes safety concerns that were removed as safety concerns and considered not important since version 13.0 of the SUBOXONE RMP. See section SVII.1.1 for the list of safety concerns that are not considered important.

- fatal overdose (including severe respiratory failure [mechanism for death by overdose])
- respiratory depression/respiratory failure
- CNS depression (including effects on driving ability)
- use in patients with head injury and increase in intracranial pressure
- peripheral oedema
- drug dependence
- allergic reaction(s)
- switching between SUBUTEX and SUBOXONE
- use in children/adolescents < 15 years old
- use in elderly patients (> 65 years old)

The following changes were made to existing important identified risks:

- "Misuse and/or abuse (injection/intranasal/paediatric use)" was changed to "Abuse, misuse and diversion"
- "Hepatitis, hepatic events, use in patients with hepatic impairment" was split into important identified risks, "Use in patients with hepatic impairment" and "Hepatic disorders"
- "Use during pregnancy, and lactation (effects on newborn and infant)" was changed to "Use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child"

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1: Presentation of Important Identified Risks and Important Potential Risks[p]

Important Identified Risk: Abuse, misuse and diversion	
Potential mechanisms	SUBOXONE can be misused or abused in a manner similar to other opioids, legal or illicit.

[p] MedDRA version 21.1 was used to classify events. MedDRA up versioning may sometimes recode and reclassify events.

	The most common pattern of abuse involves crushing the sublingual tablets and injecting the resulting extract (Cicero 2005). Based on spontaneous post-marketing reports for SUBOXONE sublingual film, the most commonly reported event considered to be abuse involves cutting the film to achieve dose.
Evidence source(s) and strength of evidence	The 2017 World Drug Report by UNODC stated that the number of past-year users of opiates and individuals who misused prescription opioids worldwide was estimated at 35.1 million people (range 28.3 to 42.7 million) (UNODC 2017). Misuse of prescription opioids remains of concern in the recent years, where, coupled with an increase in heroin and fentanyl use, it has resulted in a combined and interrelated epidemic and a rise in morbidity and mortality related to opioids (UNODC 2017). A number of cases of death due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines or when buprenorphine was not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and other depressants such as alcohol or other opioids. Sublingual buprenorphine can be misused or abused in a manner similar to other opioids and can lead to dependence in previously non-dependent individuals, overdose and potentially fatal respiratory depression. Combining buprenorphine with naloxone in SUBOXONE is intended to deter misuse and abuse of buprenorphine. Intravenous or intranasal misuse of SUBOXONE is expected to be less likely than with buprenorphine alone since the naloxone component can antagonise the opioid effect of buprenorphine and precipitate withdrawal in individuals dependent on opioids. 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. In cases of IV drug misuse, some adverse experiences 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. Many of the histories provided from post-marketing 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. A cross-over study was conducted in healthy volunteers which showed that intranasal administration represents a valuable delivery route for buprenorphine (Eriksen 1989). However, studies have also shown that buprenorphine is misused by the intranasal route (Strang 1991), and intranasal inhalation of pharmaceutical opioids is a significant predictor of illicit buprenorphine use (Daniulaityte 2012). The significant absorption of naloxone from intranasal buprenorphine/naloxone administration observed may deter the likelihood of intranasal misuse of buprenorphine/naloxone (Middleton 2011). 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.

A study was conducted to investigate 11 275 children and adolescents who were exposed to buprenorphine and reported to the US poison control centres from 2007 to 2016. The most common symptoms were drowsiness and/or lethargy (46.8%), vomiting (17.0%), and miosis (12.6%). The serious clinical effects included respiratory depression (n=891), bradycardia (n=98), coma (n=65), cyanosis (n=36), seizure (n=10), and cardiac arrest (n=6). Most exposures were among children <6 years old (86.1%). Almost half (48.1%) were admitted to a health care facility, of which 23.6% were admitted to a critical care unit; of these there were 7 children who had fatal outcomes (Post 2018).

Due to limited amount of available data, patients below the age of 18 should be closely monitored during treatment.

Sub-optimal treatment with SUBOXONE may prompt medicine misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with SUBOXONE may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines.

Characterisation of risks

To date, 24 113 events classified as "abuse, misuse and diversion" were reported with SUBOXONE sublingual tablet (reporting rate 908.5 events per 100 000 patient years). Of the 24 113 events, 602 were serious and 192 had a fatal outcome. One-hundred and thirty-seven (137) events of abuse, misuse and diversion were reported in children less than 15 years of age, of which 130 were serious and 15 had a fatal outcome.

To date, 44 060 events classified as "abuse, misuse and diversion" were reported with SUBOXONE sublingual film (reporting rate 1 068.8 events per 100 000 patient years). Of the 44 060 events, 581 were serious and 303 had a fatal outcome. Thirty-nine (39) events of abuse, misuse and diversion were reported in children less than 15 years of age, of which 38 events were serious and 3 had a fatal outcome.

Children, especially in families of patients treated with SUBOXONE, can be accidentally exposed to it.

