EU-Risk Management Plan

for

Nyxoid

(Naloxone hydrochloride intranasal formulation)

[redacted]

Administrative information on the Risk Management Plan

RMP version to be assessed as part of this application:

RMP Version number:	3.2
Data lock point for this RMP:	31 Dec 2023
Date of final sign off	01 Apr 2025

Rationale for submitting an updated RMP:

Update of the RMP was required due to removal of the PAES as an outstanding post-approval commitment, mention of a QR code linking to approved educational materials, and distribution of those materials through the non-promotional web-site nyxoid.com.

Summary of significant changes in this RMP

Section	Update
Part II, SV	SV1.2 Cumulative post-marketing exposure updated
Part II, SVII	SVII.2 New safety concerns and reclassification with a submission of an updated RMP SVII.3 Updated with post-marketing data up to the DLP
Part IV	Removal of PAES and justification
Part V.2	Addition of QR code to package and PIL and specification of distribution of educational materials through the non-promotional website nyxoid.com
Part VI, II.C	Justification for PAES completion
Part VI, II.D	Addition of QR code to package and PIL and specification of distribution of educational materials through the non-promotional website nyxoid.com
Part VII, Annex 5	Removal of the PAES protocol
Part VII, Annex 6	Addition of QR code to package and PIL and specification of distribution of educational materials through the non-promotional website nyxoid.com
Part VII, Annex 8	Updated based upon the current version 3.0

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number: 2.0

Approved with procedure: EMEA/H/C/004325 in centralised procedure

Date of approval (opinion date): 03 Feb 2022

Qualified Person for Pharmacovigilance (QPPV) name: Arthur Meiners

QPPV signature: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file

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List of Abbreviations

ACO	Addendum to Clinical Overview
ADR	Adverse drug reaction
AUC	Area under curve
CCDS	Company core data sheet
C_{max}	maximum concentration
CNS	Central nervous system
CYP	Cytochrome P450
EEA	European Economic Area
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction EMA European Medicines Agency
FDA	United States Food and Drug Administration
IM	Intramuscular
IV	Intravenous
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No observed adverse effect level
PhV	Pharmacovigilance
PK	Pharmacokinetic
PT	Preferred term (of MedDRA)
RMP	Risk management plan
SC	Subcutaneous
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA query
SNRI	Selective noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
THN	Take home naloxone
WHO	World Health Organisation
QPPV	Qualified Person Responsible for Pharmacovigilance

Part I: Product(s) Overview

Table Part I - 1: Product Overview

Active substance(s) (INN or common name)	Naloxone chloride
Pharmacotherapeutic group(s) (ATC Code)	All other therapeutic products Antidotes (V03AB15)
Marketing Authorisation Holder	Mundipharma Corporation (Ireland) Limited
Medicinal products to which this RMP refers	Nyxoid
Marketing authorisation procedure	Centralised procedure
Brief description of the product	**Chemical class** All other therapeutic products Antidotes (ATC V03AB15)
	Summary of mode of action Evidence suggests that naloxone competes for the opiate receptor sites (mu, kappa, and sigma) in the central nervous system.
	Important information about its composition Each nasal spray container delivers 1.8 mg of naloxone (as hydrochloride dihydrate).
Hyperlink to the Product Information	Summary of Product Characteristics/Package Leaflet in the eCTD Module
Indication(s) in the EEA	Current: Nyxoid is intended for immediate administration as emergency therapy for known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression in both non-medical and healthcare settings. Nyxoid is indicated in adults and adolescents aged 14 years and over. Nyxoid is not a substitute for emergency medical care.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	Current: The recommended dose is 1.8 mg administered into one nostril (one nasal spray). In some cases, further doses may be necessary. The appropriate maximum dose of Nyxoid is situation specific. If the patient does not respond, the second dose should be administered after 2-3 minutes. If the patient responds to the first administration but then relapses again into respiratory depression, the second dose should be administered immediately. Further doses (if available) should be administered in

	alternate nostrils and the patient should be monitored whilst awaiting arrival of the emergency services. Emergency services may administer further doses according to local guidelines. Paediatric population The safety and efficacy of Nyxoid in children below 14 years has not been established. No data are available. Method of administration: Nasal Use. Nyxoid should be administered as soon as possible to avoid damage to the central nervous system or death. Nyxoid contains only one dose and therefore it must not be primed or tested prior to administration. Detailed instructions on how to use Nyxoid are provided in the Package Leaflet and a Quick Start Guide is printed on the back of each blister. In addition, training is provided via a video and a Patient Information Card.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Clear, colourless to pale yellow solution. Nasal spray, solution in a single-dose container. Each nasal spray container delivers 1.8 mg of naloxone (as hydrochloride dihydrate).
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Module SI - Epidemiology of the indication(s) and target population

Indication

Nyxoid is intended for immediate administration as emergency therapy for known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression in both non-medical and healthcare settings.

Nyxoid is indicated in adults and adolescents aged 14 years and over.

Nyxoid is not a substitute for emergency medical care.

SI.1 Epidemiology of the disease

It is estimated that 82% of the 6800 drug induced deaths that are reported in Europe each year include opioids.[1] The number of non-fatal overdoses occurring each year cannot be estimated with precision, as monitoring is very limited and definitions vary between countries. Nevertheless, the available information suggests that there could be between 120 000 and 175 000 non-fatal overdoses every year in Europe.[2] Several studies have documented the frequency of non-fatal overdose with approximately half of all opioid users reporting life-time experience of at least one non-fatal overdose.[3]

The average prevalence of high-risk, or problematic, opioid use – defined by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) as injecting drug use or long duration or regular use – among adults aged 15–64 years is estimated at 0.4% (or 4 per 1000 persons), the equivalent of 1.3 million high-risk opioid users in Europe in 2014. At a national level, prevalence estimates of high-risk opioid use range from less than 1 per 1000 persons aged 15–64 years (Hungary and Turkey) to around 8 (United Kingdom) cases per 1000 persons. Around 75% of the high-risk opioid users in the European Union are reported in the United Kingdom, France, Italy, Germany and Spain[1].

Opioid overdose risk factors include injecting opioids; combining opioids with other central nervous system depressants; opioid doses greater than 100 mg/day of morphine or equivalent; loss of opioid tolerance after detoxification or incarceration and resuming opioid use; comorbid mental health, central nervous system, renal, hepatic or pulmonary diseases; young people experimenting with opioids and accidental ingestion.[4]

Naloxone has been used in hospital emergency departments and as standard clinical practice for opioid poisoning treatment for more than 40 years, having been discovered in the early 1960s and then approved as an opioid antagonist for IV, IM and SC administration. Naloxone is used to reverse respiratory and central nervous system depression accompanying opioid overdose and to reverse unwanted effects of opioids in medical use such as after general anaesthesia.

References:

1. EMCDDA. Preventing opioid overdose deaths with take-home naloxone (available: http://www.emcdda.europa.eu/system/files/publications/2089/TDXD15020ENN.pdf). ISSN 2314-9264. 2016

2. EMCDDA. European Monitoring Centre for Drugs and Drug Addiction: Annual report 2010: the state of the drugs problem in Europe. Luxembourg: 2010.

3. Strang J, Manning V, Mayet S, Best D, Titherington E, Santana L, et al. Overdose training and take-home naloxone for opiate users: prospective cohort study of impact on knowledge and attitudes and subsequent management of overdoses. Addiction. 2008; 103(10):1648-57.

4. Wermeling DP. Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. Therapeutic advances in drug safety. 2015; 6(1):20-31.

SI.2 Concomitant medication(s) in the target population

The majority of high-risk opioid users have co-morbid medical conditions which require multiple different concomitant medications. Certain patients treated in cases of suspected opioid overdose could be injecting drug users in whom the prevalence of blood borne viruses such as HIV and hepatitis B and C and bacterial infections is high[1,2,3]. These patients might therefore be on antiviral drugs, interferon or antibiotics usually for staphylococcus and streptococcal infections. These patients may also suffer from major depression and anxiety disorder which are treated with antidepressants such as selective serotonin reuptake inhibitor (SSRI), selective noradrenaline reuptake inhibitor (SNRI) or benzodiazepines. None of them are known to interact with naloxone.

References:

1. Kelly AM, Kerr D, Dietze P, Patrick I, Walker T & Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. MJA (2005); 182: 24-27

2. Crofts N, Jolley D, Kaldor J, et al. Epidemiology of hepatitis C virus infection among injecting drug users in Australia. J Epidemiol Commun Health 1997; 51: 692-697.

3. Davoli M, Perucci CA, Rapiti E, et al. A persistent rise in mortality among injection drug users in Rome, 1980 to 1991. Am J Public Health 1997; 87: 851-853

SI.3 Important co-morbidities found in the target population

For high risk opioid users who inject illicit drugs, this use is a major cause of acquiring blood- borne and other infectious diseases, including HIV, hepatitis B and C, and bacterial skin and soft tissue infections caused by staphylococcus aureus, streptococcal infections and systemic infections[1]. The main mechanism of transmission for these infections is the sharing of injection equipment among users, such as syringes, needles, drug mixing vessels and other drug preparation paraphernalia.

Studies of problematic opioid users have found a high prevalence of major depression and anxiety disorders.[2] However, it is difficult to determine cause and effect from these observational studies since it is unclear in what proportion of these cases psychiatric disorders preceded and contributed to the development of problem drug use or vice versa. Nor is it clear to what extent pre-existing psychiatric disorders have been exacerbated by high risk opioid use or vice versa. Some of the

patients who are prescribed opioids for chronic pain condition may have complex pattern of co-existing comorbidities which could be chronic in nature.

References:

1. European Centre for Disease Prevention and Control and European Monitoring Centre for Drugs and Drug Addiction. Prevention and control of infectious diseases among people who inject drugs. Stockholm: ECDC; 2011.

2. Darke S, Ross J. Polydrug dependence and psychiatric comorbidity among heroin injectors. Drug and alcohol dependence. 1997; 48(2):135-41.

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

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity:

- **Key issues identified from acute or repeat-dose toxicity studies**

Single and repeated-dose toxicity: intranasal administration

Single and 7 day-repeated intranasal administration of naloxone (free base; 4, 8 or 16 mg/kg/day) to male rats (Sprague Dawley, SD) did not cause any mortality or any treatment related changes indicative of toxicity. Intranasal administration did not cause any macroscopic or microscopic lesions in the nasal cavity and related tissues (oesophagus, larynx, lungs with bronchi, nasopharynx, olfactory bulbs, stomach and trachea). Minor clinical signs i.e. salivation (at all doses) and gasping (in a single male animal at middle dose only) were observed. Salivation was considered a secondary effect, most likely induced by small quantities of the test article migrating into the oral cavity following dosing and not a direct pharmacologic effect of the test article. Gasping was not considered of biological and toxicological relevance as it occurred in one male animal only. Following intranasal administration of naloxone (free base) at 4, 8 or 16 mg/kg, the maximum plasma concentration (Cmax) values were 4387, 7064 and 7962 ng/mL and the area under the plasma concentration-time curve to time t (AUCt) values were 1028, 1882 and 2938 ng × h/mL, respectively (NDSE 736).

Intranasal administration of naloxone in non-clinical studies did not cause any additional toxicity to that observed with oral administration nor did it identify any target organs of toxicity. Hence there is no safety concern apparent from these studies.

Single dose toxicity: oral administration

Following a single oral (gavage) administration of naloxone hydrochloride to mice (CD-1), mortality was observed at doses ≥860 mg/kg and the maximum tolerated dose (MTD) was 600 mg/kg. The clinical signs observed were tremors from doses ≥598 mg/kg and convulsions from doses ≥860 mg/kg. One male dosed with 860 mg/kg was prostrated and had respiratory difficulties and died 30 minutes after dosing (KPC/18/PSB).

