EU Risk Management Plan for

Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films

(buprenorphine hydrochloride)

RMP version to be assessed as part of this application:

RMP version number: 1.0.

Data lock point for this RMP: 12 September 2024.

Date of final sign-off: 15 October 2024

Rationale for submitting an updated RMP: Not applicable.

Summary of significant changes in this RMP: Not applicable.

Other RMP versions under evaluation: Not applicable.

Details of the currently approved RMP: Not applicable.

QPPV name: Lucía Castrillo.

Table of content

List of Abbreviations

ATC	Anatomical Therapeutic Chemical classification
CI	Confidence Interval
CYP3A4	Cytochrome P 3A4
DDD	Daily Defined Dose
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GABA	γ-aminobutyric acid
INN	International Non-proprietary Names
MAH	Marketing Authorisation Holder
MAOI	Monoamine Oxidase Inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
NAc	Nucleus Accumbens
PL	Patient Leaflet
PT	Preferred Term
PRAC	Pharmacovigilance Risk Assessment Committee
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
VTA	Ventral Tegmental Area
WHO	World Health Organization

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Buprenorphine hydrochloride.
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Drugs used in opioid dependence. ATC code: N07BC01.
Marketing Authorisation Holder (MAH)	Neuraxpharm Pharmaceuticals, S.L.
Medicinal products to which this Risk Management Plan (RMP) refers	4.
Invented name(s) in the European Economic Area (EEA)	Buprenorphine Neuraxpharm 0.4 mg sublingual films. Buprenorphine Neuraxpharm 4 mg sublingual films. Buprenorphine Neuraxpharm 6 mg sublingual films. Buprenorphine Neuraxpharm 8 mg sublingual films.
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/006188).
Brief description of the product	Chemical class: Buprenorphine is an opioid partial agonist/antagonist which attaches itself to the μ (mu) k (kappa) receptors of the brain.
	Summary of mode of action: Its activity in opioid maintenance treatment is attributed to its slowly reversible link with the μ receptors which, over a prolonged period, might minimise the need of the addicted patients for drugs. Due to its partial opioid agonist activity, buprenorphine has a wide margin of safety, which limits its depressant effects, particularly on cardiac and respiratory functions.
	Important information about its composition: Not applicable.
Hyperlink to the Product Information	Please refer to the product information text in module 1.3.1.
Indication(s) in the EEA	Current: Substitution treatment of opioid drug dependence, within a comprehensive therapeutic monitoring framework of medical, social and psychological treatment. Treatment is intended for use in adults and adolescents 15 years of age and older, who have agreed to be treated for addiction.
	Proposed: Not applicable.

Dosage in the EEA	Current: Treatment should be under the supervision of a physician experienced in the management of opiate dependence/addiction. *Initiation therapy (induction)* The recommended starting dose in adults and adolescents over 15 years of age is 2 to 4 mg, administered as a single daily dose. An additional 2 to 4 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 tablet and to observe patient response to treatment as a guide to effective dose titration according to clinical effect. *Dosage adjustment and maintenance* 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. Daily dispensing of buprenorphine is recommended, particularly during the initiation of treatment. Then, after stabilisation, the patient may be given a supply of the product sufficient for several days of treatment. However, it is recommended that the amount of the product dispensed be limited to a maximum of 7 days. *Less than daily dosing* After a satisfactory stabilisation has been achieved, the frequency of dosing may be decreased to dosing every other day at twice the individually titrated daily dose. In some patients, after a satisfactory stabilisation has been achieved, the frequency of dosing may be decreased to 3 times a week. The dose given on any one day should not exceed 24 mg buprenorphine. *Dosage reduction and termination of treatment* When clinical evaluation and the will of the patient lead to consider treatment discontinuation, it must be achieved with caution. The decision to discontinue therapy with buprenorphine after a period of maintenance or brief stabilisation should be made as part of a comprehensive treatment plan. To avoid withdrawal symptoms and potential relapse to illicit drug use, the buprenorphine dose may be progressively decreased over time in favourable cases until treatment can be discontinued. After a satisfactory period of stabilisation has been achieved, if the patient agrees, the dosage of buprenorphine may be reduced gradually; in some favourable cases, treatment may be discontinued. The availability of the sublingual tablets with doses of 0.4 mg, 4 mg, 6 mg and 8 mg, respectively, allows for a downward titration of dosage. Patients should be monitored following termination of buprenorphine treatment because of the potential for relapse.

	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: Pharmaceutical form: Sublingual film. Buprenorphine Neuraxpharm 0.4 mg sublingual films: Each sublingual film contains 0.4 mg buprenorphine (as hydrochloride). Buprenorphine Neuraxpharm 4 mg sublingual films: Each sublingual film contains 4 mg buprenorphine (as hydrochloride). Buprenorphine Neuraxpharm 6 mg sublingual films: Each sublingual film contains 6 mg buprenorphine (as hydrochloride). Buprenorphine Neuraxpharm 8 mg sublingual films: Each sublingual film contains 8 mg buprenorphine (as hydrochloride).
	Proposed: Not applicable.
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)

Not applicable since this module is not required for hybrid type of application.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable since this module is not required for hybrid type of application.

Part II: Module SIII - Clinical trial exposure

Not applicable since this module is not required for hybrid type of application.

Part II: Module SIV - Populations not studied in clinical trials

Not applicable since this module is not required for hybrid type of application.

Part II: Module SV - Post-authorisation experience

Not applicable since this module is not required for hybrid type of application.

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable since this module is not required for hybrid type of application.