Cumulatively, the most commonly reported events received are captured in the following table:

	SUBOXONE sublingual tablet		**SUBOXONE sublingual film**	
Information Reported	**Event Count**	**Rate**	**Event Count**	**Rate**
Obtained without prescription	11 601	437.1	16 512	400.6
Different indication, induction*, dosing, schedule than in approved label	1 825	68.8	6 172	149.7
Cutting tablet/film	2 049	77.2	7 899	191.6
Taking less than prescribed or self-tapering	1 561	58.8	4 540	110.1
Not taking as prescribed	2 602	98.0	2 715	65.9
IV/Intranasal/Other intentional misuse by wrong route	993	37.4	456	11.1
Taking orally	217	8.2	53	1.3

*Due to changes in induction wording in the United States Prescribing Information over time.

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). Illicit opioid and polysubstance abusers are at risk of IV and intranasal abuse of SUBOXONE. Children of opioid abusers and of those in treatment with SUBOXONE are at risk of accidental exposure. Sub-optimal treatment with SUBOXONE may prompt medication misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with SUBOXONE may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines. 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, and 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. SUBOXONE should be used with care in paediatric 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]).
Preventability	Supervised substance abuse treatment and patient education is the major activity to prevent IV and intranasal abuse of SUBOXONE. SUBOXONE 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 SUBOXONE blister (tablet) / sachet (film) safely, to never open the blister (tablet) / sachet (film) in advance, to keep them out of the reach of children and other household members, and not to take this medicine in front of children. An emergency unit should be contacted immediately in case of accidental ingestion or suspicion of ingestion. Clinicians should remain vigilant for paediatric exposures. Patients receiving buprenorphine on an outpatient basis should be educated regarding steps they can take to ensure the drug is not accessible to any young children in their homes. To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing SUBOXONE, such as to avoid prescribing multiple refills early in treatment and conducting patient follow-up visits with clinical monitoring that is appropriate for the patient's needs. SUBOXONE contains naloxone which is intended to deter misuse and abuse of the buprenorphine.

	Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBOXONE and should also be cautioned to use benzodiazepines concurrently with SUBOXONE only as directed by their physician. SUBOXONE sublingual tablets are packed in individual child-resistant packaging which will contribute toward the control of exposure risk to children. SUBOXONE sublingual film is packed in child-resistant individual sachets made between two identical layers of polymer-foil composite. Do not open the foil sachet until you are ready to use it. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Additionally, the scientific literature states that manufacturers should use unit-dose packaging for all buprenorphine products to help prevent unintentional exposure among young children (Post 2018). Health providers should inform caregivers of young children about the dangers of buprenorphine exposure and provide instructions on proper medication storage and disposal (Post 2018). The safety and efficacy of buprenorphine/naloxone in children below the age of 15 years have not been established.
Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of abuse, misuse and diversion, it is expected that the impact on the risk-benefit balance of SUBOXONE is low.
Public health impact	Opioid abuse is a major public health concern and is associated with a high level of morbidity and mortality in Europe (EMCDDA 2017). In Canada, SUBOXONE was added to Health Canada's Urgent Public Health Need list due to the major opioid abuse public health crisis. Since the prevalence of opioid abuse and misuse has increased globally, leading to an increase in deaths from overdose and individuals seeking treatment for opioid use disorders, a number of policy and educational initiatives have been implemented to help providers and patients, prescribe and use opioids more responsibly (Brady 2016). These include increasing access to effective treatments and harm reduction strategies including education, monitoring opioid cost and supply, strategic reimbursement for clinicians, and targeted research funding (Hawk 2015). Risks of infection and death due to respiratory depression constitute known public health problems posed by IV opioid abuse. Although there have been reports of abuse using SUBOXONE, the benefits of therapeutic SUBOXONE sublingual tablet and film substantially outweigh the risk of divergence.

Important Identified Risk: Use in patients with hepatic impairment	
Potential mechanisms	Many analgesics, including opioids, undergo hepatic metabolism (e.g., oxidation, dealkylation). Therefore, the potential for toxicity of these medications can increase individuals with reduced hepatic function (Soleimanpour 2016).

	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 to severe hepatic impairment compared with healthy subjects. Infection is primarily secondary to IV drug abuse.
Evidence source(s) and strength of evidence	In 2013, INDV completed the PASS Study RB-US-08-0003 (PK of Buprenorphine and Naloxone in Subjects with Mild to Severe Hepatic Impairment (Child-Pugh Classes A, B, and C), in HCV- Seropositive, and in Healthy Volunteers). The objective was to quantify the impact of hepatic impairment or HCV infection on the PK of buprenorphine or naloxone and their major metabolites. PK parameters were derived from 33 subjects. Compared with healthy subjects, for patients with severe hepatic impairment, total and peak exposures increased to 281.4 % [90 % confidence interval 187.1-423.3] and 171.8 % [117.9-250.2] for buprenorphine, 1401.9 % [707.6-2777.5] and 1129.8 % [577.2-2211.4] for naloxone. For moderate hepatic impaired subjects, naloxone total and peak exposure increased to 317.6 % [164.9-611.5] and 270.0 % [141.9-513.9]. For buprenorphine, only total exposure increased to 163.9 % [110.8-242.3]. Changes in maximum observed plasma concentration, area under the plasma concentration-time curve from time zero to time of the last quantifiable concentration, and area under the plasma concentration-time curve from time zero to infinity of buprenorphine or naloxone in subjects with mild hepatic impairment or with hepatitis C virus infection were within twofold of those of healthy subjects. Serious adverse events were not observed (Nasser 2015).
Characterisation of risks	To date, 3 275 events in patients with a history of hepatic disease have been reported with SUBOXONE sublingual tablet. Of these, 397 events were serious, and 32 had a fatal outcome. To date, 2 152 events in patients with a history of hepatic disease have been reported with SUBOXONE sublingual film. Of these, 355 events were serious, and 14 had a fatal outcome.
Risk factors and risk groups	Patients who are positive for viral hepatitis or having existing liver dysfunction are at greater risk of liver injury. IDUs are at risk of contracting infectious diseases (EMCDDA 2017).
Preventability	As buprenorphine/naloxone PK 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 (SUBOXONE Sublingual Tablet SmPC 2015). SUBOXONE should be used with caution in patients with moderate hepatic impairment. In patients with severe hepatic insufficiency, the use of buprenorphine/naloxone is contraindicated. 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.

Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of use in patients with hepatic impairment, it is expected that the benefit-risk balance of SUBOXONE remains positive.
Public health impact	Hepatitis is a common health concern among opioid dependent IDUs. However, the public health impact is low, as the risk can be largely minimised if the product is used as per the reference safety information.

Important Identified Risk: Hepatic disorders	
Potential mechanisms	Many analgesics, including opioids, undergo hepatic metabolism (e.g., oxidation, dealkylation). Therefore, the potential for toxicity of these medications can increase in individuals with reduced hepatic function (Soleimanpour 2016). 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 to severe hepatic impairment compared with healthy subjects. Infection is primarily secondary to IV drug abuse.
Evidence source(s) and strength of evidence	Section 4.4 of the SUBOXONE SmPC states that 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 medicines) and ongoing injecting drug use) may have a causative or contributory role.
Characterisation of risks	To date, 644 events classified as "hepatic disorders" were reported with SUBOXONE sublingual tablet (reporting rate 24.3 events per 100 000 patient years). Of these, 284 events were serious, and 11 had a fatal outcome. To date, 528 events classified as "hepatic disorders" were reported with SUBOXONE sublingual film (reporting rate 12.8 events per 100 000 patient years). Of these, 296 events were serious, and 3 had a fatal outcome.
Risk factors and risk groups	Patients with viral hepatitis or existing liver dysfunction are at greater risk of liver injury. IDUs are at risk of contracting infectious diseases (EMCDDA 2017).
Preventability	As buprenorphine/naloxone PK 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 (SUBOXONE Sublingual Tablet SmPC 2015). SUBOXONE should be used with caution in patients with moderate hepatic impairment. In patients with severe hepatic insufficiency, the use of buprenorphine/naloxone is contraindicated. 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.
Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of hepatic disorders, it is expected that the benefit-risk balance of SUBOXONE remains positive.
Public health impact	Hepatitis is a common health concern among opioid dependent IDUs. However, the public health impact is low, as the risk can be largely minimised if the product is used as per the reference safety information.

Important Identified Risk: Drug withdrawal syndrome	
Potential mechanisms	SUBOXONE is a combination of naloxone and buprenorphine, a partial agonist at the mu-opiate receptor. Chronic administration produces dependence of the opioid type. The withdrawal syndrome is typically milder than seen with full agonists (e.g., morphine) and may be delayed in onset. Withdrawal can occur upon abrupt discontinuation or rapid taper, dose omission, and treatment initiation before objective and clear signs of withdrawal are evident. Parenteral misuse of naloxone by individuals physically dependent on opioid full agonists (e.g. heroin, morphine, or methadone) may produce sudden and intense withdrawal symptoms.
Evidence source(s) and strength of evidence	Section 4.8 of the SUBOXONE SmPC states that cases in patients presenting with marked drug dependence, initial administration of buprenorphine can produce a drug withdrawal syndrome similar to that associated with naloxone. Section 4.8 of the SUBOXONE SmPC also states that the most commonly reported treatment-related adverse reactions reported during the pivotal clinical studies using SUBOXONE sublingual tablets included symptoms commonly associated with drug withdrawal (i.e. insomnia, headache, nausea and hyperhidrosis). Symptoms of opioid withdrawal (dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhoea, pupillary dilation, piloerection, or sweating, diarrhoea, yawning, fever, insomnia) may cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (DSM-5).
Characterisation of risks	To date, 8 661 events classified as "drug withdrawal syndrome" were reported with SUBOXONE sublingual tablet (reporting rate 326.3 events per 100 000 patient years). Of these, 172 events were serious, and 2 had a fatal outcome. To date, 7 868 events classified as "drug withdrawal syndrome" were reported with SUBOXONE sublingual film (reporting rate 190.9 events per 100 000 patient years). Of these, 159 events were serious, and none had a fatal outcome.