Following a single oral (gavage) administration of naloxone hydrochloride to Sprague-Dawley (SD) rats, the LD50 was slightly in excess of 800 mg/kg. The clinical signs observed were hypoactivity, tremor and convulsions at doses ≥1000 mg/kg (KPC/17/PSB).

Following a single oral administration of naloxone hydrochloride to New Zealand White (NZW) rabbits, the LD50 was ~2500 mg/kg. The clinical signs observed were convulsions and tremors at doses ≥2500 mg/kg (KPC/19/PSB).

Repeated dose toxicity: oral administration

Repeated dose oral toxicity studies with naloxone hydrochloride included 4 weeks in mice (KPC/21/C and rats KPC/22/C), 13 weeks in mice (N003003E), rats (KPC/23/C) and dogs (KPC/28/C), 39 weeks in dogs (N003003D) and 52 weeks in rats (KPC/24/87).

In mice (CD-1), following 4 weeks repeat dietary administration, the NOAEL was the highest dose tested (800 mg/kg/day; KPC/21/C) and following 13 weeks repeat dietary administration the NOAEL was 180 mg/kg/day, mainly based on the slight decrease in body weight associated with dietary

exposures of ≥500 mg/kg/day. In the 13 weeks repeat toxicity study, at the NOAEL dose, the plasma level was 59 ng/mL. Clinical signs observed at 1500 and 3000 mg/kg/day included rough coat and decreased faeces (also noted at 500 mg/kg/day in females). There were no naloxone-related macroscopic or microscopic findings and no sex differences observed. The plasma concentrations of naloxone hydrochloride increased proportionally with dose for both sexes (N003003E).

In rats (SD), following 4 weeks repeat dietary administration, the MTD was >800 mg/kg/day (KPC/22/C) and following 13 weeks repeat dietary administration the NOAEL was <50 mg/kg/day based on clinical signs of hypoactivity at this dose (KPC/23/C). Following 52 weeks repeat dietary administration the NOAEL was <25 mg/kg/day based on the retardation of growth. Increased relative liver weights (all treated groups) and increased relative kidney weights were recorded in the 75 and 225 mg/kg/day groups; however, no microscopic findings in these or other organs were noted at any doses.

In dogs (Beagles), following 13 weeks repeated oral (capsules) administration, emesis and salivation were noted in the highest dose tested (100 mg/kg/day) and salivation was observed in one male animal at Day 2 in the middle dose (30 mg/kg/day). The MTD was considered 100 mg/kg/day based on absence of other findings (KPC/28/C). Following 39 weeks repeated oral (capsules) administration; the NOAEL was 75 mg/kg/day (the high dose tested from day 4-5). The high dose, originally 125 mg/kg/day, was decreased to 75 mg/kg/day as one female was sacrificed for humane reasons on Day 3 and similar findings of disorientation, ataxia and convulsions were observed in one high dose male and additional high-dose females. In the study, salivation was noted at the middle and high doses of 25 and 75 mg/kg/day; without any other treatment related changes. At the NOAEL dose (75 mg/kg/day), the plasma Cmax was 70 ng/mL and the AUC0-24h was 286 ng × h/mL at week 39 (N003003D).

In dogs (Beagle) the NOAEL for naloxone was 10 mg/kg/day (free base) when administered twice daily for 1-hour intravenous infusions for 15 days. At this dose the plasma Cmax was 876 ng/mL and the AUC0-∞ was 68906 ng × min/mL (NDSE 706).

- NDSE-736 (2003). A 1-day and 7-day intranasal safety study in male rats with naloxone HCl dihydrate.
- KPC/18/PSB (1984). Single dose (oral) limit test in the mouse: naloxone.
- KPC/17/PSB (1984). Single dose (oral) limit test in the rat: naloxone.
- KPC/19/PSB (1984). Single dose (oral) limit test in the rabbit: naloxone.
- KPC/21/C (1985). 28-day dietary range finding study in the mouse: naloxone.
- KPC/22/C (1985). 28-day oral range finding study in the rat: naloxone.
- N003003E (1999). 3-month oral toxicity study of naloxone HCl in mice.
- KPC/23/C (1985). 13-week oral toxicity study in the rat: naloxone.
- KPC/24/87 (1987). 52-week dietary study in the rat: naloxone.
- KPC/28/C (1985). 13-week oral toxicity study in the dog: naloxone.
- N003003D (1999). 9-month oral toxicity study of naloxone HCl in dogs.
- NDSE-706 (2004). 2-week intermittent intravenous infusion toxicity and toxicokinetic study with naloxone hydrochloride in dogs.

- **Reproductive/ developmental toxicity**

No reproductive studies were conducted following intranasal administration of naloxone hydrochloride.

Studies with orally administered naloxone hydrochloride revealed no effect on fertility and reproductive performance in the rat at the highest dose tested (800 mg/kg/day) (KPC/32/86).

- KPC/32/86 (1986). Naloxone: rat fertility and general reproductive performance study

The non-clinical reproductive studies do not highlight any concerns on fertility and reproductive performance following oral administration in the rat at 800 mg/kg/day, the highest dose tested.

No developmental toxicity studies were conducted following intranasal administration of naloxone hydrochloride.

Orally administered naloxone hydrochloride was not teratogenic in the rat (KPC/33/85) or rabbit (KPC/35/85) at the maximum doses tested (800 mg/kg/day and 400 mg/kg/day, respectively).

In a pre-natal and post-natal development study in rats, naloxone hydrochloride at a highest dose of 800 mg/kg/day produced mortality and significant maternal toxicity in rats and resulted in increased pup deaths in the immediate postpartum period. However, in surviving pups, no effects on development or behaviour were observed. Mild maternal toxicity was also observed in rats that received200 mg/kg/day; however, there were no adverse effects on F1 pups (KPC/34/85).

- KPC/33/85 (1985). Naloxone: Rat Teratology Study.
- KPC/35/85 (1985). Naloxone: Rabbit Teratology Study.
- KPC/34/85 (1986). Naloxone: Rat Peri and Post Natal Study.

The non-clinical developmental toxicity studies do not highlight any teratogenic potential following oral administration in the rat (800 mg/kg/day) and the rabbit (400 mg/kg/day), at the highest doses tested.

- **Genotoxicity**

Naloxone hydrochloride was tested in a battery of standard genotoxicity studies by the Applicant.

Naloxone hydrochloride was not mutagenic in the S. typhimurium bacterial (TA1535, TA1537, TA1538, TA98 and TA100) mutagenicity test with or without metabolic activation at concentrations of up to 5000 µg/plate (70/8409).

Naloxone hydrochloride induced a positive mutagenic response in the absence and presence of metabolic activation in the L5178Y mouse lymphoma mutation assay (71/8409). In a subsequent study, naloxone hydrochloride induced a positive mutagenic response with predominately small colony mutants in the absence and presence of metabolic activation in the L5178Y mouse lymphoma mutation assay (N003003C).

Naloxone hydrochloride caused a non dose related increase in chromosomal aberration in the presence of metabolic activation that was statistically significant at concentrations of 375 and 1500 µg/mL but not at 750 or 3000 µg/mL. In the absence of S9, there was no increase in aberration (including or excluding gaps) at any concentration of naloxone hydrochloride (74/8506).

Naloxone hydrochloride (up to 2000 mg/kg) was considered to be non-clastogenic in an in vivo mouse micronucleus assay (N003003A). Naloxone hydrochloride was not mutagenic in the bacterial

reverse mutation assay, but was positive in mouse lymphoma assay and was clastogenic in vitro, however, naloxone was not clastogenic in vivo.

Overall, the weight of evidence indicates that naloxone hydrochloride poses minimal, if any, risk for human genotoxicity.

- **Carcinogenicity**

Naloxone hydrochloride was tested in two carcinogenicity studies in transgenic mice (Tg.rasH) (ONU-N-009) and rats (N003003F).

Naloxone hydrochloride was not carcinogenic in a 26-week study in TgrasH2 mice and in a rat 2-year study. At the highest dose tested in Tg.rasH2 mice (200 mg/kg/day), the plasma Cmax resulted in a 375-fold and the AUC0-24h a 178-fold safety margin over the exposures achieved following a single intranasal dose (4 mg) in human subjects.

Naloxone hydrochloride was not carcinogenic in a 2-year rat study at the high dose tested (100 mg/kg/day). At 100 mg/kg/day, at the end of the study, the plasma concentration was 21 ng/mL (N003003F).

- 70/8409 (1984). Bacterial mutagenicity tests: naloxone chlorhydrate.
- 71/8409 (1986). Test for gene mutation in L5178Y mouse lymphoma cells treated with naloxone.
- N003003C (1998). Mammalian cell mutagenesis testing on naloxone hydrochloride using the L5178Y/tk+/- mouse lymphoma cell assay with colony sizing, with and without metabolic activation.
- 74/8506 (1986). Metaphase analysis of human lymphocytes treated with naloxone.
- N003003A (1998). Bone marrow micronucleous test in mice treated with naloxone hydrochloride.
- ONU-N-009 (2012). Naloxone hydrochloride: 26 week repeated dose oral carcinogenicity study in Tg.rasH2 mice.
- N003003F (2002). Two-year oral oncogenicity study of naloxone hydrochloride in Sprague Dawley rats.

Overall, the weight of evidence indicates that naloxone hydrochloride poses minimal, if any, risk for human carcinogenicity.

- **Nephrotoxicity**

Nephrotoxicity studies were not conducted following intranasal administration of naloxone hydrochloride by the Applicant.

In the orally administered single (KPC/18/PSB and KPC/17/PSB) and repeated dose toxicity studies in rodents (KPC/21/C, N003003E, KPC/22/C, KPC/23/C and KPC/24/87) and dogs (KPC/28/C and N003003D) and in the intravenous repeated dose toxicity study in dogs (NDSE-706), no changes were observed in kidney function and no microscopic findings were observed.

The following findings were observed: Following a single oral administration of naloxone hydrochloride (1000 mg/kg) to rats, one female rat died soon after dosing and at necropsy, the

kidney, lungs, spleen were very pale and the liver was very dark in colour; no additional kidney related findings were observed (KPC/17/PSB).

Following oral repeated administration of naloxone hydrochloride (200 mg/kg/day) to rats, at Day 28 one male died. This rat exhibited piloerection, hypothermia and weight loss. Macroscopic examination showed a distended urinary bladder with red areas on the walls of the lumen and pale kidneys with the surrounding renal adipose tissue being red and gelatinous. No other kidney-related findings were observed in this and other animals in the study (KPC/22/C). Following 13 weeks oral repeat administration of naloxone hydrochloride (3000 mg/kg/day) to mice, the absolute weight of the kidney (and kidney to brain ratio) was decreased (N003003E). Following 52-week oral repeat administration of naloxone hydrochloride to rats, the relative kidney weights were increased in males (25, 75 and 225 mg/kg/day) and females (75 and 225 mg/kg/day) (KPC/24/87).

- KPC/18/PSB (1984). Single dose (oral) limit test in the mouse: naloxone.
- KPC/17/PSB (1984). Single dose (oral) limit test in the rat: naloxone.
- KPC/21/C (1985). 28-day dietary range finding study in the mouse: naloxone.
- N003003E (1999). Three-month oral toxicity study of naloxone hydrochloride in mice.
- KPC/22/C (1985). 28-day oral range finding study in the rat: naloxone.
- KPC/23/C (1985). 13-week oral toxicity study in the rat: naloxone.
- KPC/24/87 (1987). 52-week dietary study in the rat: naloxone.
- KPC/28/C (1985). 13-week oral toxicity study in the dog: naloxone.
- N003003D (1999). Nine-month oral toxicity study of naloxone HCl in dogs.
- NDSE-706 (2004). 2-week intermittent intravenous infusion toxicity and toxicokinetic study with naloxone hydrochloride in dogs.