Part II: Module SVII - Identified and potential risks

The RMP for Buprenorphine Neuraxpharm is an update of the previously submitted RMP (version 0.3) in order to comply with the Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur RMP Assessment Report for Buprenorphine Neuraxpharm (EMEA/H/C/006188).

The following table includes those safety concerns included in previous RMPs and those proposed for this new version (version 0.4):

Summary of safety concerns for buprenorphine-containing products			
	RMP version 0.1	**RMP version 0.2**	**RMP versions 0.3 and 0.4**
Important identified risks	• None.	• Use in patients with severe respiratory insufficiency. • Use in patients with severe hepatic impairment. • Use in patients with acute alcoholism or delirium tremens. • Abuse and misuse. • Withdrawal reactions in opioid-dependent patients. • Concomitant use of other medications (Cytochrome P 3A4 [CYP3A4] inhibitors; benzodiazepines; other central nervous system depressants; Monoamine Oxidase Inhibitors [MAOI]; and serotonergic medicinal products). • Overdose.	• Use in patients with severe respiratory insufficiency. • Use in patients with severe hepatic impairment. • Use in patients with acute alcoholism or delirium tremens. • Abuse and misuse. • Withdrawal reactions in opioid-dependent patients. • Concomitant use of other medications (CYP3A4 inhibitors; benzodiazepines; other central nervous system depressants; MAOI; and serotonergic medicinal products). • Overdose.
Important potential risks	• None.	• Use in patients with various disease states (renal impairment; head injuries; increased intracranial pressure; hypotension; prostatic hypertrophy; and urethral stenosis). • Medication error. • Concomitant use of gabapentinoids.	• Use in patients with various disease states (renal impairment; head injuries; increased intracranial pressure; hypotension; prostatic hypertrophy; and urethral stenosis). • Concomitant use of gabapentinoids.
Missing information	• None.	• Use in pregnancy.	• Use in pregnancy.

Justification of new list of safety concerns with a submission of this RMP in comparison with the reference medicinal product (Buvidal):

According to the request of the PRAC Rapporteur RMP Assessment Report for Buprenorphine Neuraxpharm (EMEA/H/C/006188), the list of safety concerns for the product has been aligned with those for Buvidal (v 2.4), except those safety concerns linked to the pharmaceutical form (Buvidal is a prolonged-release solution for injection, and Buprenorphine Neuraxpharm is a sublingual film).

Additionally, the MAH was requested to thoroughly discuss the risk of medication error that could be related to the pharmaceutical form "sublingual film" and the risk of abuse and misuse with this specific

pharmaceutical form (sublingual film). The risk of medication error was removed from the list of safety concerns compared to the RMP version 0.2 since no additional risk minimisation activities are needed, and it does not impact the overall risk-benefit profile of the product (please refer to SVII.1.1 for further details). Therefore, only the risk that differ from the risks of the reference product Buvidal, "abuse and misuse", and related to the pharmaceutical form "sublingual film" will be characterised in section SVII.3.

Recently, the following clarification has been added to the Company's labelling and package leaflet to facilitate the correct use of the product, and avoid/minimise the adverse effects related to a wrong use:

LABELLING

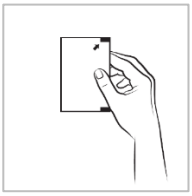
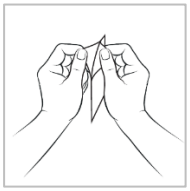
[…]
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
{Sachet}
METHOD OF ADMINISTRATION

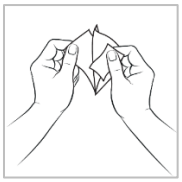
Read the package leaflet before the use.

Keep out of the sight and reach of children.

Do not swallow or chew.

Keep the film under your tongue until it dissolves.

Step 1  **-Step 2** 

Step 3  **Step 4** 

Step 5  **Step 6** 

PACKAGE LEAFLET

[…]

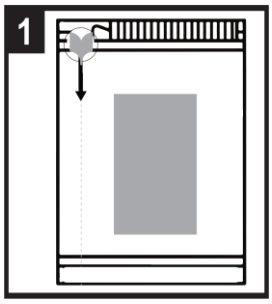
Instructions for taking this medicine

This medicine is taken by mouth, as a film to be put under your tongue.

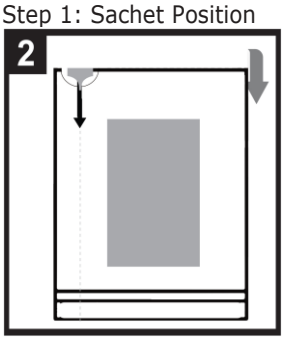
Take the dose once a day, at approximately the same time.

It is advisable to moisten your mouth before taking the film.

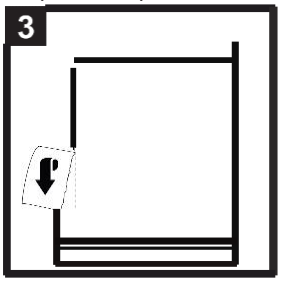
How to remove the film from the sachet:



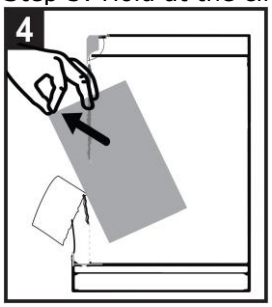
Step 1: Sachet Position



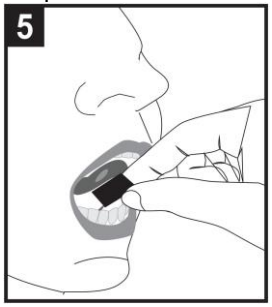
Step 2: To open the sachet, start by folding the sachet backwards at the dotted line.