	Of note, the event of "drug withdrawal syndrome" neonatal has been excluded from this risk as it is included in the "use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child" risk.
Risk factors and risk groups	SUBOXONE use can be associated with risk of withdrawal in the following clinical situations: • Chronic administration can produce physical dependence of the opioid type, characterised by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. • Withdrawal symptoms may be associated with suboptimal dosing with SUBOXONE. A patient who is under-dosed with SUBOXONE may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines. • Initiation of SUBOXONE treatment can precipitate withdrawal in opioid-dependent patients (i.e., physically dependent on an opioid other than buprenorphine), particularly if taken before objective and clear signs of withdrawal are evident.
Preventability	Prior to treatment initiation with SUBOXONE, the prescriber should be aware that SUBOXONE may precipitate opioid withdrawal signs and symptoms in individuals physically dependent on opioids other than buprenorphine. Consideration should be given to the type of opioid being used (e.g., long- or short-acting), the time since last opioid use and the degree of opioid dependence. To avoid precipitating withdrawal, induction with buprenorphine/naloxone should be undertaken when objective and clear signs of opioid withdrawal are evident. Abrupt discontinuation of SUBOXONE treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset.
Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of drug withdrawal syndrome, it is expected that the benefit-risk balance of SUBOXONE remains positive.
Public health impact	No negative public health impact is expected due to risk of withdrawal associated with SUBOXONE use.

Important Identified Risk: Use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child	
Potential mechanisms	Buprenorphine is transferred across the placenta to the neonate (Farid 2008), thus, a foetus of a pregnant female using SUBOXONE can be exposed to buprenorphine. Chronic use of SUBOXONE 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. Animal studies on buprenorphine demonstrate dose-related maternal, embryo, and foetal toxicity and dose-related behavioural changes in offspring, but no congenital malformations (Heel 1979). Concentrations of buprenorphine and metabolites are low in human milk and maternal plasma (Jansson 2016). The dose of buprenorphine and norbuprenorphine received via milk during maternal maintenance treatment is unlikely to cause any acute adverse effects in the breastfed infant (Illett

	2012). Buprenorphine inhibits lactation in rats. The limited data on sublingual naloxone exposure in pregnancy are not sufficient to evaluate a drug-associated risk. It is unknown whether naloxone is excreted in human breast milk.
Evidence source(s) and strength of evidence	Section 4.6 of the SUBOXONE SmPC states towards the end of pregnancy buprenorphine may induce respiratory depression in the new-born 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 from several hours to several days after birth. A PASS (Indivior (PE-US001) 2014), 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 section 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 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 during pregnancy without development of any adverse events. A total of 1 789 cases involved a pregnant woman/foetus or infant with TMEs of interest in pregnancy reported 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 post marketing 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).
Characterisation of risks	To provide the number of adverse events classified as "Drug exposure during pregnancy/lactation", general events coded that do not reflect adverse events have been excluded (e.g., pregnancy, maternal/foetal exposure during pregnancy, no adverse event, off label use, substance abuse, etc.) from the events calculated with a reporting rate. To date, 11 770 events classified as "Drug exposure during pregnancy/lactation" were reported with SUBOXONE sublingual tablet (including 5 510 events for a reporting rate of 207.6 events per 100 000 patient years). To date, 1 746 of the 5 510 reported events associated with drug exposure during pregnancy or lactation were considered to be serious. Of these, 27 events had a fatal outcome. To date, 9 067 events classified as "Drug exposure during pregnancy/lactation" were reported with SUBOXONE sublingual film (including 5 631 events for a reporting rate of 136.6 events per 100 000 patient years). To date, 1 310 of the 5 631 reported events associated with drug exposure during pregnancy or lactation were considered to be serious. Of these, 29 events had a fatal outcome. Chronic use of SUBOXONE 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.
Risk factors and risk groups	Women with OUD 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 (SAMSHA 2016).
Preventability	*Pregnancy*: SUBOXONE should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus. 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 from 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*: Breastfeeding should be discontinued during treatment with SUBOXONE.
Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of drug exposure during pregnancy/lactation (effects on new-born and infant), it is expected that the impact on the risk-benefit balance of SUBOXONE is low.

Public health impact	Buprenorphine use during pregnancy is known to contribute to neonatal drug withdrawal syndrome. Additionally, nonclinical data also suggest potential toxicity of SUBOXONE to embryo/foetus. 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.

There are no safety concerns considered as important potential risks to be included in the summary of safety concerns.

SVII.3.2. Presentation of the Missing Information

No patient populations have been considered as missing information to be included in the list of safety concerns.

Part II: Module SVIII - Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important identified risks	• Abuse, misuse and diversion • Use in patients with hepatic impairment • Hepatic disorders • Drug withdrawal syndrome • Use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child
Important potential risk	None
Missing information	None

Part III: Pharmacovigilance Plan (Including Post-authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine PhV includes review of information regarding adverse events reported with the use of SUBOXONE from ICSR review, signal detection, aggregate reports review, and literature reviews.

Routine PhV activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for SUBOXONE

Annex 4 includes special interest group questionnaires for the purpose to obtain additional, structured information. These targeted follow-up questionnaires, listed below for each risk, will facilitate the capture of clinically relevant and complete information at the time of the initial report and during subsequent attempts to obtain follow-up.

- Abuse, misuse and diversion
  - Misuse / Abuse
  - Paediatric accidental exposure / paediatric intoxication
- Use in patients with hepatic impairment
  - Hepatic events / drug related hepatic disorders
- Hepatic disorders
  - Hepatic events / drug related hepatic disorders
- Drug withdrawal syndrome
  - Drug withdrawal syndrome
- Use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child
  - Pregnancy
  - Breastfeeding (lactation)
  - Neonatal withdrawal

Other forms of routine PhV activities for any safety concerns

No other forms of routine PhV activities are currently being conducted for any safety concerns for SUBOXONE.