The non-clinical repeat dose toxicity studies, following oral administration, do not indicate any concerns related to nephrotoxicity.

- **Hepatotoxicity**

Hepatotoxicity studies were not conducted following intranasal administration of naloxone hydrochloride by the Applicant.

In the oral, single (KPC/18/PSB and KPC/17/PSB) and repeated dose toxicity studies in rodents (KPC/21/C, N003003E, KPC/22/C, KPC/23/C and KPC/24/87) and dogs (KPC/28/C and N003003D) and in the intravenous repeated dose toxicity study in dogs (NDSE-706), no changes were observed in liver function and no microscopic findings were observed.

The following findings were observed: Following a single oral administration of naloxone hydrochloride (1000 mg/kg) to rats, in the one female rat that died soon after dosing, the liver was very dark in colour and the lungs, spleen and kidneys were very pale; no additional liver related findings were observed. In the one male rat dosed with 800 mg/kg (found dead and at the necropsy), marked accentuation of the lobular pattern of the liver, which was pale and mottled, was noted. No additional liver related findings were observed (KPC/17/PSB).

Following oral repeat administration of naloxone hydrochloride to rodents and non- rodents, the weight of the liver was increased in mice following 13-week oral administration (1500 and 3000

mg/kg/day) (N003003E); in rats following 4 and 13 weeks (800 mg/kg/day) (KPC/22/C; KPC/23/C) and 52 weeks (75 and 225 mg/kg/day) (KPC/24/87). However, no liver-related clinical pathology parameters and no macroscopic and microscopic findings were observed.

- KPC/18/PSB (1984). Single dose (oral) limit test in the mouse: naloxone.
- KPC/17/PSB (1984). Single dose (oral) limit test in the rat: naloxone.
- KPC/21/C (1985). 28-day dietary range finding study in the mouse: naloxone.
- N003003E (1999). 3-month oral toxicity study of naloxone HCl in mice.
- KPC/22/C (1985). 28-day oral range finding study in the rat: naloxone.
- KPC/23/C (1985). 13-week oral toxicity study in the rat: naloxone.
- KPC/24/87 (1987). 52-week dietary study in the rat: naloxone.
- KPC/28/C (1985). 13-week oral toxicity study in the dog: naloxone.
- N003003D (1999). 9-month oral toxicity study of naloxone HCl in dogs.
- NDSE-706 (2004). 2-week intermittent intravenous infusion toxicity and toxicokinetic study with naloxone HCl in dogs.

The non-clinical repeat dose toxicity studies, following oral administration, do not indicate any concerns related to hepatotoxicity.

Safety pharmacology

- **Cardiovascular effects**

Naloxone hydrochloride at a concentration significantly higher than those anticipated at therapeutic plasma level (0.69 µM; 250 ng/mL) produced negligible inhibition (18%) of the hERG potassium channel in vitro (NDSE-585). Moreover, results of electrocardiogram and blood pressure examinations in toxicology studies in the dog showed that administration of naloxone hydrochloride (oral for 39 weeks or intravenous for 2 weeks) did not alter either the blood pressure or the electrocardiogram recordings (N003003D) and (NDSE-706).

- NDSE-585 (2001). K Channel (hERG) for 29 compounds, Cerep study number 4920.
- N003003D (1999). Nine-month oral toxicity study of naloxone hydrochloride in dogs.
- NDSE-706 (2004). 2-week intermittent intravenous infusion toxicity and toxicokinetic study with naloxone hydrochloride in dogs

Overall, the weight of evidence of the non- clinical studies, following oral administration, indicates that naloxone poses minimal risk for the human cardiovascular system.

- **Central Nervous System effects**

Following intranasal administration of naloxone hydrochloride (free base; 4, 8 or 16 mg/kg/day) to rats, the main CNS related clinical signs observed was salivation at all doses. The plasma Cmax values were 4387, 7064 and 7962 ng/mL and the AUC0-∞ values were 1029, 1884 and 2942 ng.h/mL, respectively. However, salivation has been considered to be a secondary effect, most likely induced by small quantities of the test item migrating into the oral cavity following dosing and not a direct pharmacologic effect of the test article (NDSE- 736).

• NDSE-736 (2003). A 1-day and 7-day intranasal safety study in male rats with naloxone hydrochloride dihydrate.

Following intravenous repeated administration of naloxone to dogs no CNS signs were noted at the NOAEL the highest dose tested (10 mg/kg/day) when administered twice daily with 1-hour intravenous infusions for 15 days. At this dose the plasma Cmax was 876 ng/mL and the AUC0-∞ was 68906 ng × min/mL in males and females respectively (NDSE 706).

• NDSE-706 (2004). 2-week intermittent intravenous infusion toxicity and toxicokinetic study with naloxone HCl in dogs.

Following single and repeat oral administration to mice, rats, rabbits and dogs, CNS related clinical signs were observed.

The non-clinical studies performed following a single oral dose administration to rodents and rabbits indicate that naloxone caused tremor, convulsion, respiratory difficulties and hypoactivity at approximately the lethal doses in the animal species tested.

The non-clinical study performed following intranasal administration indicates that naloxone caused salivation at exposure significantly higher than the human therapeutic exposure. At the lowest dose that causes salivation (4 mg/kg), the plasma Cmax resulted in a 729-fold safety margin over the plasma Cmax values, achieved following a single intranasal dose administration (4 mg) in human subjects (Cmax 6.02 ng/mL) and the AUCt values resulted in a 102-fold safety margin over the AUCt values, achieved following a single intranasal dose administration (4 mg) in human subjects (AUCt 10 ng × h/mL) (MR903-1501).

The non-clinical study performed following intravenous administration in the dog did not cause any CNS effects at significantly higher exposure levels than that achieved in humans (plasma Cmax was 146 fold higher than in human subjects following a single intranasal dose administration of naloxone at 4 mg), (MR903-1501).

MR903-1501. A study to compare the pharmacokinetics of intranasal MR903 (1 mg, 2 mg and 4 mg) and naloxone hydrochloride given via intramuscular and intravenous routes.

Single dose toxicity studies (oral)

In mice the following was observed (KPC/18/PSB):

- Tremor from 598 mg/kg (MTD was 600 mg/kg/day).
- Convulsion and respiratory difficulties from 860 mg/kg (mortality observed at doses ≥860 mg/kg).

In rats the following was observed (KPC/17/PSB):

- Hypoactivity from 1000 mg/kg (LD50 was ≥800 mg/kg).
- Tremor from 1419.5 mg/kg (LD50 was ≥800 mg/kg).
- Convulsions from 2413 mg/kg (LD50 was ≥800 mg/kg).

In rabbits the following was observed (KPC/19/PSB):

- Tremor and convulsions from 2500 mg/kg (LD50 was 2500 mg/kg/day).
- KPC/18/PSB (1984). Single dose (oral) limit test in the mouse: naloxone.

- KPC/17/PSB (1984). Single dose (oral) limit test in the rat: naloxone.
- KPC/19/PSB (1984). Single dose (oral) limit test in the rabbit: naloxone.

Repeated dose toxicity studies (oral)

The non-clinical studies performed following repeated oral dose administration indicate that naloxone caused disorientation, ataxia and convulsions at lethal dose in the dog (N003003D); whereas the other clinical signs of rough coat, decreased faeces and hypoactivity at doses above the NOAEL in rodents.

In mice the following was observed (N003003E):

- Rough coat from 1500 mg/kg/day.
- Decreased faeces from 500 mg/kg/day.

In rats the following was observed:

- Hypoactivity from 50 mg/kg/day (KPC/23/C).

In dogs the following was observed:

- Emesis and salivation from 100 mg/kg/day (KPC/28/C).
- Disorientation, ataxia and convulsions from 125 mg/kg/day (N003003D).
- Salivation from 25 mg/kg/day (N003003D).
- N003003E (1999). 3-month oral toxicity study of naloxone HCl in mice.
- KPC/23/C (1985). 13-week oral toxicity study in the rat: naloxone.
- KPC/28/C (1985). 13-week oral toxicity study in the dog: naloxone.
- N003003D (1999). 9-month oral toxicity study of naloxone hydrochloride in dogs.
- **Mechanisms for drug interactions**

No specific non-clinical drug interaction studies following intranasal administration have been performed by the Applicant.

However, data from the literature reports that naloxone is extensively and rapidly metabolised by conjugation with glucuronic acid and is excreted in the urine as conjugated metabolites.[1,2,3,4,5,6] There is no evidence of naloxone having metabolic interaction or being an inhibitor of cytochrome P450 (CYPs) enzymes. There is no evidence from the literature that naloxone, exhibits any significant drug/drug interaction.

Other toxicity-related information or data

None

References:

1. Weinstein SH, Pfeffer M, Schor JM, Indindoli L, Mintz M (1971). Metabolites of naloxone in human urine. J Pharm Sci 60(10): 1567-1568.

2. Weinstein SH, Pfeffer M, Schor JM (1973a). Metabolism and pharmacokinetics of naloxone. Adv Biochem Psychopharmacol 8(0): 525-535.

3. Weinstein SH, Pfeffer M, Schor JM, Franklin L, Mintz M, Tutko ER (1973b). Absorption and distribution of naloxone in rats after oral and intravenous administration. J Pharm Sci 62(9): 1416-1419.

4. IPCS (1993). IPCS/CEC evaluation of antidotes series: naloxone, flumazenil and dantrolene as antidotes. INCHEM.

5. Yamano S, Nakamoto N, Toki S (1999). Purification and characterization of rat liver naloxone reductase that is identical to 3alpha-hydroxysteroid dehydrogenase. Xenobiotica 29(9): 917-930.

6. Van Dorp E, Yassen A, Dahan A (2007). Naloxone treatment in opioid addiction: the risks and benefits. Expert Opin Drug Saf 6(2): 125-132.

SII.1 Conclusions on non-clinical data

Safety concerns
Important identified risks None identified from non-clinical data
Important potential risks (not refuted by clinical data or which are of unknown significance) None anticipated
Important missing information Pregnancy Breast feeding

Part II: Module SIII - Clinical trial exposure

SIII.1 Brief overview of development

The first patent for naloxone was filed in 1961 and in the USA naloxone was first licensed by FDA in 1971, followed by approvals in a number of European countries and the rest of the world. Naloxone is a specific opioid antagonist that acts competitively at opioid receptors. It demonstrates a very high affinity for the opioid receptor sites and therefore displaces both opioid agonists and partial antagonists. It has very low oral bioavailability.

The use of naloxone has become standard clinical practice in opioid overdose treatment since the 1970s, as a quick acting opioid antagonist for IV, IM and SC administration. Naloxone has remained the drug of choice in the treatment of opioid overdose and has not been superseded by any other short acting opioid antagonist. Whilst still used in post-operatively and in obstetrics, the use of naloxone to treat overdose in opioid abusers has become increasingly important, with the point of treatment evolving from initial emergency room care to use by paramedics administering naloxone in the pre-hospital setting, using injectable dosage forms.

A body of clinical literature spanning four decades as accumulated to support the safety and efficacy of naloxone. A number of articles have been referenced in specific sections of this risk management plan.

More recently, there have been two main trends: i) research to develop more easily administered forms of naloxone with special focus on intra nasal dosage, though they have been used in improvised forms for administration in Europe ii) development of initiatives to support the distribution of naloxone to opioid abusers in the community and those released from prison, as a life saving measure in the event of opioid overdose. This has resulted in the establishment of take home naloxone programmes in a number of European countries, often with local or regional range only, and in USA. Some of these programmes have piloted the use of intranasal naloxone whilst other have developed strategies, with appropriate medico- legal support, to make IM forms available for use by addicts and their family and friends as a significant part of harm reduction.