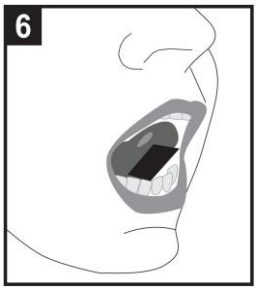
Step 3: Hold at the circle and tear downwards to open the sachet.



Step 4: Take out of the film from the open end of the sachet.



Step 5: Hold the film in between two fingers by the outside edges and place under the tongue.



Step 6: Place film either to the left or middle or right.
Place the sublingual film under the tongue (sublingual use) as advised by your doctor.

Keep the film in place under the tongue until it dissolves completely. This will take 10 to 15 minutes.

Do not chew or swallow the film, as the medicine will not work, and you may get withdrawal symptoms.

Do not consume any food or drink until the film has completely dissolved.

If an additional film is necessary to achieve the prescribed dose, place the additional film under the tongue only after the first film has been completely dissolved.

Do not split the film or subdivide into smaller doses.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Medication error

Medication errors are most common at the ordering or prescribing stage. Typical errors include the healthcare provider writing the wrong medication, the wrong route or dose, or the wrong frequency. These ordering errors account for almost 50% of medication errors. Data show that nurses and pharmacists identify anywhere from 30% to 70% of medication-ordering errors. It is obvious that medication errors are a pervasive problem, but the problem is preventable in most cases [Tariq, 2023].

Opioids are one of the most frequently reported drug classes in medication errors causing patient harm [**¡Error! No se encuentra el origen de la referencia.**, 2016]. Reported opioid errors are usually associated with administration and prescribing and frequently cause uncontrolled pain as well as overdoses [Dy, 2007].

Buprenorphine has a better safety profile in overdose when not used in combination with other drugs, such is the case. This is due to the partial agonist effect that causes a ceiling-dose effect, a ceiling effect on respiratory depression [Strain, 1997], and a bell-shaped curve in overdose where even fewer opioid effects occur than with a moderate dose [Johnson, 2003]. Additionally, the product is a sublingual preparation. Because of this, it is poorly absorbed orally, and therefore, buprenorphine is considered safer than other opioids in accidental overdose (eg, children) where the tablets have been swallowed [Ministry of Health, 2010].

Overall abuse of the buprenorphine tablet is greater than that of the sublingual film formulation. For those who continue to abuse buprenorphine, use by alternate route-of-administration was, in general, lower for the film [Butler, 2018].

- ***Children accidental exposure***

Children and adolescents who grow up in households with opioid misuse and opioid use disorders may experience a myriad of adverse consequences, such as accidental opioid poisoning. Opioid prescriptions

in the United States significantly increased during the decade before 2012 and have remained at significantly high rates, with ~70.6 prescriptions dispensed per 100 persons in 2015. Parental opioid use may increase child and adolescent access to these drugs, which can result in accidental poisoning. Between 2000 and 2015, there were 188,468 poison control centre reports of child or adolescent prescription opioid exposure. There was a two-fold increase in the incidence of paediatric hospitalisation for opioid poisonings between 1997 and 2012; the annual incidence rate in 2012 was 3.71 per 100,000 children. The increased rates of opioid prescribing have been paralleled by increasing rates of individuals entering treatment for opioid use disorders. Although buprenorphine was only involved in 3.3% of poison control centre reports, buprenorphine poisoning frequently (47.1%) required treatment in a health care facility [Winstanley, 2019].

A retrospective review of buprenorphine overdoses in 56 children < 6 years of age reported no fatalities and results showed that children who ingested > or = 2 mg of buprenorphine were more likely to experience clinical effects, and all of the children who ingested > 4 mg experienced some effect. No child ingesting < 4 mg experienced a severe effect. Authors concluded that buprenorphine overdoses are generally well tolerated in children, with significant central nervous system and respiratory depression occurring in only 7% [Hayes, 2008].

In a retrospective cross-sectional study including 2,380 cases of unintentional exposure to any of 3 buprenorphine sublingual formulations involving children aged 28 days to less than 6 years, 18 cases (5.0%) involved exposure to buprenorphine-naloxone film. The results found that exposures to buprenorphine sublingual formulations among children aged ≤ 5 years involved tablet rather than the film formulations. The most common adverse events reported were lethargy (438 cases), respiratory depression (231), miosis (197), and vomiting (150), and similar adverse events were observed following exposure to all three formulations. Although no cases of life-threatening toxicity or death were observed in children who ingested the film. Because of the comparatively small number of film formulation exposures, this study was unable to detect a difference between formulations in severity outcomes [Lavonas, 2013].

The potential risk of medication error may be serious and medical attention should be immediately sought for patients who have been exposed to more than the recommended dose. However, considering the poor oral absorption of the sublingual film presentation, and the fact that it would be difficult to remove it once in contact with the mouth, the potential impact of medication errors related to the sublingual film formulation in public health is expected to be low.

The SmPC of the products provides information on dosing, method of administration, and precautions to be taken before administering the product, to avoid medication error, under the section 4.2. Furthermore, in section 4.4 of the SmPC it is stated that the treatment should be under the supervision of a physician experienced in the management of opiate dependence/addiction, in order to avoid misuse, abuse and diversion. This information is also available in section 3 of the Patient Leaflet, in which specific pictograms and wording (Step 6) have been added in order to avoid the risk of medication error.