III.2 Additional Pharmacovigilance Activities

There were 5 completed studies considered additional PhV activities for SUBOXONE Tablet. These 5 completed studies are described in Annex 2.

III.3 Summary Table of Additional Pharmacovigilance Activities

All studies considered additional PhV activities for SUBOXONE have been completed.

Part IV: Plans for Post-authorisation Efficacy Studies

There are no planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Abuse, misuse and diversion	Routine risk communication: Sections 4.2, 4.4, 4.5, 6.5, and 6.6 of both the SUBOXONE sublingual tablet SmPC and the proposed SUBOXONE sublingual film SmPC and section 3: Taking SUBOXONE sublingual film of the proposed SUBOXONE sublingual film Package Leaflet (PL) Routine risk minimisation activities recommending specific clinical measures to address the risk: Supervised substance abuse treatment and patient education is the major activity to prevent IV and intranasal abuse of SUBOXONE. SUBOXONE 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 SUBOXONE sublingual tablet 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 medicine in front of children. An emergency unit should be contacted immediately in case of accidental ingestion or suspicion of ingestion. Clinicians should remain vigilant for paediatric exposures. Patients receiving buprenorphine on an outpatient basis should be educated regarding steps they can take to ensure the drug is not accessible to any young children in their homes. To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing SUBOXONE, such as to avoid prescribing multiple refills early in treatment and conducting patient follow-up visits with clinical monitoring that is appropriate for the patient's needs. SUBOXONE contains naloxone which is intended to deter misuse and abuse of the buprenorphine. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBOXONE and should also be cautioned to use benzodiazepines concurrently with SUBOXONE only as directed by their physician. SUBOXONE sublingual tablets are packed in individual child-resistant packaging which will contribute toward the control of exposure risk to children. SUBOXONE sublingual film is packed in child-resistant individual sachets made between two identical layers of polymer-foil composite. Do not open the foil sachet until you are ready to use it.

Safety concern	Routine risk minimisation activities
	Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Additionally, the scientific literature states that manufacturers should use unit-dose packaging for all buprenorphine products to help prevent unintentional exposure among young children (Post 2018). Health providers should inform caregivers of young children about the dangers of buprenorphine exposure and provide instructions on proper medication storage and disposal (Post 2018). The safety and efficacy of buprenorphine/naloxone in children below the age of 15 years have not been established. Other routine risk minimisation measures beyond the Product Information: Legal status: Special and restricted medical prescription Pack size: SUBOXONE sublingual tablets available in 7- or 28-tablet blister packs SUBOXONE sublingual films available in packs of 7, 14, 28 or 30 individual sachets.
Use in patients with hepatic impairment	Routine risk communication: Sections 4.2, 4.3 and 4.4 of both the SUBOXONE sublingual tablet SmPC and the proposed SUBOXONE sublingual film SmPC and section 2 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: As buprenorphine/naloxone PK 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. SUBOXONE should be used with caution in patients with moderate hepatic impairment. In patients with severe hepatic insufficiency, the use of buprenorphine/naloxone is contraindicated. 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 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. Other routine risk minimisation measures beyond the Product Information: None
Hepatic disorders	Routine risk communication: Section 4.4 of both the SUBOXONE sublingual tablet SmPC and the proposed SUBOXONE sublingual film SmPC, and sections 2 and 4 of the PL Routine risk minimisation activities recommending specific clinical measures to address the risk: 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.

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: None
Drug withdrawal syndrome	Routine risk communication: Sections 4.2 and 4.4 of both the SUBOXONE sublingual tablet SmPC and the proposed SUBOXONE sublingual film SmPC, and section 2 of the PL Routine risk minimisation activities recommending specific clinical measures to address the risk: Prior to treatment initiation with SUBOXONE, the prescriber should be aware that SUBOXONE may precipitate opioid withdrawal signs and symptoms in individuals physically dependent on opioids other than buprenorphine. Consideration should be given to the type of opioid being used (e.g., long- or short-acting), the time since last opioid use and the degree of opioid dependence. To avoid precipitating withdrawal, induction with buprenorphine/naloxone should be undertaken when objective and clear signs of opioid withdrawal are evident. Abrupt discontinuation of SUBOXONE treatment is not recommended as it may result in an opioid withdrawal syndrome that may be delayed in onset. Patients should be monitored following medical withdrawal because of the potential for relapse. Other routine risk minimisation measures beyond the Product Information: None
Use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child	Routine risk communication: Section 4.6 of both the SUBOXONE sublingual tablet SmPC and the proposed SUBOXONE sublingual film SmPC, and section 2 of the PL Routine risk minimisation activities recommending specific clinical measures to address the risk: *Pregnancy*: SUBOXONE should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus. 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 from 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*: Breastfeeding should be discontinued during treatment with SUBOXONE. Other routine risk minimisation measures beyond the Product Information: None

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of SUBOXONE.