The use of an intranasal form removes the risk of needle stick injuries which might occur with injectable naloxone. It also opens up use of the product to ‘first responders’ at scene of a suspected

opioid overdose who may be lay persons, not trained or necessarily legally permitted to give naloxone by injection. The intranasal form of naloxone is generally well tolerated and is not known to have any specific adverse drug reactions beyond what is seen with the injectable forms. In the scientific literature, there is a lack of information regarding administration site reactions when intranasal naloxone is administered and is therefore considered as a missing information.

In view of the unmet medical need for an effective, reliable and easy to use intranasal preparation of naloxone in Europe, the applicant has developed an intranasal spray. The applicant has conducted a Phase 1 study to determine the pharmacokinetic profile of Nyxoid compared with an intramuscular dosage form. The details of the study are provided below.

SIII.2 Clinical Trial exposure

Below is the exposure data of the clinical trial (CT) MR903 1501 conducted for the development of Nyxoid. In total 38 subjects received study medication (in a cross-over design) but one subject only received IV naloxone and was therefore not exposed to Nyxoid.

Table SIII.2.3: Duration of exposure (totals)

Duration of exposure (at least)	Persons	Person time
Single application (1d)	37	103d
Total person time	37	103d

Each patient received up to 3 doses

Table SIII.2.4: By dose (totals)

Dose of exposure	Persons	Person time
1mg	33	33d
2mg	36	36d
4mg	34	34d
Total	37	103d

Table SIII.2.5: By age group and gender (totals)

	Persons		Person time	
Age group	M	F	M	F
<= 65 years	26	11	72d	31d
> 65 years	0	0	0d	0d
Total	26	11	72d	31d

Table SIII.2.6: By ethnic or racial origin (totals)

Ethnic/racial origin	Persons	Person time
Asian	2	5d
Black or African American	7	19d
Native Hawaiian or other Pacific Islander	1	2d
White	25	71d
Other	2	6d
Total	37	103d

Table SIII.2.7: Special Populations (totals)

	Persons	Person time
Pregnant women	0	0d
Lactating women	0	0d
Renal impairment (specify or categorise)	0	0d
Hepatic impairment (specify or categorise)	0	0d
Cardiac impairment (heart disease congential)	1	3d
Sub populations with genetic polymorphism (specify)	0	0d
Total	1	3d

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

SIV.1 Exclusion criteria in the pivotal clinical studies within the development programme

Exclusion criterion which will remain as contraindications	
Criteria	**Implications for target population**
Known sensitivity and/or contraindication to naloxone or related compounds or excipients	No implication to the study population as it is common practice not to expose patient to a drug, to which the patient is known to experience hypersensitivity. Though the patient with opioid overdose may be unconscious while the drug is administered, Nyxoid will be used as a life saving measure where the benefit of its use will outweigh the risk involved. In the event that such patients receive Nyxoid, they may experience an administration site reaction such as nasal irritation, swelling etc. However, there is lack of data regarding this ADR in patients who have received IN naloxone.

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	**Reason for being an exclusion criterion**	**Justification for not being a contraindication**
Any abnormal nasal anatomy, nasal symptoms (e.g. blocked and/or runny nose, nasal polyps) or using any product sprayed into the nasal cavity within 7 days or 5 times the drug half-life (whichever is longer) prior to study drug administration.	The objective of the clinical Phase I study was to assess the pharmacokinetics of intranasal (IN) naloxone compared with naloxone given as an intramuscular (IM) and intravenous (IV) dose. In order to minimize the influence of confounding factors on the PK assessment, volunteers fulfilling any of these criteria were excluded from the study.	This exclusion criterion is not related to any efficacy or safety issue. Exposing any patient with abnormal nasal anatomy or nasal symptoms to IN naloxone does not put the patient at risk and therefore adding this exclusion criterion as a contraindication is not justified.
Female subjects who are pregnant or lactating.	Ethical reason as no experience in pregnant and lactating women exists and efficacy can be established in non-pregnant women.	Pregnancy: This is considered as missing information. There are no adequate data from the use of naloxone in pregnant women. The non-clinical reproductive studies do not highlight any concerns on fertility. The potential risk for humans is unknown. Breast feeding: It is unknown whether naloxone is excreted in human breast milk and it has not been established whether infants who are breast-fed are affected by naloxone. Therefore, the SmPC mentions that caution should be exercised when naloxone is administered to a nursing mother. No specific concern has been identified in the post marketing data. Moreover, Nyxoid will be used as a life saving measure where the benefit of its use will outweigh the risk involved.
QTcF interval of > 450 msec.	General precaution to assess the complete medical history of the patient for health	The causality of cardiac related events reported in the scientific literature to use

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	**Reason for being an exclusion criterion**	**Justification for not being a contraindication**
	problems which may make them not suitable for the clinical trial.	naloxone has not been established and these events were noticed in patient with pre-existing cardiac pathology. Sinus arrhythmia, bradycardia, cardiac fibrillation and cardiac arrest are mentioned as ADRs in section 4.8. Besides Nyxoid will be used as a life saving measure where the benefit of its use will outweigh the risk involved.
Any history of conditions that might interfere with drug absorption, distribution, metabolism or excretion.	General precaution to assess the complete medical history of the patient for health problems which may make them not suitable for the clinical trial.	This exclusion criterion had the intention to exclude subjects on the basis of complete medical history and medical judgement, and is not specific enough to serve as a contraindication.
Any history of hay fever/seasonal allergy/rhinitis in the subject's recent medical history that may be symptomatic during the course of the study.	So as not to affect the absorption of naloxone from the nasal mucosa during nasal administration.	This exclusion criterion is not related to any efficacy or safety issue. Exposing any patient with history of hay fever/seasonal allergy/rhinitis to IN naloxone does not put the patient at risk and therefore adding this exclusion criterion as a contraindication is not justified.
Any history of significant cardiovascular, pulmonary, hematologic, neurological, psychiatric, endocrine, immunologic or dermatologic disease.	General precaution to assess the complete medical history of the patient for health problems which may make them not suitable for the clinical trial.	This exclusion criterion had the intention to exclude subjects on the basis of complete medical history and medical judgement, and is not specific enough to serve as a contraindication. Some of the systemic events in the literature so not assign causality to the use of naloxone. Nyxoid will be used as a life saving measure where

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	**Reason for being an exclusion criterion**	**Justification for not being a contraindication**
		the benefit of its use will outweigh the risk involved.
Any significant illness during the 4 weeks preceding entry into this study.	General precaution to assess the complete medical history of the patient for health problems which may make them not suitable for the clinical trial.	This exclusion criterion had the intention to exclude subjects on the basis of complete medical history and medical judgement, and is not specific enough to serve as a contraindication.
Current or recent (within 7 days prior to screening visit) upper respiratory tract infection.	So as not to affect the absorption of naloxone after nasal administration.	This exclusion criterion is not related to any efficacy or safety issue. Exposing any patient with upper respiratory tract infection to IN naloxone does not put the patient at risk and therefore adding this exclusion criterion as a contraindication is not justified.
Use of any medication including vitamins, herbal and/or mineral supplements during the 7 days preceding the initial dose or during the course of this study.	To minimise the potential confounding in a trial designed to assess the pharmacokinetics of nasal administration of the drug.	No interaction studies have been performed.
Refusal to abstain from food 8 hours preceding and 4 hours following study drug administration.	To minimise the potential confounding in a trial designed to assess the pharmacokinetics of nasal administration of the drug.	Food is not known to have any interaction with naloxone. There is no specific safety related issue. Therefore does not serve as a contraindication.
Refusal to abstain from caffeine or xanthine containing food or beverages and grapefruit juice within 48 hours before IMP administration and for the duration of study confinement.	To minimise the potential confounding in a trial designed to assess the pharmacokinetics of nasal administration of the drug.	There is no known interaction of caffeine, xanthine or grapefruit juice with naloxone and therefore does not serve as a contraindication.
Alcohol intake	To minimise the potential confounding in a trial designed to assess the	There is no known interaction of alcohol with naloxone and

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	**Reason for being an exclusion criterion**	**Justification for not being a contraindication**
	pharmacokinetics of nasal administration of the drug.	therefore does not serve as a contraindication.
History of smoking within 90 days.	To minimise the potential confounding in a trial designed to assess the pharmacokinetics of nasal administration of the drug.	Smoking is not known to have any effect on mechanism of action of naloxone and therefore does not serve as a contraindication.
Blood or blood products donated.	To minimise the potential confounding in a trial designed to assess the pharmacokinetics of nasal administration of the drug.	IN naloxone has a short half-life and will be used in clinical practice as an antidote to opioid overdose. Consequently, it is extremely unlikely that traces or metabolites of naloxone are found in the blood of subjects who have used it, after they have fully recovered and they decide to donate blood and blood products.

SIV.2 Limitations of ADR detection common to clinical trial development programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare	In the phase I CT (MR903 1501) conducted by the marketing authorisation holder (MAH) a total of 38 subjects were exposed for 103 person days during the Nyxoid development program	Such exposure in clinical trial program only allows for detection of ADRs with a frequency of at least 1 in 38/3 = 1 in 12, based on the 'rule of threes'. However, based on the extensive post marketing exposure of this established product rare ADRs are being detected and seen in various MAH product labels
Due to prolonged exposure	In the phase I CT (MR903 1501) conducted by the MAH a total of 38 subjects were exposed for 103 person days during the Nyxoid development program	According to the proposed indication Nyxoid is intended for short-term use in the setting of acute opioid overdose. Therefore, prolonged exposure is not anticipated in clinical practice.
Due to cumulative effects	In the phase I CT (MR903 1501) conducted by the MAH a total of 38 subjects were exposed for 103 person days during the Nyxoid development program	According to the proposed indication Nyxoid is intended for short-term use in the setting of acute opioid overdose. Therefore, prolonged exposure leading to accumulation is not anticipated in clinical practice. Since naloxone is used in case of acute care settings of opioid overdose only, and it has no pharmacological action of its own, long term use of this drug is not expected.
Which have a long latency	In the phase I CT (MR903 1501) conducted by the MAH each patient was followed up for four days after the Nyxoid administration. No formal clinical studies to	Based on the extensive post marketing experience of this established product including the off-label intranasal administration is some studies,

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
	identify the effects of long latency are conducted	the implication should be minimal, if at all.
Recurrence of respiratory depression due to wearing off of naloxone effect when administered to opioid overdosed patients	This was a phase I CT (MR903 1501) conducted by the MAH on healthy volunteers. Therefore, the event of 'recurrence of respiratory depression' observed in opioid overdose patients, could not be identified in this CT population.	According to published literature the occurrence of the ADR 'recurrence of opioid toxicity' and consequently 'recurrence respiratory depression' could be approximately 16 to 26%. The risk of 'recurrence of respiratory depression' has been identified as an important identified risk. Refer to Part II, SVII.3 for details.
Precipitation of opioid withdrawal effects	This was a phase I CT (MR903 1501) conducted by the MAH on healthy volunteers. Therefore the event of 'precipitation of opioid withdrawal effects' observed in opioid overdose patients, could not be identified in this CT population	According to published literature the occurrence of the 'precipitation of opioid withdrawal effects' could be <20%. The risk of ''precipitation of opioid withdrawal effects' has been identified as an important identified risk. Refer to Part II, SVII.3 for details.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table Part II: Module SIV - 1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Children	There is very limited experience on the use of naloxone administered IN in paediatric patients. However, the use of naloxone in paediatric patients is supported by evidence from adequate and well-controlled studies of naloxone in adults with additional data from a number clinical studies (controlled and uncontrolled) in which neonates and paediatric patients received parenteral naloxone