Additionally, a recommendation to store the product safely for avoiding misuse and/or accidental exposure is also included in the SmPC of the product, a long with the inclusion of the warning to keep out of the sight and reach of children on the box and the primary packaging. The SmPC has been also updated to specify that the films are packed in child-resistant individual sachets.

In addition, the strength of each dosage is directly imprinted on the sachet and on one side of the sublingual films, which will be always on front side at the time film gets packed in pouch. This impression facilitates the identification as a medicinal product and the strength by the patient, reducing the risk of medication error. Besides at the corner of the sachets, the instructions on how to open the sachet are written.

Mock-up for the primary packaging of Buprenorphine sublingual films 0.4 mg (strength used as an example)

Overall, the package leaflet now included clear instructions on how to remove the film from the sachet, and how to place it in the mouth to be dissolved and absorbed. This is a complex process for children, since 6 steps should be followed prior to place buprenorphine film in mouth to be finally absorbed. It is important to point out that the film needs a total of 10 to 15 minutes to be dissolved, and that shewing or swallowing should be avoided for absorption. This complexity added to the poor oral absorption of the sublingual film presentation, and its difficulty of removal once in contact with the mouth, aims to prevent from accidental exposures occurring not only in this special population but also in the general population.

Taken into account that the treatment should be under the supervision of an experienced physician in the management of opiate dependence/addiction, that the strength of each dosage is directly imprinted on the sublingual films, and the information provided in the text of SmPC concerning the dosing, method administration and precautions to be taken before administering the product, the mentioned measures are considered sufficient to avoid mistakes between the different strengths and medication errors by the final user.

Therefore, no additional risk minimisation activities are needed.

Overall, medication errors do not impact the overall risk-benefit profile of buprenorphine for the approved indication, and therefore, it has been removed from the list of the safety concerns according to the Guideline on good pharmacovigilance practices Module V – Risk management systems (Rev 2) (EMA/838713/2011 Rev 2, 28 March 2017) as there are neither additional pharmacovigilance activities nor additional risk minimisation measures.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

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

Important Identified Risk: Abuse and misuse *(Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs): Intentional device misuse, Intentional misuse of drug delivery system, Intentional*

product misuse, Drug abuse, Drug abuser, Drug use disorder, Substance abuse, Substance abuser, Substance use disorder)

Potential mechanisms:

Many opiate actions are related to the specific neuroanatomic locations of μ receptors. Reinforcing and euphoric effects of opiates occur in the mesolimbic dopaminergic pathway from the Ventral Tegmental Area (VTA) to the Nucleus Accumbens (NAc), where opiates increase synaptic levels of dopamine. This increase is due to inhibition of GABAergic neurons that inhibit both the activity of neurons within the VTA and the NAc. The positive subjective effects of opioid drugs also include μ receptor desensitization and internalization, potentially related to stimulation of ß-arrestin signalizing pathways. However, the "high" only occurs when the rate of change in dopamine is fast. Large, rapidly administered doses of opiates block γ-aminobutyric acid (GABA) inhibition and produce a burst of VTA dopamine neuron activity that is associated with "high" in all abused drugs. Therefore, routes of administration that slowly increase opiate blood and brain levels, such as oral and transdermal routes, are effective for analgesia and sedation but do not produce an opiate "high" that follows smoking and intravenous routes [Messing, 2015].

Evidence source(s) and strength of evidence:

Worldwide, about 275 million people (or 5.5% of the global population aged 15-64 years) used drugs at least once in 2019. Among them, about 62 million people used opioids. About 36.3 million people suffered from drug use disorders in 2019. Most people dependent on opioids used illicitly cultivated and manufactured heroin, but the proportion of those using prescription opioids is growing [WHO, 2021].

The number of people addicted to opioids, sedative or hypnotic medications, and stimulants (e.g., cocaine, amphetamines) is not known precisely and fluctuates with the supply of drugs and social trends. According to the 2014 National Survey on Drug Use and Health, 7.1 million people aged 12 or older had an illicit drug use disorder; this represents 2.7% of the population of that age [McKeown, 2016].

Opioids are the most abused drugs in the chronic pain setting. The prevalence of lifetime substance use disorders ranges from 36% to 56% in patients treated with opioids for chronic back pain; 43% of this population has current substance use disorder and 5% to 24% have aberrant medication-taking behaviours. About 14% to 16% of pain patients not having substance use disorder use illicit drugs in combination with prescription drugs for pain, while 34% of patients with substance use disorder combine legal pain medication with illicit drug use [Manchikanti, 2008].

Even though buprenorphine is only a partial opioid agonist and has mild addictive potential, some people still misuse the drug. Particularly, buprenorphine tablets are misused by crushing them and either snorting the powder or dissolving the power and using it as an intravenous solution [Kumar, 2023].

Controlled human and animal studies indicate that buprenorphine has a lower dependence liability than pure agonist analgesics. In humans, limited euphorigenic effects have been observed with buprenorphine. This may result in some abuse of the medicinal product.

Buprenorphine exhibits a ceiling agonist effect at high doses, and because of its high affinity for the μ-receptor buprenorphine can interfere with the binding of pure μ-agonists, such as morphine. Because of this, concurrent use of buprenorphine blocks the "high" ordinarily received from abuse of high-potency opioid agonists, such as hydromorphone, and early studies suggested that abuse liability was low by the sublingual route [Lavonas, 2014].

The results showed that sublingual film product had lower abuse and diversion rates than either tablet formulation in all programs. The reasons for these relative priorities are not clear, but the relationships are statistically robust and have remained consistent over at least 2 years of observation in each program [Lavonas, 2014].