V.3. Summary of Risk Minimisation Measures

Table Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Abuse, misuse and diversion	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.5, 6.5, and 6.6 PL section 3 Other routine risk minimisation measures beyond the Product Information: Legal status: Special and restricted medical prescription Pack size: SUBOXONE sublingual tablets available in 7- or 28-tablet blister packs SUBOXONE sublingual films available in packs of 7, 14, 28 or 30 individual sachets Additional risk minimisation measures: None	AE follow-up form for adverse reaction
Use in patients with hepatic impairment	Routine risk minimisation measures: SmPC sections 4.2, 4.3 and 4.4 PL section 2 Additional risk minimisation measures: None	AE follow-up form for adverse reaction
Hepatic disorders	Routine risk minimisation measures: SmPC section 4.4 PL sections 2 and 4 Additional risk minimisation measures: None	AE follow-up form for adverse reaction
Drug withdrawal syndrome	Routine risk minimisation measures: SmPC sections 4.2 and 4.4 PL section 2 Additional risk minimisation measures: None	AE follow-up form for adverse reaction
Use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Additional risk minimisation measures: None	AE follow-up form for adverse reaction

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for SUBOXONE (buprenorphine / naloxone)

This is a summary of the risk management plan (RMP) for SUBOXONE. The RMP details important risks of SUBOXONE, how these risks can be minimised, and how more information will be obtained about SUBOXONE's risks.

SUBOXONE's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how SUBOXONE should be used.

This summary of the RMP for SUBOXONE should be read in the context of all this information including the assessment report of the evaluation and its plain language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of SUBOXONE's RMP.

I. The medicine and what it is used for

SUBOXONE is authorised for 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. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction (see SmPC for the full indication). It contains buprenorphine / naloxone as the active substance and it is given by sublingual route (tablet or film) or by buccal route (film).

Further information about the evaluation of SUBOXONE's benefits can be found in SUBOXONE's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of SUBOXONE, together 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 package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size – the amount of medicine in a pack is chosen 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 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, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of SUBOXONE 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 SUBOXONE. 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);

List of important risks and missing information	
Important identified risks	Abuse, misuse and diversion Use in patients with hepatic impairment Hepatic disorders Drug withdrawal syndrome Use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified risk: Abuse, misuse and diversion	
Evidence for linking the risk to the medicine	Sublingual buprenorphine can be misused or abused in a manner similar to other opioids and can lead to dependence in previously non-dependent individuals, overdose and potentially fatal respiratory depression. Combining buprenorphine with naloxone in SUBOXONE is intended to deter misuse and abuse of buprenorphine. Intravenous or intranasal misuse of SUBOXONE is expected to be less likely than with buprenorphine alone since the naloxone component can antagonise the opioid effect of buprenorphine and precipitate withdrawal in individuals physically dependent on opioids. Abuse of a medicinal product is defined as persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects [Guideline on good pharmacovigilance practices (GVP), Annex I - Definitions]. Misuse of a medicinal product is defined as situations where a medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing

Important identified risk: Abuse, misuse and diversion	
	authorisation [Guideline on good pharmacovigilance practices (GVP), Annex I - Definitions]. Misuse of a medicinal product for illegal purposes (diversion) is defined as misuse with the additional connation of an intention of misusing the medicinal product to cause an effect in another person. This includes, amongst others: the sale, to other people, of medicines for recreational purposes and use of a medicinal product to facilitate assault [Guideline on good pharmacovigilance practices (GVP), Annex I - Definitions].
Risk factors and risk groups	Illicit opioid and polysubstance abusers are at risk of IV and intranasal abuse of SUBOXONE. Sub-optimal treatment with SUBOXONE may prompt medication misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with SUBOXONE may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.2, 4.4, 4.5, 6.5, and 6.6* *PL section 3* *Legal status:* *The product is being submitted under special and restricted medical prescription* *Pack size:* *SUBOXONE sublingual tablets available in 7- or 28-tablet blister packs* *SUBOXONE sublingual films available in packs of 7, 14, 28 or 30 individual sachets* Additional risk minimisation measures *None*

Important identified risk: Use in patients with hepatic impairment	
Evidence for linking the risk to the medicine	The effects of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study. Both buprenorphine and naloxone are extensively metabolised, and plasma levels were found to

	be higher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment.
Risk factors and risk groups	Patients with moderate to severe hepatic impairment could be at increased risk.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.2, 4.3 and 4.4* *PL section 2* Additional risk minimisation measures *None*

Important identified risk: Hepatic disorders	
Evidence for linking the risk to the medicine	Cases of acute hepatic injury have been reported in opioid-dependent patients both in clinical trials and in post-marketing adverse event reports for buprenorphine.
Risk factors and risk groups	Patients with viral hepatitis or existing liver dysfunction are at greater risk of liver injury.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4* *PL sections 2 and 4* Additional risk minimisation measures *None*

Important identified risk: Drug withdrawal syndrome	
Evidence for linking the risk to the medicine	In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a drug withdrawal syndrome similar to that associated with naloxone.
Risk factors and risk groups	Withdrawal can occur upon abrupt discontinuation or rapid taper, dose omission, sub-optimal dosing and treatment initiation before objective and clear signs of withdrawal are evident.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.2 and 4.4* *PL section 2*

	Additional risk minimisation measures *None*

Important identified risk: Use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child	
Evidence for linking the risk to the medicine	Use during pregnancy may lead to opioid toxicity and withdrawal symptoms in the newborn. Buprenorphine is excreted in human breast milk and may lead to opioid toxicity in the child.
Risk factors and risk groups	Women who are pregnant or breastfeeding while being treated with buprenorphine.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6* *PL section 2* 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 SUBOXONE.