Type of special population	Exposure
	hydrochloride in doses ranging from 0.005 mg/kg to 0.01 mg/kg. Safety and effectiveness are also supported by use of other naloxone products (IV, IM or SC) in the post-marketing setting, as well as data available in the medical literature and clinical practice guidelines.[1,2,3] Moreover, The MR903 1501 study conducted by the MAH has demonstrated that IN formulation of Nyxoid is anticipated to deliver therapeutic concentrations comparable with the IM standard of care in the event of opioid overdose.
Elderly	There have been no specific studies for use in the elderly. Extensive clinical experience with naloxone is considered to have demonstrated the therapeutic value of naloxone. The efficacy and safety of this product is not expected to be any different from those in other adult populations and the benefit of its use on single occasion far outweighs the risk. However, considering the fact that there is lack of clinical trial data and limited information on the use of IN naloxone in elderly subjects, use in elderly is considered as missing information.
Pregnant or breast feeding women	Pregnancy For naloxone no sufficient clinical data on exposed pregnancies are available. The potential risk for humans is unknown. 'Studies in animals do not show any concerns on reproductive toxicity'. (Refer Part II, SII). Naloxone crosses the placenta, and may precipitate withdrawal in the fetus as well as in the opioid-dependent mother. However, the limited available data on naloxone use in pregnant women are not sufficient to inform a drug-associated risk. Naloxone is intended to act as an antidote in a life-threatening opioid overdose. The benefit-risk of the use of naloxone must be considered before use. In light of the lack of clinical trial data and limited post-marketing experience, use of naloxone in pregnant women is considered missing information. Naloxone is intended to act as an antidote in a life-threatening opioid overdose

Type of special population	Exposure
	and therefore the benefit of administering the drug outweighs any risk to the patient. Lactation There is no information regarding the presence of naloxone in human milk, or the effects of naloxone on the breastfed infant or on milk production. Studies in nursing mothers have shown that naloxone does not affect prolactin or oxytocin hormone levels. Naloxone is intended to act as an antidote in a life-threatening opioid overdose. Caution should be exercised when naloxone is administered to a nursing mother. In light of the lack of clinical trial data and limited post-marketing experience, use of naloxone in breastfeeding (lactating) women is considered missing information.
Patients with other relevant co-morbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with a disease severity different from the inclusion criteria in the clinical trial population	Not included into clinical development programme.
Patients of different racial and/or ethnic origin	There have been no specific studies conducted to determine the relevance of polymorphisms. Naloxone is a well-established drug and no particular efficacy issue has emerged from its post marketing experience in various ethnic groups. The benefit of administering naloxone in opioid overdose patient outweighs any risk involved.
Sub-populations carrying known and relevant polymorphisms	There have been no specific studies conducted to determine the relevance of polymorphisms. Naloxone is a well-established drug and no particular efficacy issue has emerged from its post marketing experience due to polymorphism. The benefit of administering naloxone in opioid an overdose patient outweighs any risk involved.
Patients with other relevant co-morbidity	There are no adequate data to support a drug-associated risk in patients with other relevant co-morbidity and who are in receipt of other

Type of special population	Exposure
	pharmacological agents. Naloxone is intended to act as an antidote in a life-threatening opioid overdose and therefore the benefit of administering the drug outweighs any risk to the patient. Certain patients may have damaged nasal mucosa as a result of snorting of illicit drugs over prolonged period. If intranasal naloxone was to be administered to such patients, there may be a risk of lack of effect of naloxone due to inadequate absorption through the damaged nasal mucosa. Information is currently lacking in the scientific literature.

References:

1. Boyer, E. W., Mccance-katz, E. F. & Marcus, S. Methadone and Buprenorphine Toxicity in Children. Am. J. Addict. 19, 89–95 (2009).

2. Maxwell, L. G. et al. The Effects of a Small-Dose Naloxone Infusion on Opioid- Induced Side Effects and Analgesia in Children and Adolescents Treated with Intravenous Patient-Controlled Analgesia: A Double-Blind, Prospective, Randomized, Controlled Study. Anesth Analg 100, 953–8 (2005).

3. McGuire, W. & Fowlie, P. W. Naloxone for narcotic exposed newborn infants: systematic review.McGuire W, Fowlie PW. Arch Dis Child Fetal Neonatal Ed. 2003 Jul;88(4): F308-11.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Estimates of patient exposure are usually calculated according to a standard approach from sales data obtained from all countries in which IN naloxone is sold.

The cumulative patient exposure figure was estimated based on the total quantity of sold packs. Each pack contains 2 nasal sprays and each nasal spray contains one single dose of naloxone.

SV.1.2 Exposure

Worldwide cumulative distribution is estimated at 567,649 packs (each containing 2 units), equivalent to the same number of potential single patient uses. However, the quantity of packs that have been made available to individuals but remain unused is unknown as the product is only used when needed. Considering that a single unit may also be sufficient for treatment, the upper limit of exposure is the total number of units which would be 567,649 packs multiplied by 2.

A more detailed cumulative distribution of Nyxoid by region up to the DLP of 31 Dec 2023 is provided in the table below:

Table Part II: Module SV - 1: Cumulative worldwide post-authorisation patient exposure by region till 31 Dec 2023

Nyxoid (Naloxone hydrochloride dihydrate) 1.8 mg nasal spray, solution in a single-dose container			
Region		Countries	Total Packs
	Europe	[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		All European countries	304,437
	Asia Pacific (APAC)		262,573
	Middle East and North Africa (MENA)		375
	[redacted]		[redacted]
	[redacted]		[redacted]
	Latin America (LATAM)		-
	Unspecified		264
	Total		567,649

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

Potential for misuse for illegal purposes

As naloxone is an opioid antagonist intended for the treatment of opioid overdose, and naloxone is almost inert in the absence of an agonist drug (such as an opioid), naloxone has no obvious abuse potential. While diversion of naloxone could occur if opioid abusers/misusers wanted to protect themselves from overdose, in such a cases the drug would be used for its intended purpose, and therefore the diversion of the naloxone would simply help circumvent any inequalities in access to it.[1]

References:

1. Strang et al: BMJ. Heroin overdose: the case for take-home naloxone. 1996 Jun 8; 312(7044):1435-6.

Part II: Module SVII - Identified and potential risks

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

The safety concerns as stated in RMP version 1.1, dated 13-Oct-2016 are included in Table Part II: Module SVII - 1.

Table Part II: Module SVII - 1: Safety concerns in RMP version 1.1

Category	Safety Concern
Important identified risks	Reoccurrence of respiratory depression Precipitation of acute opioid withdrawal effects
Important potential risks	Lack of efficacy due to medication error
Missing information	Use in pregnancy and breast feeding Use in elderly Use in patients with hepatic impairment Use in patients with renal impairment

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

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Potential for harm from overdose

If naloxone is administered in the absence of opioids, as in case of non-opioid users, it is unlikely to produce any pharmacological activity. Studies of subcutaneous naloxone administration have not found any subjective effects, and even extremely high-dose of intravenous naloxone (up to 5.4-mg/kg boluses and 4 mg/kg/h) has been administered without adverse effects[1,2], although mild elevations in blood pressure and decreased performance in memory tests were seen with doses exceeding 20 mg[3]. Therefore, intentional overdose of Nyxoid by the non-opioid users is not expected. When administered to patients with opioid overdose, high doses of naloxone can cause precipitation of opioid withdrawal effects. This is an important identified risk for this product. Refer to Part II, SVII for details on this risk.

References:

1. Michael B. Bracken, et al A Randomized, Controlled Trial of Methylprednisolone or Naloxone in the Treatment of Acute Spinal-Cord Injury — Results of the Second National Acute Spinal Cord Injury StudyN Engl J Med 1990; 322:1405-1411

2. Groeger JS, Inturrisi CE. High-dose naloxone: pharmacokinetics in patients in septic shock. Crit CareMed. 1987 Aug;15 (8):751-6.

3. EMCDDA. Preventing opioid overdose deaths with take-home naloxone (available:http://www.emcdda.europa.eu/system/files/publications/2089/TDXD15020E NN.pdf). ISSN 2314-9264. 2016.

Effect of device failure

The product is supplied in a carton with two blister packs with peelable blister labels. This blister pack comprises a rigid plastic tray with a foil back. The plastic tray is designed to prevent any damage to the devices due to rough handling. As each carton of Nyxoid is proposed to hold two devices (within separate blister packs), this gives the opportunity to administer the second dose in case the user has difficulty in operating the first device.

Potential for paediatric off-label use

The key value for IV /IM administration of naloxone in children is - that the dose can be easily titrated according to weight, thus reducing risk of adverse effects of the drug. This approach also requires close monitoring of children in health care settings. As Nyxoid is a fixed dose nasal spray, its dose cannot be titrated to suit the specific requirements of children. It is not anticipated that Nyxoid would displace the use of IV/IM forms in paediatric population and occurrence of off-label use of Nyxoid in paediatric population would be minimal.

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

The list of safety concerns has not been changed since previously submitted RMP update.

Important identified risks:

- Reoccurrence of respiratory depression
- Precipitation of acute opioid withdrawal effects

Risk-benefit impact:

All identified risks for naloxone represent safety concerns with acceptable impact on the benefit-risk profile of Nyxoid. These risks may have serious or even fatal outcomes, if not appropriately and timely managed. Some of them may even significantly impact patients' quality of life. Vast majority of all identified risks requires a specific, but still a routine monitoring for timely detection.

Important Potential Risk:

- Lack of efficacy due to medication error

Risk-benefit impact:

The potential risk associated with naloxone use represent safety concern with acceptable impact on the benefit-risk profile of Nyxoid. However, if confirmed, they may be re-classified as important identified risks, potentially resulting in re-evaluation of the benefit-risk profile (at least for certain subpopulations of full target population, depending on their further characterisation).

Missing information:

- Use in pregnancy and breastfeeding
- Use in elderly
- Use in patients with hepatic impairment
- Use in patients with renal impairment
- Administration site reaction
- Decreased response due to impaired nasal mucosa

Risk-benefit impact:

All missing information associated with naloxone use safety concern with acceptable impact on the benefit-risk profile of Nyxoid. However, as product matures, the gaps in knowledge about the safety of a medicinal product for Nyxoid use in particular patient subpopulations within approved indication, the classification as missing information might not be appropriate anymore once new data become available, or when there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to the areas of missing information.

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

While lack of efficacy due to medication error remains as an important potential risk, the results of the PAES to date and large scale THN programs conducted in Sweden and Australia indicate Nyxoid use by consumer to be effective and without significant issue.

No new safety concerns have been included or reclassified in the list of safety concerns with this update.

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 - Recurrence of respiratory depression: MedDRA 26.1 Acute Central Respiratory Depression SMQ (Narrow terms only).

Potential mechanisms:

Naloxone is a competitive μ-opioid receptor antagonist which competes with opioids thereby reversing the respiratory depression caused by them by preventing their metabolites from exercising

influence on the receptor's normal functioning. However, since naloxone has a shorter half-life than some opioids, the naloxone-induced blockade of opioid receptors can wear off and respiratory depression can return.

Evidence source(s) and strength of evidence:

Kerr D, Kelly AM, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction (Abingdon, England). 2009; 104(12):2067-74.

Kelly AM, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. The Medical journal of Australia. 2005; 182(1):24-7.

Barton ED, Colwell CB, Wolfe T, Fosnocht D, Gravitz C, Bryan T, et al. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. The Journal of emergency medicine. 2005; 29(3):265-71.

EMCDDA. Preventing opioid overdose deaths with take-home naloxone (available:http://www.emcdda.europa.eu/system/files/publications/208 9/TDXD15020ENN.pdf). ISSN 2314-9264. 2016.

Warner-Smith M, Darke S, Day C. Morbidity associated with non-fatal heroin overdose. Addiction (Abingdon, England). 2002; 97(8):963-7.

Strang J. Looking beyond death: paying attention to other important consequences of heroin overdose. Addiction (Abingdon, England). 2002; 97(8):927-8.

Dahan A, Aarts L, Smith TW. Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression. Anesthesiology. 2010; 112(1):226-38.