It is unclear whether buprenorphine tablet formulations can be manipulated for parenteral administration in a way that provides more euphoria ("a better high") than the film formulation. This could be due to intrinsic advantages of the film formulation or due to longer access to and experience with the tablets. Quantitative data about routes of abuse and qualitative data garnered from interviews with buprenorphine abusers entering treatment may provide an explanation. Structured surveillance of common Internet forums devoted to illicit drug use shows that buprenorphine abusers prefer the tablets because they perceive the film formulation as "weak," from a euphoria perspective [Lavonas, 2014].

Characterisation of the risk:

Buprenorphine can be misused or abused similarly to other opioids, legal or illicit. Some risks of misuse and abuse include overdose, spread of blood borne viral or localised and systemic infections, respiratory depression and hepatic injury. Buprenorphine misuse by someone other than the intended patient poses the additional risk of new drug dependent individuals using buprenorphine as the primary drug of abuse, and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicine is not safeguarded against theft.

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

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

Note that in previously submitted RMP (version 0.2) post-marketing experience was included. However, this section was deleted as none of the reported cases were associated with the use of the sublingual film form.

Risk factors and risk groups:

Patients with a personal or family history of drug abuse or alcoholism are potentially at risk as these patients may be more likely to abuse the product. Among users of chronic opioid therapy there was a strong inverse relationship between age and a diagnosis of opioid abuse/dependence. Mental health and substance use disorders were associated with an increased risk of opioid abuse/dependence. Effects of substance use disorders were especially strong, although mental health disorders were more common. Concerning opioid exposure; lower days of supply and lower average doses were all associated with lower likelihood of a diagnosis of opioid abuse/dependence [Edlund, 2010].

Preventability:

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

Impact on the risk-benefit balance of the product:

Adverse drug reactions caused by drug abuse may result in hospitalisation, intensive care treatment and even be fatal. Especially, excessive intoxication may induce miosis, vomiting, cardiovascular collapse, impaired consciousness and coma, convulsions and respiratory depression as well as respiratory arrest. No additional pharmacovigilance activities or additional risk minimisation measures are deemed necessary.

Public health impact:

The potential impact in public health is expected to be low, providing that precautions and risk factors are taken into account.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Use in patients with severe respiratory insufficiency. • Use in patients with severe hepatic impairment. • Use in patients with acute alcoholism or delirium trements. • Abuse and misuse. • Withdrawal reactions in opioid-dependent patients. • Concomitant use of other medications (CYP3A4 inhibitors; benzodiazepines; other central nervous system depressants; MAOI; and serotonergic medicinal products). • Overdose.
Important potential risks	• Use in patients with various disease states (renal impairment; head injuries; increased intracranial pressure; hypotension; prostatic hypertrophy; and urethral stenosis). • Concomitant use of gabapentinoids.
Missing information	• Use in pregnancy.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted for the products included in this RMP.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities will be conducted.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

No planned or on-going post-authorisation efficacy studies have been imposed.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

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
Use in patients with severe respiratory insufficiency.	Routine risk communication: *Summary of Product Characteristics (SmPC) section 4.3.* *SmPC section 4.4.* *Patient Leaflet (PL) section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *According to Section 4.3, the product is contraindicated in case of severe respiratory insufficiency.* *Section 4.4 of the SmPC states that buprenorphine should be used with care in patients with asthma or respiratory insufficiency (e.g. chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis (curvature of spine leading to potential shortness of breath)). Patients with the physical and/or pharmacological risk factors above should be monitored, and dose reduction may be considered.* *Buprenorphine may cause severe, possibly fatal, respiratory depression in children and nondependent persons in case of accidental or deliberate ingestion. Patients must be warned to store the sachet safely, to never open the sachet in advance, to keep them out of the reach of children and other household members, and not to use this medicinal product in front of children. An emergency unit should be contacted immediately in case of accidental ingestion or suspicion of ingestion.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.*
Use in patients with severe hepatic impairment.	Routine risk communication: *SmPC section 4.2.* *SmPC section 4.3.* *SmPC section 4.4.* *SmPC section 5.2.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Section 4.2 and 4.4 of the SmPC states that baseline liver function tests and documentation of viral hepatitis status are recommended prior to*