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

There are no studies required for SUBOXONE.

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

SPECIAL INTEREST QUESTIONS FOR BUPRENORPHINE CONTAINING PRODUCT

Table of Contents

Abuse, misuse and diversion

Misuse/Abuse

1. How is product *[name of INDV product(s) or name of active ingredient(s)]* being used (e.g. injection, intranasal, etc.) and for how long? What was it prescribed for?

2. If taking product not as prescribed (e.g. injection, intranasal, etc.), have there been any unfavorable side effects? If yes, what symptoms have been experienced?

3. How was product obtained (e.g. prescription, obtained from a friend, bought off the street)?

4. What dose of product was being used?

5. What other medications/substances have been used (e.g. alcohol, benzodiazepines, gabapentinoids, or other opioids such as methadone, oxycontin, vicodin, etc.)?

6. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

Paediatric accidental exposure / paediatric intoxication

1. How old was the child exposed to product *[name of INDV product(s) or name of active ingredient(s)]*?

2. Please specify the dosage, route of administration, frequency and strength of the product child was exposed to.

3. What signs and symptoms did the child experience and for how long?

4. Was a physician seen? Was treatment received? If so, provide treatment details.

5. Did the child require lifesaving equipment for the treatment of intoxication?

6. Was the child hospitalized? If so, please provide dates of hospitalization and discharge.

7. Did the child recover? If so please provide the resolution date along with treatment received and outcome.

8. Was there any additional drug along with product child exposed to? If yes, please provide the dosage, route of administration, frequency and strength.

9. How many times was the child exposed?

10. Does the child still have any symptoms now?

11. How is the child overall growing and meeting all milestones?

12. If a consumer report, may we contact the child's physician/pediatrician? If yes, please provide name and contact information.

Use in patients with hepatic impairment

Hepatic events / drug related hepatic disorders

1. Were baseline liver function tests done prior to starting product *[name of INDV product(s) or name of active ingredient(s)]*? If yes, please provide results.

2. Did the hepatic enzymes increase after taking product? Please provide lab results (e.g. AST, ALT, ALP, total bilirubin, INR). If yes, on which day after the start on product were the increased enzymes detected?

3. Did the event result in an ER visit or hospitalization? If yes, what was the duration of hospitalization?

4. Please specify if the patient/subject underwent any additional relevant laboratory/diagnostic investigations. If yes, please specify the findings.

5. Is there a history of hepatitis (e.g. Hepatitis A, B or C, etc.), HIV infection, or any other viral infection? If so, please provide relevant medical history and/or relevant treatment/concomitant medications.

6. Please specify if the patient/subject consumed alcohol. If so, how much a day and for how long.

7. Please specify the dosage, route of administration, frequency and strength of product given to the patient/subject.

8. Was product stopped after hepatic enzymes increased? If yes, did the event resolve? If yes, please provide the date of resolution. What was the outcome?

9. Was product restarted after the event resolved? If yes, did the hepatic enzymes increase after the re-start of product?

10. Please specify if the patient/subject was taking any hepatotoxic drugs (e.g. acetaminophen, aspirin, non-steroidal anti-Inflammatory drug(s) (NSAIDs), steroids, antibiotics, oral contraceptives, statins, herbal medicines, etc.) before the onset of hepatic event. If yes, please provide medication's dose and start/stop dates.

11. Please specify if the patient/subject underwent any relevant laboratory/diagnostic investigations. If yes, please specify the findings.

12. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

Hepatic disorders

Hepatic events / drug related hepatic disorders

1. Were baseline liver function tests done prior to starting product *[name of INDV product(s) or name of active ingredient(s)]*? If yes, please provide results.

2. Did the hepatic enzymes increase after taking product? Please provide lab results (e.g. AST, ALT, ALP, total bilirubin, INR). If yes, on which day after the start on product were the increased enzymes detected?

3. Did the event result in an ER visit or hospitalization? If yes, what was the duration of hospitalization?

4. Please specify if the patient/subject underwent any additional relevant laboratory/diagnostic investigations. If yes, please specify the findings.

5. Is there a history of hepatitis (e.g. Hepatitis A, B or C, etc.), HIV infection, or any other viral infection? If so, please provide relevant medical history and/or relevant treatment/concomitant medications.

6. Please specify if the patient/subject consumed alcohol. If so, how much a day and for how long.

7. Please specify the dosage, route of administration, frequency and strength of product given to the patient/subject.

8. Was product stopped after hepatic enzymes increased? If yes, did the event resolve? If yes, please provide the date of resolution. What was the outcome?

9. Was product restarted after the event resolved? If yes, did the hepatic enzymes increase after the re-start of product?

10. Please specify if the patient/subject was taking any hepatotoxic drugs (e.g. acetaminophen, aspirin, non-steroidal anti-Inflammatory drug(s) (NSAIDs), steroids, antibiotics, oral contraceptives, statins, herbal medicines, etc.) before the onset of hepatic event. If yes, please provide medication's dose and start/stop dates.

11. Please specify if the patient/subject underwent any relevant laboratory/diagnostic investigations. If yes, please specify the findings.

12. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

Drug withdrawal syndrome

Drug withdrawal syndrome

1. When did withdrawal begin?

2. Had there been a recent switch of medications (e.g. methadone to Suboxone tablet/film, Suboxone tablet to Suboxone film, Subutex to Suboxone tablet, Suboxone/Subutex to generic Suboxone, etc.)?

3. Was there a change in dosing (e.g. 16 mg to 24 mg)? If yes, please provide start and stop dates. How long after change in dosing did the withdrawal symptoms start?

4. When did withdrawal symptoms occur? (e.g. within 6 hours, or within 24 hours, etc.). Please provide start and stop dates.

5. Was medical attention or treatment received for the withdrawal? If yes, describe.

6. Have withdrawal symptoms been experienced before?

7. Have withdrawal symptoms resolved? If yes, please provide stop date.

8. How severe were the withdrawal symptoms (e.g. mild, moderate, or severe)?

9. Does patient/subject believe the withdrawal symptoms were caused by product?

10. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

Use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child

Pregnancy

1. Please provide start/stop dates, dose, frequency and route of product *[name of INDV product(s) or name of active ingredient(s)]* since initial start date (including any dosing changes).

2. Was there any switch of drugs (e.g. SUBOXONE to SUBUTEX) or change in dosage of medication (e.g. 6 to 12 mg) during pregnancy? Please provide details. Also, when did the switch of drug or change in dosage occur during the pregnancy? e.g. (first/second/third trimester).

3. Please confirm and provide last menstrual period and expected date of delivery.

4. Please provide relevant pregnancy history (e.g. previous pregnancies, outcomes, complications, miscarriages, births, delivery complications, congenital defects during previous pregnancies (if any), etc.)

5. Please provide relevant maternal medical history (e.g. diabetes, hypertension, thyroid disorder, etc.)

6. Were any prescription medications, over-the-counter drugs, herbal supplements, recreational drugs (e.g. cocaine, cannabis, LSD), alcohol, excessive caffeine, or tobacco consumed during pregnancy? If so, what, how much? Was the medication/drug/alcohol/tobacco stopped? During what trimester of pregnancy?

7. Is there a family history of birth defects? If so, what were the birth defects?

8. What was the outcome of the delivery (e.g. normal vaginal birth, emergent caesarean section, elective caesarean section, induced labor)? Premature or full term? Miscarriage or elective abortion? If miscarriage, at how many weeks' gestation?

9. **For spontaneous abortions (miscarriage) only:** Was there any physical trauma to the abdomen prior to the miscarriage (e.g. fall, traffic accident, etc.)? If so, how long before the miscarriage did the physical trauma occur?

10. Please provide the baby's date of birth, sex, weight, length and APGAR scores, if available along with gestation age at birth (in weeks).

11. During pre-natal visits, were there any abnormal maternal findings (e.g. uterine fibroid, placental or amniotic fluid abnormalities, ectopic pregnancy) or foetal findings (e.g. congenital defects)? Were any relevant laboratory/diagnostic investigations conducted? If yes, please specify the findings.

12. Did patient/subject or baby develop any respiratory symptoms? If so, what were the symptoms? What was the treatment and outcome? Please include the date of resolution/recovery.

13. Did the baby have neonatal withdrawal? If so, what were the symptoms?

14. Did the baby require prolonged hospitalization or treatment? If yes, what exactly was the reason for prolonged hospitalisation? What was the treatment and outcome? Please provide dates of delivery, discharge and resolution/recovery.

15. Has the baby experienced any feeding problems? Has he/she met growth and development milestones to date? May we contact patient/subject for a two-year follow-up to obtain information about the baby's growth and developmental milestones?

16. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

Breastfeeding (Lactation)

1. Did mother breastfeed? For how long? Did she switch back to product *[name of INDV product(s) or name of active ingredient(s)]* while breastfeeding?

2. Were there any problems experienced during breastfeeding?

3. Did baby have any developmental delays or symptoms of withdrawal after breastfeeding was stopped?

4. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

Neonatal withdrawal

1. What medications were taken during the pregnancy? Please include name, dose, frequency and indication used for.

2. When was product *[name of INDV product(s) or name of active ingredient(s)]*?

3. Did the mother have a recent switch of medications (e.g. methadone to SUBOXONE tablet/film, SUBOXONE tablet to SUBOXONE film, SUBUTEX to SUBOXONE tablet, SUBOXONE/SUBUTEX to generic SUBOXONE, etc.)?

4. What were the signs and symptoms of neonatal withdrawal (agitation, apnoea, blood pressure increased, bradycardia, convulsion, crying, dehydration, diarrhoea)?

5. Was there a change in dosing (e.g. 16 mg to 24 mg)? If yes, please provide start date of new dosage and stop date of previous dosage.

6. When was the neonate diagnosed with withdrawal? Was diagnosis made by a physician?

7. How severe were the withdrawal symptoms (e.g. mild, moderate, severe)?

8. Was treatment received for withdrawal? If so, please provide name, dose, start/stop dates of treatment.

9. How long was the baby in the hospital due to withdrawal?

10. Did all of the symptoms resolve prior to discharge?

11. Is the baby feeding well and meeting growth and development milestones?

12. If a consumer report, may we contact your physician and/or paediatrician? If yes, please provide name and contact information.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Not applicable