Characterisation of the risk:

Frequency: Randomised trials show the frequency of recurrence of respiratory depression (defined as a spontaneous respiration rate of <10 breaths per minute), subsequent to administration of IN naloxone, to range from 18.1% to 26%.[1,2] 16% of the IN naloxone response group required additional doses of IV naloxone after initial response due to "recurrent somnolence" or "slow response'.[3] In a Finnish study, of the 47 presumed heroin –overdose patients taken to the emergency department for further monitoring who had been given naloxone and respond to it, 25% (12 people) needed further naloxone to be administered in the emergency department because of signs of recurrent opioid toxicity.[4]

Severity and nature of risk: Respiratory depression, and its recurrence, is potentially life threatening. If death does not occur, respiratory depression may lead to peripheral neuropathy, paralysis, pneumonia and nerve palsy[5] which can reduce an individual's quality of life and wellbeing, the consequences of which can be a requirement for life-long, regular health-care attention and support accompanied by significant loss of independence.[6]

Post-marketing data: Up to the DLP of 31 Dec 2023, 3 worldwide cases were reported with a total of 3 events included in the search strategy for respiratory depression.The reported MedDRA PTs include: Bradypnoea (n=2) and Respiratory failure (n=1). All three cases were reported from post-marketing sources (2 cases from literature and 1 case from spontaneous), originating within Europe.

Due to Nyxoid being used only when needed, the incidence of respiratory depression could not be accurately estimated based on cumulative distribution, other than that the absolute number of reports were very infrequent relative to the distribution.

Risk factors and risk groups:

Risk factors include the specific opioid used, opioid dose, administration mode, concurrent medication, underlying disease, state of arousal and exogenous stimulatory factors.[7]

Preventability:

To prevent this event, Nyxoid doses may need to be repeated. After administration of Nyxoid further monitoring of the patient is required depending on the type of opioid which was overdosed.

Impact on the risk-benefit balance of the product:

The impact of this risk on benefit-risk balance of naloxone is acceptable in the light of anticipated benefits of the therapy.

Public health impact:

The patient already has had life-threatening / potentially disabling respiratory Depression. Administration of Nyxoid will not lead to any further increased risk.

Important Identified Risk - Precipitation of acute opioid withdrawal effects: MedDRA 26.1 Drug withdrawal SMQ (Broad)

Potential mechanisms:

Naloxone is a pure opioid receptor antagonist. It works by reversing the depression of central nervous system and respiratory system caused by opioids. In patients who are dependent on opioids, administration of naloxone can precipitate opioid withdrawal symptoms, which may appear within minutes of naloxone administration. The severity of the withdrawal symptoms is related to the dose of naloxone and the degree and type of opioid dependence.

Evidence source(s) and strength of evidence:

Kerr D, Kelly AM, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction (Abingdon, England). 2009; 104(12):2067-74.

Kelly AM, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. The Medical journal of Australia. 2005; 182(1):24-7.

Barton ED, Colwell CB, Wolfe T, Fosnocht D, Gravitz C, Bryan T, et al. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. The Journal of emergency medicine. 2005; 29(3):265-71.

Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, Zandifar S. Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomized clinical trial. Archives of medical science: AMS. 2014;10(2):309-14.

EMCDDA. Preventing opioid overdose deaths with take-home naloxone (available:http://www.emcdda.europa.eu/system/files/publications/208 9/TDXD15020ENN.pdf). ISSN 2314-9264. 2016.

Wermeling, D. P. (2015). "Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access." Ther Adv Drug Saf 6(1): 20-31).

Characterisation of the risk:

Frequency: Randomised trials show the frequency of precipitation of opioid withdrawal effects, subsequent to administration of IN naloxone, to be <20%.[1,2] None of the naloxone responders was reported to have severe withdrawal reactions from either IV or IN naloxone.[3] In another study, there was a difference in the rates of agitation after naloxone treatment between the two study groups, with patients who received IV treatment showing higher rates (n = 12) than those who received IN treatment (n = 0).[4]

Severity and nature of risk: In persons with physical dependence on opioids, naloxone can produce moderate to severe withdrawal symptoms which appear within minutes of administration and subside after approximately two hours.5 Despite the fact that opioid withdrawal is not life-threatening, withdrawal reactions can be very distressing to the patient and can complicate the medical care of patients with comorbid medical conditions.

Post-marketing data: Up to the DLP of 31 Dec 2023, 5 worldwide cases were reported with a total of 5 events included in the search strategy for precipitation of acute opioid withdrawal.The reported MedDRA PTs include: Withdrawal syndrome (n=3), Drug withdrawal syndrome (n=1) and Rebound effect (n=1). All five cases were reported from post-marketing sources (4 cases from spontaneous and 1 case from literature) with 3 cases originating within Europe and 2 cases from outside Europe.

Due to Nyxoid being used only when needed, the incidence for precipitation of acute opioid withdrawal effects could not be accurately estimated based on cumulative distribution, other than that the absolute number of reports were very infrequent relative to the distribution.

Risk factors and risk groups:

The risk factors include the dose of naloxone administered, the dose of opioids taken and their relative affinities for the opioid receptor.

Preventability:

Nyxoid must be given with caution to patients who have received high doses of opioids or are physically dependent on opioids; since, too rapid reversal of the opioid effect can cause an acute withdrawal syndrome in such patients.

Impact on the risk-benefit balance of the product:

The impact of this risk on benefit-risk balance of naloxone is acceptable in the light of anticipated benefits of the therapy.

Public health impact:

Public health impact is probably very low as the event of withdrawal is not per se life-threatening or potentially permanently disabling.

Important Potential Risk - Lack of efficacy due to medication error: MedDRA 26.1 – At least one PT term indicating a lack of effect (Drug ineffective, Drug ineffective for unapproved indication, Therapeutic response decreased, Therapeutic response shortened, Therapy non-responder, Treatment failure) in addition to at least one PT term indicating a medication error (Dose calculation error, Medication error, Wrong technique in device usage process, Accidental underdose, Drug administration error, Inappropriate schedule of drug administration, Incorrect dosage administered, Incorrect dose administered, Incorrect drug administration rate, Poor quality drug administered).

Potential mechanisms:

Not applicable.

Evidence source(s) and strength of evidence:

Not applicable.

Characterisation of the risk:

Frequency: GVP Module VI refers to medication error as "any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient or consumer". The real rate is estimated to be between 2 and 14% of patients admitted to hospital, with estimations of around 1–2% of patients being harmed as a result. However, the data on frequency regarding ‘lack of efficacy due to medication error’ is lacking.

Severity and nature of risk: Lack of efficacy due to medication error is a potentially life-threatening situation. If the carer makes an error in administering the product to the patient, the drug will not reach its target receptors thus leading to death of the patient, unless the emergency assistance arrives on time to rescue the patient. In absence of appropriate risk minimization measures, the risk could be severe in nature. While managing an opioid overdose patient, the HCPs are expected to follow the local protocol. Despite this, there is a small chance of medication error by HCPs who may use IN naloxone (Nyxoid) instead of IV naloxone in some cases. However, the nature of risk here is low, as IN naloxone may still be effective in such patients depending upon the nature of overdose. If not, the HCP would likely have access to IV naloxone to manage the patient.

Post-marketing data: Up to the DLP of 31 Dec 2023, no cases were reported with events in the search strategy.

Risk factors and risk groups:

Risk factors include user having inadequate or insufficient information regarding Nyxoid administration to the patient in the emergency situation of opioid overdose.

Preventability:

To prevent this event, the HCPs, patients and carers must be trained on how to correctly administer the product and steps to be followed while managing the patient. Clear instructions on when to use Nyxoid as a part of patient management should be made available to the users in the Product Information and educational material.

Impact on the risk-benefit balance of the product:

The impact of this risk on benefit-risk balance of naloxone is acceptable in the light of anticipated benefits of the therapy.

Public health impact:

The patient already has had life-threatening / potentially disabling respiratory depression. Incorrect administration of Nyxoid will not lead to any further risk.

SVII.3.2. Presentation of the missing information

Use in pregnancy and breastfeeding

Evidence source:

No reproductive studies were conducted following intranasal administration of naloxone hydrochloride.

Studies with orally administered naloxone hydrochloride revealed no effect on fertility and reproductive performance in the rat at the highest dose tested (800 mg/kg/day) (KPC/32/86).

The non-clinical reproductive studies do not highlight any concerns on fertility and reproductive performance following oral administration in the rat at 800 mg/kg/day, the highest dose tested.

No developmental toxicity studies were conducted following intranasal administration of naloxone hydrochloride.

Orally administered naloxone hydrochloride was not teratogenic in the rat (KPC/33/85) or rabbit (KPC/35/85) at the maximum doses tested (800 mg/kg/day and 400 mg/kg/day, respectively).

In a pre-natal and post-natal development study in rats, naloxone hydrochloride at a highest dose of 800 mg/kg/day produced mortality and significant maternal toxicity in rats and resulted in increased pup deaths in the immediate postpartum period. However, in surviving pups, no effects on development or behaviour were observed. Mild maternal toxicity was also observed in rats that received 200 mg/kg/day; however, there were no adverse effects on F1 pups (KPC/34/85).

The non-clinical developmental toxicity studies do not highlight any teratogenic potential following oral administration in the rat (800 mg/kg/day) and the rabbit (400 mg/kg/day), at the highest doses tested.

Population in need of further characterisation:

There are no adequate data from the use of naloxone in pregnant women. The potential risk for humans is unknown. The risk benefit of the medicinal product must be considered before use. In pregnant women who are opioid dependent, naloxone administration can cause withdrawal symptoms in new-born infants.

It is unknown whether naloxone is excreted in human breast milk and it has not been established whether infants who are breast-fed are affected by naloxone. Therefore, caution should be exercised when naloxone is administered to a nursing mother but there is no need to discontinue breast-feeding.

Use in elderly

Evidence source:

There have been no specific studies for use in the elderly. Extensive clinical experience with naloxone is considered to have demonstrated the therapeutic value of naloxone. The efficacy and safety of this product is not expected to be any different from those in other adult populations and the benefit of its use on single occasion far outweighs the risk. However, considering the fact that

there is lack of clinical trial data and limited information on the use of IN naloxone in elderly subjects, use in elderly is considered as missing information.

Population in need of further characterisation:

There are no adequate data from the use of intranasal naloxone in elderly. The potential risks for the elderly are unknown. The benefit of using Nyxoid in elderly patients with opioid overdose is considered to outweigh the risk.

Use in patients with hepatic impairment

Evidence source:

Hepatotoxicity studies were not conducted following intranasal administration of naloxone hydrochloride by the Applicant.

In the oral, single (KPC/18/PSB and KPC/17/PSB) and repeated dose toxicity studies in rodents (KPC/21/C, N003003E, KPC/22/C, KPC/23/C and KPC/24/87) and dogs (KPC/28/C and N003003D) and in the intravenous repeated dose toxicity study in dogs (NDSE-706), no changes were observed in liver function and no microscopic findings were observed.Population in need of further characterisation:

There are no adequate data from the use of intranasal naloxone in patients with hepatic impairment. Whilst the potential risk of use of Nyxoid in these patients is unknown, benefit of using Nyxoid on a single occasion in a critical patient of opioid overdose is considered to outweigh the risk.

Use in patients with renal impairment

Evidence source:

Nephrotoxicity studies were not conducted following intranasal administration of naloxone hydrochloride by the Applicant.

The non-clinical repeat dose toxicity studies, following oral administration, do not indicate any concerns related to nephrotoxicity.

Population in need of further characterisation:

There are no adequate data from the use of intranasal naloxone in patients with renal impairment. Whilst the potential risk of use of Nyxoid in these patients is unknown, benefit of using Nyxoid on a single occasion in a critical patient of opioid overdose is considered to outweigh the risk.