Safety concern	Routine risk minimisation activities
	commencing therapy. In addition, patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. Buprenorphine should be used with caution in patients with moderate hepatic impairment. Regular monitoring of liver function is recommended. *According to Section 4.3, the product is contraindicated in case of severe hepatic insufficiency.* *Section 4.4 of the SmPC indicates that when a hepatic event is suspected, further biological and etiological evaluation is required. Depending upon the findings, the medicinal product may be discontinued cautiously. If the treatment is continued, hepatic function should be monitored closely.* *Section 2 of the PL states that regular blood tests may be conducted by your doctor to monitor the condition of your liver, and advice to contact a doctor in case of any liver problems before starting treatment with Buprenorphine Neuraxpharm.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.*
Use in patients with acute alcoholism or delirium tremens.	Routine risk communication: *SmPC section 4.3.* *SmPC section 4.4.* *SmPC section 4.5.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *According to Section 4.3, the product is contraindicated in case of acute alcoholism or delirium tremens.* *Section 4.4 of the SmPC warns that a patient who is under-dosed with buprenorphine may continue responding to uncontrolled withdrawal symptoms and craving by self-medicating with alcohol (…).* *Section 4.5 of the SmPC and section 2 of the PL recommends avoid taking buprenorphine together with alcoholic drinks or medications containing alcohol.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.*
Abuse and misuse.	Routine risk communication: *SmPC section 4.4.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimisation activities
	Section 4.2 of the SmPC recommends daily dispensing of buprenorphine is recommended, particularly during the initiation of treatment. Then, after stabilisation, the patient may be given a supply of the product sufficient for several days of treatment. However, it is recommended that the amount of the product dispensed be limited to a maximum of 7 days. *Section 4.4 of the SmPC states that to minimise the risk of misuse, abuse and diversion, physicians should take appropriate precautions when prescribing and dispensing buprenorphine, such as to avoid prescribing multiple refills early in treatment and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability.* *Section 2 of the PL recommends keeping buprenorphine in a safe place to protect it from theft and avoiding giving the medicine to anyone else.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.*
Withdrawal reactions in opioid-dependent patients.	Routine risk communication: *SmPC section 4.2.* *SmPC section 4.4.* *SmPC section 4.5.* *SmPC section 4.6.* *SmPC section 4.8.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *As per Section 4.2 of the SmPC, prior to treatment initiation, consideration should be given to the type of opioid dependence, the time since last opioid use and the degree of opioid dependence. To avoid precipitating withdrawal, induction with or buprenorphine only should be undertaken when objective and clear signs of withdrawal are evident (demonstrated by a score indicating mild to moderate withdrawal on the validated Clinical Opioid Withdrawal Scale, COWS). For patients dependent upon heroin or short-acting opioids, the first dose of buprenorphine must be taken when signs of withdrawal appear, but not less than 6 hours after the patient last used opioids. For patients receiving methadone, the dose of methadone must be reduced to a maximum of 30 mg/day before beginning buprenorphine therapy. The first dose of buprenorphine should be taken only when signs of withdrawal appear, but not less than 24 hours after the patient last used methadone.* *In addition, to avoid withdrawal symptoms and potential relapse to illicit drug use, the buprenorphine dose may be progressively decreased over time in favourable cases until treatment can be discontinued. After a satisfactory period of stabilisation has been achieved, if the patient*

Safety concern	Routine risk minimisation activities
	agrees, the dosage of buprenorphine may be reduced gradually; in some favourable cases, treatment may be discontinued. *Section 4.4 of the SmPC recommends to monitor patients during the switching period from methadone to buprenorphine. To avoid precipitating withdrawal, induction with buprenorphine should be undertaken when objective signs of moderate withdrawal are evident.* *Section 4.5 of the SmPC warns that buprenorphine should be used cautiously when co-administered with naltrexone and nalmefene since for opioid dependent patients currently receiving buprenorphine treatment, naltrexone or nalmefene may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms. Also, that in a clinical study performed in healthy volunteers, the combination of buprenorphine with either rifampicin or rifabutin shows a 70% and 35% reduction, respectively, in plasma buprenorphine levels and onset of withdrawal symptoms in 50% of the 12 volunteers. Therefore it is recommended that patients receiving buprenorphine should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered, and the dose of buprenorphine or CYP3A4 inducer may need to be adjusted accordingly.* *Section 4.6 of the SmPC clearly indicates that chronic use of buprenorphine by the mother at the end of pregnancy, at any dose, may cause a withdrawal syndrome (high-pitched cry, poor feeding, abnormal sleep, irritability, tremor, hypertonia, myoclonus, or convulsions) in the neonate. Also, that very small amounts of buprenorphine and its metabolite pass into mother's milk. These amounts are not sufficient to prevent withdrawal syndrome which can be delayed in breastfed infants.* *Section 4.8 of the SmPC collects Drug withdrawal syndrome and Drug withdrawal syndrome neonatal as a well-known undesirable effects for the product.* *Section 2 of the PL recommends to leave at least 6 hours after using a short-acting opioid (e.g. morphine, heroin) or at least 24 hours after using a long-acting opioid such as methadone.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.*
Concomitant use of other medications (CYP3A4 inhibitors; benzodiazepines; other central nervous system depressants; MAOI; and serotonergic medicinal products).	Routine risk communication: *SmPC section 4.4.* *SmPC section 4.5.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimisation activities
	As per section 4.4 and 4.5 of the SmPC patients receiving buprenorphine should be closely monitored, and may require dose-reduction if combined with potent CYP3A4 inhibitors. *Section 2 of the PL indicates that buprenorphine must not be use if the patient is taking methadone, opioid analgesics, naltrexone and nalmefene. Additionally, it is not recommended to use buprenorphine with tramadol, codeine, dihydrocodeine, ethylmorphine and alcohol.* *Furthermore, this sections advice to contact a doctor when taking benzodiazepines, other medicinal products that may cause central nervous system depression and recommends close monitoring and states that, in some cases, a dose adjustment by a doctor may be required.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.*
Overdose.	Routine risk communication: *SmPC section 4.4.* *SmPC section 4.5.* *SmPC section 4.9.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Section 4.2 and 4.4 of the SmPC recommends monitoring for signs and symptoms of toxicity or overdose in patients with hepatic impairment. In addition section 4.2 of the SmPC recommends monitoring those patients switching between buprenorphine sublingual film and other buprenorphine medicinal products.* *Section 4.5 of the SmPC specifies that buprenorphine should be used cautiously when co-administered with opioid analgesics due to the potential for overdose.* *As per section 4.9 of the SmPC, in the event of overdose, general supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient.* *Section 2 of the PL recommends going to an emergency centre or hospital in case od overdose.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.*
Use in patients with various disease states (renal impairment; head injuries; increased intracranial pressure; hypotension;	Routine risk communication: *SmPC section 4.2.* *SmPC section 4.4.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimisation activities
prostatic hypertrophy; and urethral stenosis).	*As per section 4.2 and 4.4 of the SmPC, caution is recommended when dosing patients with severe renal impairment. In addition, section 4.4 recommends caution when using in patients with head injury. intracranial lesions and increased cranial pressure, or history of seizure, hypotension, prostatic hypertrophy or urethral stricture.* *Section 2 of the PL recommends consulting a doctor in case of low blood pressure, recent head injury or brain disease, urinary disorder (especially linked to enlarged prostate in men) and kidney disease.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.*
Concomitant use of gabapentinoids.	Routine risk communication: *SmPC section 4.4.* *SmPC section 4.5.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Section 4.4 and 4.5 states that concomitant prescribing with sedative medicinal products such as benzodiazepines (e.g. diazepam, temazepam, alprazolam), gabapentinoids (e.g. pregabalin, gabapentin) or related medicinal products such as barbiturates (e.g. phenobarbital) or chloral hydrate, should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe buprenorphine concomitantly with sedative medicinal products, the lowest effective dose of the sedative medicines should be used, and the duration of treatment should be as short as possible. The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms. Patients should be cautioned to use gabapentinoids (such as pregabalin and gabapentin) concurrently with this product only as directed by their physician.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.*
Use in pregnancy.	Routine risk communication: *SmPC section 4.6.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Section 4.6 of the SmPC states that buprenorphine should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus, and recommends daily dose adjustments, to maintain the efficacy*