Administration site reaction

Evidence source:

No implication to the study population as it is common practice not to expose patient to a drug, to which the patient is known to experience hypersensitivity. Though the patient with opioid overdose may be unconscious while the drug is administered, Nyxoid will be used as a life saving measure where the benefit of its use will outweigh the risk involved. In the event that such patients receive Nyxoid, they may experience an administration site reaction such as nasal irritation, swelling etc. However, there is lack of data regarding this ADR in patients who have received IN naloxone.

Population in need of further characterisation:

There are no adequate data from the use of intranasal naloxone in patients with administration site reaction. Whilst the potential risk of use of Nyxoid in these patients is unknown, benefit of using Nyxoid on a single occasion in a critical patient of opioid overdose is considered to outweigh the risk.

Decreased response due to impaired nasal mucosa

Evidence source:

There are no adequate data about decreased response due to use of IN naloxone in patients with impaired nasal mucosa. The potential risk for humans is unknown and the use of IN naloxone in this patient population is considered missing information.

Population in need of further characterisation:

There are no adequate data from the use of intranasal naloxone in patients with damage to their inner nasal membrane. Whilst the potential risk of use of Nyxoid in these patients is unknown, benefit of using Nyxoid on a single occasion in a critical patient of opioid overdose is considered to outweigh the risk.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns.

Summary of safety concerns	
Important identified risks	Reoccurrence of respiratory depression Precipitation of acute opioid withdrawal effects
Important potential risks	Lack of efficacy due to medication error
Missing information	Use in pregnancy and breastfeeding Use in elderly Use in patients with hepatic impairment Use in patients with renal impairment Administration site reaction Decreased response due to impaired nasal mucosa

Part III: Pharmacovigilance Plan

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities are considered sufficient for Nyxoid.

III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

No additional pharmacovigilance activities for Nyxoid are proposed.

III.3 Summary Table of additional Pharmacovigilance activities

There are no on-going and planned categories 1-3 safety studies included in the Pharmacovigilance Plan.

Part IV: Plans for post-authorisation efficacy studies

On the basis of the totality of the evidence collected and presented by the MAH as summarized in the Addendum to Clinical Overview (ACO), the MAH is of the opinion that current scientific evidence from the PAES and from published studies from THN programmes in different EU countries and Australia meets the intended requirements of the PAES and hence the MA Post-Approval Commitment has been fulfilled. No additional post-authorisation efficacy data are deemed necessary to address the proper utilisation of intranasal naloxone in the real world situation.

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

V.1 Routine risk minimisation measures

Table V.1.1: Recurrence of respiratory depression

Safety concern:	**Recurrence of respiratory depression**
Objective(s) of the risk minimisation measures	To raise awareness about the possibility of the event thereby reducing the risk of the event occurring
Routine risk minimisation measures	SmPC sections 4.4 and 4.7 PL section 2 and 3 Other routine risk minimisation measures: A second device will be provided within the pack for administration to the patient in case needed. Back of the blister will consist of quick start guide for the use of lay persons to manage the patient. Nyxoid will be available as Prescription only medication.

Table V.1.2: Precipitation of acute opioid withdrawal effects

Safety concern:	**Precipitation of acute opioid withdrawal effects**
Objective(s) of the risk minimisation measures	To raise awareness about the possibility of the event and thereby reducing the risk of the event occurring.
Routine risk minimisation measures	SmPC sections 4.4, 4.6 and 4.8 PL sections 2 and 4 Other routine risk minimisation measures: Pack size, posology limits the dose, dose frequency to minimise the risk of precipitation of acute opioid withdrawal effects. Back of the blister will consist of quick start guide for the use of lay persons to manage the patient. Nyxoid will be available as Prescription only medication.

Table V.1.3: Lack of efficacy due to medication error

Safety concern:	**Lack of efficacy due to medication error**
Objective(s) of the risk minimisation measures	To raise awareness about the possibility of the event thereby reducing the risk of the event occurring.
Routine risk minimisation measures	SmPC section 4.2 PL section 3 Other routine risk minimisation measures The Quick start guide on the blister will detail the method of administration of Nyxoid. Nyxoid will be available as Prescription only medication.

Table V.1.4: Use in pregnancy and breastfeeding

Safety concern:	**Use in pregnancy and breastfeeding**
Objective(s) of the risk minimisation measures	To communicate what is known and that there are knowledge gaps in regard to the safety of naloxone administration during pregnancy and breastfeeding.
Routine risk minimisation measures	SmPC section 4.6 PL Section 2 Other routine risk minimisation measures Nyxoid will be available as Prescription only medication.

Table V.1.5: Use in elderly

Safety concern:	**Use in elderly**
Objective(s) of the risk minimisation measures	So that the drug gets prescribed through informed HCP who will have knowledge on the use of drug and can therefore inform the patient/carer
Routine risk minimisation measures	Other routine risk minimisation measures Nyxoid will be available as Prescription only medication.

Table V.1.6: Use in hepatic impairment

Safety concern:	**Use in hepatic impairment**
Objective(s) of the risk minimisation measures	So that the drug gets prescribed through informed HCP who will have knowledge on the use of drug and can therefore inform the patient/carer

Routine risk minimisation measures	Other routine risk minimisation measures Nyxoid will be available as Prescription only medication.

Table V.1.7: Use in renal impairment

Safety concern:	**Use in renal impairment**
Objective(s) of the risk minimisation measures	So that the drug gets prescribed through informed HCP who will have knowledge on the use of drug and can therefore inform the patient/carer
Routine risk minimisation measures	Other routine risk minimisation measures Nyxoid will be available as Prescription only medication

Table V.1.8: Administration site reaction

Safety concern:	**Administration site reaction**
Objective(s) of the risk minimisation measures	To raise awareness about the possibility of the event thereby reducing the risk of the event occurring.
Routine risk minimisation measures	Other routine risk minimisation measures Nyxoid will be available as Prescription only medication.

Table V.1.9: Decreased response due to impaired nasal mucosa

Safety concern:	**Decreased response due to impaired nasal mucosa**
Objective(s) of the risk minimisation measures	To raise awareness about the possibility of the event thereby reducing the risk of the event occurring.
Routine risk minimisation measures	SmPC section 4.4 PL section 2 Other routine risk minimisation measures Nyxoid will be available as Prescription only medication.

V.2 Additional Risk Minimisation Measures

Educational and Training Measures

The elements of the educational materials are reflected in the PIL and a Quick Start Guide (GQC) on the inner packaging blister (identification of overdose, instructions for Nyxoid use and additional actions to take). The following educational materials are also provided,

- HCP Guidance Documents (HGD) designed to provide guidance to the HCPs to make them aware that they must communicate the aforementioned important risks to the patient and/or carer which are related to the use of Nyxoid, to minimise their occurrence and severity. The HGD also guides HCPs on how Nyxoid is used so the administration technique can be shared and passed onto the patient/carer; as well as information on what to do if a patient is potentially experiencing an overdose

- Patient Information Card (PIC) to instruct the patient and/or carer and inform them about how to manage a patient with a suspected overdose using Nyxoid to further minimise the occurrence and severity of the aforementioned important risks

- Video demonstrating how to use Nyxoid in patients with suspected opioid overdose to further illustrate the steps to be carried out.

Following are the important risks for which additional risk minimisation measures are existing:

- Reappearance of slow or weak breathing

- Abrupt onset drug withdrawal symptoms

- Drug not achieving its intended results in patient due to error in administering medication

Objective:

The educational materials are aimed at persons at risk of opioid overdose (i.e., patients), and/or their family or friends (carers) willing to offer future assistance to such persons. The objective of the key elements of the training material are to:

- Provide guidance to the HCPs to make them aware that they must communicate the aforementioned important risks to the patient and/or carer which are related to the use of Nyxoid, to minimise their occurrence and severity.

- Instruct the patient and/or carer on the symptoms of overdose and inform them about how to manage a patient with a suspected overdose using Nyxoid to further minimise the occurrence and severity of the aforementioned important risks.

Rationale for the additional risk minimisation activity:

The aim of the materials is to increase the likelihood of correct identification of overdose by carriers of Nyxoid, correct administration of Nyxoid to patients with suspected overdose, and correct

management of overdose patients to reduce the risks of recurrence of respiratory depression and manage possible withdrawal if it occurs.

- Target audience and planned distribution path:

The above materials will be submitted for approval to the national authorities of countries where Nyxoid is marketed, and will be posted on the non-promotional website nyxoid.com once approved. The files can be freely downloaded and printed as needed from this website.

A QR code on the package and in the PIL provides a link to nyxoid.com so that all carers (HCPs, carriers of Nyxoid, patients) can quickly reach the materials.

Nyxoid.com does not use extensive tracking cookies for legal reasons. It does use functional cookies so that a previous country choice is followed on a next visit from the same source ensuring the minimum delay in reaching the materials.

Where national authorities require paper-based distribution, the company will either inform HCPs of the availability of the materials on nyxoid.com through a paper-based distribution of that information, or continue to supply paper copies, as agreed with the national authority.•

Plans to evaluate the effectiveness of the interventions and criteria for success:

The non-promotional website nyxoid.com does not use extensive tracking cookies for legal reasons but does use functional cookies. This, together with the information in server logs, is expected to allow analysis of numbers of visits to different pages and of number of downloads of files. This should allow monitoring for changes in pattern of visits / downloads at the country level before and after roll-out of the QR code and shifting to (mostly) electronic distribution. Such information will be presented in the PBRERs.

V.3 Summary of risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Recurrence of respiratory depression	Routine risk minimisation measures: SmPC sections 4.4 and 4.7: PL section 2 and 3 Other routine risk minimisation measures: A second device will be provided within the pack for administration to the patient in case needed. Back of the blister pack will consist of quick start guide for immediate identification of the use of the product. Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: HCP Guidance Document, Patient information card and Video demonstrating how to use Nyxoid will be provided as part of training/ educational material	Routine pharmacovigilance activities are sufficient for Nyxoid
Precipitation of acute opioid withdrawal effects	Routine risk minimisation measures: SmPC section 4.4, 4.6 and 4.8 PL Sections 2 and 4 Other routine risk minimisation measures. Pack size, posology mentions the dose, dose frequency to minimise the risk of precipitation of acute opioid withdrawal effects. Back of the blister pack will consist of quick start guide for immediate identification of the use of the product. Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: HCP Guidance Document, Patient information card and Video demonstrating how to use Nyxoid will be provided as part of training/ educational material	Routine pharmacovigilance activities are sufficient for Nyxoid
Lack of efficacy due to medication error	Routine risk minimisation measures: SmPC section 4.2	Routine pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL Section 3 Other routine risk minimisation measures The Quick start guide on the blister will detail the method of administration of Nyxoid. Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: HCP Guidance Document, Patient information card and Video demonstrating how to use Nyxoid will be provided as part of training/ educational material	activities are sufficient for Nyxoid
Pregnancy and breast feeding	Routine risk minimisation measures: SmPC section 4.6 PL Section 2 Other routine risk minimisation measures: Package leaflet will contain the relevant sections from the SmPC. Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: Not proposed	Routine pharmacovigilance activities are sufficient for Nyxoid
Use in elderly	Other routine risk minimisation measures Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: Not proposed	Routine pharmacovigilance activities are sufficient for Nyxoid
Use in hepatic impairment	Other routine risk minimisation measures Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: Not proposed	Routine pharmacovigilance activities are sufficient for Nyxoid
Use in renal impairment	Other routine risk minimisation measures Nyxoid will be available as Prescription only medication Additional risk minimisation measures:	Routine pharmacovigilance activities are sufficient for Nyxoid

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Not proposed	
Administration site reactions	Other routine risk minimisation measures Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: Not proposed	Routine pharmacovigilance activities are sufficient for Nyxoid
Decreased response due to impaired nasal mucosa	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Other routine risk minimisation measures Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: Not proposed	Routine pharmacovigilance activities are sufficient for Nyxoid

Part VI: Summary of the risk management plan

Summary of risk management plan for Nyxoid (naloxone hydrochloride)

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

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

This summary of the RMP for Nyxoid 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 Nyxoid's RMP.

I. The medicine and what it is used for

Nyxoid is authorised for immediate administration as emergency therapy for known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression in both non-medical and healthcare settings (see SmPC for the full indication). It contains naloxone hydrochloride as the active substance, and it is given by nasal route.

Further information about the evaluation of Nyxoid's benefits can be found in Nyxoid'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 Nyxoid, together with measures to minimise such risks and the proposed studies for learning more about Nyxoid's 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 the case of Nyxoid, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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 Nyxoid is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Nyxoid 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 Nyxoid. 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	Reoccurrence of respiratory depression Precipitation of acute opioid withdrawal effects
Important potential risks	Lack of efficacy due to medication error
Missing information	Use in pregnancy and breastfeeding Use in elderly Use in patients with hepatic impairment Use in patients with renal impairment Administration site reaction Decreased response due to impaired nasal mucosa

II.B Summary of important risks

Recurrence of respiratory depression	
Evidence for linking the risk to the medicine	Kerr D, Kelly AM, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction (Abingdon, England). 2009; 104(12):2067-74. Kelly AM, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. The Medical journal of Australia. 2005; 182(1):24-7.

	Barton ED, Colwell CB, Wolfe T, Fosnocht D, Gravitz C, Bryan T, et al. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. The Journal of emergency medicine. 2005; 29(3):265-71. EMCDDA. Preventing opioid overdose deaths with take-home naloxone (available: http://www.emcdda.europa.eu/system/files/publications/2089/TDXD15020ENN.pdf). ISSN 2314-9264. 2016. Warner-Smith M, Darke S, Day C. Morbidity associated with non-fatal heroin overdose. Addiction (Abingdon, England). 2002; 97(8):963-7. Strang J. Looking beyond death: paying attention to other important consequences of heroin overdose. Addiction (Abingdon, England). 2002; 97(8):927-8. Dahan A, Aarts L, Smith TW. Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression. Anesthesiology. 2010; 112(1):226-38.
Risk factors and risk groups	Risk factors include the specific opioid used, opioid dose, administration mode, concurrent medication, underlying disease, state of arousal and exogenous stimulatory factors.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.7: PL section 2 and 3 Other routine risk minimisation measures: A second device will be provided within the pack for administration to the patient in case needed. Back of the blister pack will consist of quick start guide for immediate identification of the use of the product. Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: HCP Guidance Document, Patient information card, and Video demonstrating how to use Nyxoid will be provided as part of training/ educational material available from nyxoid.com for countries where Nyxoid is on the market

Precipitation of acute opioid withdrawal effects	
Evidence for linking the risk to the medicine	Kerr D, Kelly AM, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction (Abingdon, England). 2009; 104(12):2067-74.

	Kelly AM, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. The Medical journal of Australia. 2005; 182(1):24-7. Barton ED, Colwell CB, Wolfe T, Fosnocht D, Gravitz C, Bryan T, et al. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. The Journal of emergency medicine. 2005; 29(3):265-71. Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, Zandifar S. Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomized clinical trial. Archives of medical science: AMS. 2014;10(2):309-14. EMCDDA. Preventing opioid overdose deaths with take-home naloxone (available: http://www.emcdda.europa.eu/system/files/publications/2089/TDXD15020ENN.pdf). ISSN 2314-9264. 2016. Wermeling, D. P. (2015). "Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access." Ther Adv Drug Saf 6(1): 20-31).
Risk factors and risk groups	The risk factors include the dose of naloxone administered, the dose of opioids taken and their relative affinities for the opioid receptor.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4, 4.6 and 4.8 PL Sections 2 and 4. Other routine risk minimisation measures. Pack size, posology mentions the dose, dose frequency to minimise the risk of precipitation of acute opioid withdrawal effects. Back of the blister pack will consist of quick start guide for immediate identification of the use of the product. Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: HCP Guidance Document, Patient information card, and Video demonstrating how to use Nyxoid will be provided as part of training/ educational material available from nyxoid.com for countries where Nyxoid is on the market

Lack of efficacy due to medication error	
Evidence for linking the risk to the medicine	Not applicable.
Risk factors and risk groups	Risk factors include user having inadequate or insufficient information regarding Nyxoid administration to the patient in the emergency situation of opioid overdose.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 PL section 3. Other routine risk minimisation measures The Quick start guide on the blisters will detail the method of administration of Nyxoid. Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: HCP Guidance Document, Patient information card, Quick Start Guide, and Video demonstrating how to use Nyxoid will be provided as part of training/ educational material available from nyxoid.com for countries where Nyxoid is on the market.

Use in pregnancy and breastfeeding	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 PL Section 2 Other routine risk minimisation measures: Package leaflet will contain the relevant sections from the SmPC. Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: Not proposed

Use in elderly	
Risk minimisation measures	Other routine risk minimisation measures: Nyxoid will be available as Prescription only medication. Additional risk minimisation measures:

	None proposed.

Use in patients with hepatic impairment	
Risk minimisation measures	Other routine risk minimisation measures: Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: None proposed.

Use in patients with renal impairment	
Risk minimisation measures	Other routine risk minimisation measures: Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: None proposed.

Administration site reaction	
Risk minimisation measures	Other routine risk minimisation measures: Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: None proposed.

Decreased response due to impaired nasal mucosa	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Other routine risk minimisation measures Nyxoid will be available as Prescription only medication. Additional risk minimisation measures: None proposed.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

On the basis of the totality of the evidence collected and presented by the MAH as summarized in the Addendum to Clinical Overview, the current scientific evidence from the Post-Authorisation Effectiveness Study (PAES) and from published studies from take home naloxone (THN) programmes in different European Unioncountries, the United Kingdom and Australia meets the intended requirements of the PAES and hence the marketing authorisation Post-Approval Commitment has been fulfilled. No additional post-authorisation efficacy data are deemed necessary to address the proper utilisation of intranasal naloxone in the real world.

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

There are no other studies required for Nyxoid.

II.D Educational materials

In addition to the information in the patient information leaflet and the quick start guide (GQC) on the blister of the Nyxoid inner packaging blister, the following educational materials are available through the non-promotional website nyxoid.com:

- Health care professional (HCP) Guidance Documents (HGD) designed to provide guidance to the HCPs to make them aware that they must communicate the aforementioned important risks to the patient and/or carer which are related to the use of Nyxoid, to minimise their occurrence and severity. The HGD also guides HCPs on how Nyxoid is used so the administration technique can be shared and passed on to the patient/carer, as well as information on what to do if a patient is potentially experiencing an overdose.
- Patient Information Card (PIC) to instruct the patient and/or carer and inform them about how to manage a patient with a suspected overdose using Nyxoid to further minimise the occurrence and severity of the aforementioned important risks.
- Video demonstrating how to use Nyxoid in patients with suspected opioid overdose to further illustrate the steps to be carried out.

A QR code on the package and in the patient information leaflet provides a link to the non-promotional website nyxoid.com. Carers (health care professionals, carriers of Nyxoid, patients) can quickly reach the materials by scanning the code with their mobile devices.

The educational materials can be freely downloaded to e.g. mobile phones, or printed, to have them at hand when needed.

Nyxoid.com does not track individual visitors but information on the number of visits to different pages will be analysed to country level to assess the effectiveness of the electronic distribution of the educational materials.

Part VII Annexes

Table of context

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable as there are no specific adverse event follow up forms.

Annex 6 - Details of proposed additional risk minimisation activities

Educational and Training Measures

Purpose:

- Training for persons at risk of opioid overdose (patients), and their family or friends (carers) willing to offer future assistance to such persons, in order to understand the use of Nyxoid in situations of known or suspected opioid overdose and to draw attention to educational material provided by the Health Care Professional (HCP) and Quick Start Guide (QSG) and package leaflet in the product carton intended for end users who could be either the patient or the carer.
- Provision of clear information on:
    - what to do in the case of a known or suspected opioid overdose
    - the importance of calling quickly for emergency medical assistance
    - administration method of Nyxoid
    - how to deal with the important identified risks of precipitation of withdrawal effects and recurrence of respiratory depression.

Training Delivery (see further details below)

- It is envisaged that training and supply of educational material for patients and carers will be conducted by Health Care Professionals (HCPs) in usual contact at clinics, healthcare facilities providing services or treatment for persons at risk of overdose, and/or pharmacies likely to dispense Nyxoid, according to the health infra-structure appropriate to each country where the product is placed upon the market, post approval.
- The MAH will provide training & educational materials to help HCPs, familiarise themselves with the Nyxoid spray and its use and to support HCPs in giving training to persons at risk of opioid overdose, and also their carers if willing to participate.
- The nationally approved educational materials will be posted on the non-promotional website nyxoid.com, from where they can be freely downloaded and printed as needed to allow (re-)training.
- QR codes on the package and in the PIL will link to nyxoid.com to allow quick access with mobile devices.

Elements of Training and Educational Material

Key elements of Educational Materials

In addition to the quick start guide on the inner packaging blisters for Nyxoid, the following materials will be provided:

- HCP Guidance Document (HGD)
- Patient/Carer Information Card (PIC)
- Video demonstrating the use Nyxoid in patients with suspected opioid overdose.

Core Content:

- HCP Guidance Document (subject to approval)
    - A list of what the educational/training material contains, which is:
        - An HCP guidance document with training delivery instructions
        - A Patient Information Card
        - A video (could be accessed via a link) demonstrating the use Nyxoid in patients with suspected opioid overdose.
    - A brief introduction of Nyxoid
    - Rationale for training programme, which is to help the patient, and potential Nyxoid end users, understand how to manage a known or suspected opioid overdosed patient and to mitigate the risks associated with Nyxoid use.
    - HGD detailing what information the HCP needs to share to train the patient/carer on the PIC and the video.
    - Information that the HCP needs to hand over the PIC to the patient/carers which will have the link to the video.
    - Reference to the QSG on the inner packaging blister for Nyxoid and package leaflet within the product carton.

- Patient Information Card
    - Reinforcing key aspects of the information provided in the ‘Package Leaflet’ and ‘QSG’ with the help of text and pictograms, including:
        - Information about Nyxoid as a naloxone containing product and the fact that it cannot replace provision of basic life support.

- Identification of signs of suspected opioid overdose, especially respiratory depression and to check the airways and breathing.
- Emphasis on the need to make an immediate emergency call for an ambulance.
- How to use the nasal spray to correctly administer Nyxoid.
- Placing the patient into recovery position and administering the second dose if required, in this position.
- Management and monitoring of the patient till the emergency medical assistance arrives.
- Awareness of possible important risks such as opioid withdrawal symptoms as consequence of opioid reversal by naloxone and recurrence of overdose symptoms.
- Reference to the QSG at the back of blister.

- Video demonstrating how to use Nyxoid in the person suspected of opioid overdose
  - Steps detailing management of a patient which are aligned with information in PIC and package leaflet available

Details of Delivery of the Educational Materials

- National approval for the Nyxoid educational materials will be obtained in each country where Nyxoid is on the market. After approval, the materials will be posted on the non-promotional website nyxoid.com, from which the materials can be freely downloaded and printed as needed.
- QR codes on the package and in the patient information leaflet will link to nyxoid.com to ensure that all carers (HCPs, patients, carriers of Nyxoid) can quickly reach the materials when needed.
- Nyxoid.com does not use tracking cookies. The functional cookies do allow setting the preferred country, so that on next visits from the same source, the chosen country is immediately reached.
- Where required by national authorities, the company will either inform relevant HCPs of the availability of the educational materials on nyxoid.com and the QR code on the packaging and PIL which links to this site, or distribute paper based materials, as locally agreed.