Safety concern	Routine risk minimisation activities
	of the treatment and neonatal monitoring if the mother is treated up to the end of the pregnancy. *Section 2 of the PL advise to contact a doctor in case of pregnancy or if the patient is planning to have a baby.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.*

V.2 Additional Risk Minimisation Measures

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

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
Use in patients with severe respiratory insufficiency.	Routine risk minimisation measures: *SmPC section 4.3.* *SmPC section 4.4.* *PL section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Use in patients with severe hepatic impairment.	Routine risk minimisation measures: *SmPC section 4.2.* *SmPC section 4.3.* *SmPC section 4.4.* *SmPC section 5.2.* *PL section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Use in patients with acute alcoholism or delirium tremens.	Routine risk minimisation measures: *SmPC section 4.3.* *SmPC section 4.4.* *SmPC section 4.5.* *PL section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Abuse and misuse.	Routine risk minimisation measures: *SmPC section 4.4.* *PL section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Withdrawal reactions in opioid-dependent patients.	Routine risk minimisation measures: *SmPC section 4.2.* *SmPC section 4.4.* *SmPC section 4.5.* *SmPC section 4.6.* *SmPC section 4.8.* *PL section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Concomitant use of other medications (CYP3A4 inhibitors; benzodiazepines; other central nervous system depressants; MAOI; and serotonergic medicinal products).	Routine risk minimisation measures: *SmPC section 4.4.* *SmPC section 4.5.* *PL section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Overdose.	Routine risk minimisation measures: *SmPC section 4.4.* *SmPC section 4.5.* *SmPC section 4.9.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Use in patients with various disease states (renal impairment; head injuries; increased intracranial	Routine risk minimisation measures: *SmPC section 4.2.* *SmPC section 4.4.* *PL section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
pressure; hypotension; prostatic hypertrophy; and urethral stenosis).		*None.*
Concomitant use of gabapentinoids.	Routine risk minimisation measures: *SmPC section 4.4.* *SmPC section 4.5.* *PL section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Use in pregnancy.	Routine risk minimisation measures: *SmPC section 4.6.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*

Part VI: Summary of the risk management plan

Summary of risk management plan for Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films (buprenorphine hydrochloride)

This is a summary of the risk management plan (RMP) for Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films. The RMP details important risks of Buprenorphine Neuraxpharm 0.4 mg, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg sublingual films, how these risks can be minimised, and how more information will be obtained about Buprenorphine Neuraxpharm 0.4 mg,4 mg, 6 mg, 8 mg sublingual films' risks and uncertainties (missing information).

Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films' Summary of Product Characteristics (SmPC) and their package leaflet give essential information to healthcare professionals and patients on how Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films should be used.

This summary of the RMP for Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films 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 Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films' RMP.

I. The medicine and what it is used for

Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films are authorised for treatment of opioid drug dependence, within a comprehensive therapeutic monitoring framework of medical, social and psychological treatment (see SmPC for the full indication). They contain buprenorphine hydrochloride as the active substance and they are given by sublingual route of administration.

Further information about the evaluation of Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films' benefits can be found in Buprenorphine Neuraxpharm 0.4 mg, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg sublingual films' EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/buprenorphine-neuraxpharm

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

Important risks of Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films, together with measures to minimise such risks and the proposed studies for learning more about Buprenorphine Neuraxpharm 0.4 mg, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg sublingual films' 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 so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

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

If important information that may affect the safe use of Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films. 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	• Use in patients with severe respiratory insufficiency. • Use in patients with severe hepatic impairment. • Use in patients with acute alcoholism or delirium trements. • Abuse and misuse. • Withdrawal reactions in opioid-dependent patients. • Concomitant use of other medications (Cytochrome P 3A4 [CYP3A4] inhibitors; benzodiazepines; other central nervous system depressants; monoamine oxidase inhibitors [MAOI]; and serotonergic medicinal products). • Overdose.
Important potential risks	• Use in patients with various disease states (renal impairment; head injuries; increased intracranial pressure; hypotension; prostatic hypertrophy; and urethral stenosis). • Concomitant use of gabapentinoids.
Missing information	• Use in pregnancy.

II.B Summary of important risks

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

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Use in patients with severe respiratory insufficiency.	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.3. *SmPC section 4.4.* *PL section 2.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.* Additional risk minimisation measures: *None.*	*None.*
Use in patients with severe hepatic impairment.	Routine risk minimisation measures: *SmPC section 4.2.* *SmPC section 4.3.* *SmPC section 4.4.* *SmPC section 5.2.* *PL section 2.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Use in patients with acute alcoholism or delirium tremens.	Routine risk minimisation measures: *SmPC section 4.3.* *SmPC section 4.4.* *SmPC section 4.5.* *PL section 2.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Abuse and misuse.	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.4. *PL section 2.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.* Additional risk minimisation measures: *None.*	*None.* Additional pharmacovigilance activities: *None.*
Withdrawal reactions in opioid-dependent patients.	Routine risk minimisation measures: *SmPC section 4.2.* *SmPC section 4.4.* *SmPC section 4.5.* *SmPC section 4.6.* *SmPC section 4.8.* *PL section 2.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Concomitant use of other medications (CYP3A4 inhibitors; benzodiazepines; other central nervous system depressants; MAOI; and serotonergic medicinal products).	Routine risk minimisation measures: *SmPC section 4.4.* *SmPC section 4.5.* *PL section 2.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Overdose.	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.4. *SmPC section 4.5.* *SmPC section 4.9.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.* Additional risk minimisation measures: *None.*	Additional pharmacovigilance activities: *None.*
Use in patients with various disease states (renal impairment; head injuries; increased intracranial pressure; hypotension; prostatic hypertrophy; and urethral stenosis).	Routine risk minimisation measures: *SmPC section 4.2.* *SmPC section 4.4.* *PL section 2.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Concomitant use of gabapentinoids.	Routine risk minimisation measures: *SmPC section 4.4.* *SmPC section 4.5.* *PL section 2.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Medicinal product subject to special and restricted medical prescription.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Use in pregnancy.	Routine risk minimisation measures: *SmPC section 4.6.* Other routine risk minimisation measures beyond the Product Information:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: Medicinal product subject to special and restricted medical prescription. Additional risk minimisation measures: *None.*	*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 Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Buprenorphine Neuraxpharm 0.4 mg, 4 mg, 6 mg, 8 mg sublingual films.

Part VII: Annexes

Table of contents

Annex 7 – Other supporting data (including referenced material)

Butler SF, Black RA, Severtson SG, Dart RC, Green JL. Understanding abuse of buprenorphine/naloxone film versus tablet products using data from ASI-MV® substance use disorder treatment centers and RADARS® System Poison Centers. J Subst Abuse Treat. 2018;84:42-49.

Dy SM, Shore AD, Hicks RW, Morlock LL. Medication errors with opioids: results from a national reporting system. J Opioid Manag. 2007;3(4):189-94.

Edlund MJ, Martin BC, Fan MY, Devries A, Braden JB, Sullivan MD. Risks for opioid abuse and dependence among recipients of chronic opioid therapy: results from the TROUP study. Drug Alcohol Depend. 2010;112(1-2):90-8.

Hayes BD, Klein-Schwartz W, Doyon S. Toxicity of buprenorphine overdoses in children. Pediatrics. 2008;121(4):e782-6.

Heneka N, Shaw T, Rowett D, Lapkin S, Phillips JL. Exploring Factors Contributing to Medication Errors with Opioids in Australian Specialist Palliative Care Inpatient Services: A Multi-Incident Analysis. J Palliat Med. 2018;21(6):825-35.

Johnson RE, Strain EC, Amass L. 2003. Buprenorphine: how to use it right. Drug and Alcohol Dependence 70: S59–77.

Kumar R, Viswanath O, Saadabadi A. Buprenorphine. Buprenorphine, 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459126/.

Lavonas EJ, Banner W, Bradt P, Bucher-Bartelson B, Brown KR, Rajan P, Murrelle L, Dart RC, Green JL. Root causes, clinical effects, and outcomes of unintentional exposures to buprenorphine by young children. J Pediatr. 2013;163(5):1377-83.e1-3.Lavonas EJ, Severtson SG, Martinez EM, Bucher-Bartelson B, Le Lait MC, Green JL, et al. Abuse and diversion of buprenorphine sublingual tablets and film. J Subst Abuse Treat. 2014;47(1):27-34.

Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. Pain Physician 2008; 11(2 Supl): S63-88.

McKeown NJ. Withdrawal Syndromes. 2016. Available at: http://emedicine.medscape.com/article/819502-overview#a7.

Messing RO. Biology of psychiatric disorders. In: Fauci AS, Kasper DL; Hauser SL, Longo DL, Jameson JL, Loscalzo J editors. Harrison's principles of internal medicine. 19th ed. McGraw Hill, New York; 2015. eChapter 468.

Ministry of Health. 2010. New Zealand Clinical Guidelines for the Use of Buprenorphine (with or without Naloxone) in the Treatment of Opioid Dependence. Wellington: Ministry of Health.

Strain EC, Walsh S, Preston KL, et al. 1997. The effects of buprenorphine in buprenorphine maintained volunteers. Psychopharmacology 129: 329–38.

Tariq RA, Vashisht R, Sinha A, et al. Medication Dispensing Errors and Prevention. 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK519065/.

Winstanley EL, Stover AN. The Impact of the Opioid Epidemic on Children and Adolescents. Clin Ther. 2019;41(9):1655-62. World Health Organization (WHO), Opioid overdose. 2021. Available at: https://www.who.int/news-room/fact-sheets/detail/opioid-overdose.