14 September 2017
EMA/CHMP/690823/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nyxoid

International non-proprietary name: naloxone

Procedure No. EMEA/H/C/004325/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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Administrative information

Name of the medicinal product:	Nyxoid
Applicant:	Mundipharma Corporation Limited Milton Road Cambridge Science Park Cambridge CB4 0AB UNITED KINGDOM
Active substance:	NALOXONE HYDROCHLORIDE DIHYDRATE
International Non-proprietary Name/Common Name:	naloxone
Pharmaco-therapeutic group (ATC Code):	all other therapeutic products, antidotes (V03AB15)
Therapeutic indication(s):	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.
Pharmaceutical form(s):	Nasal spray, solution in single-dose container
Strength(s):	1.8 mg
Route(s) of administration:	Nasal use
Packaging:	single dose spray container
Package size(s):	2 spray containers

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List of abbreviations

BDP	Bulk drug product
CEP	Certificate of Suitability
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CPP	Critical process parameters
CU	Content uniformity
DDU	Delivered dose uniformity
DSC	Differential Scanning Calorimetry
CQA	Critical quality attributes
GMP	Good manufacturing practices
EC	European Commission
EDQM	European Directorate for the Quality of Medicines & Healthcare
ERA	Extended risk assessment
FAO	Food and Agriculture Organization of the United Nations
HDPE	High Density Polyethylene
HLRA	High level risk assessment
HPLC	High performance liquid chromatography
IPC	In-process control
IRMP	Integrated risk mitigation plan
MV	mass variation
NMT	Not more than
Ph.Eur.	European Pharmacopoeia
PRA	Process risk assessment
QbD	Quality by design
QP	Qualified person
q.s.	*quantum satis* (the amount which is sufficient)
QTPP	Quality target product profile
SCFM	Standard cubic feet of gas per minute

SmPC	Summary of Product Characteristics
TAMC	Total aerobic microbial count
TGA	Thermo-Gravimetric Analysis
TYMC	Total yeasts/moulds count
TSE	Transmissible spongiform encephalopathy
UDS	Unit dose
UDVs	Unit dose vials
UV	Ultraviolet
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mundipharma Corporation Limited submitted on 1 November 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Nyxoid, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 November 2015. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 10a of Directive 2001/83/EC.

The applicant applied for the following indication:

Nyxoid is intended for emergency use for known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression in:

- the home or other non-medical setting
- a health facility setting

For this reason, Nyxoid should be carried by persons at risk of, or likely to witness such events.

Nyxoid is indicated in adults and children.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is

composed of administrative information, complete quality data, a bioequivalence study with the reference medicinal product Naloxon HCl B. Braun and appropriate non-clinical and clinical data

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Naloxon HCl B. Braun 0.4mg/ml, solution for injection
- Marketing authorisation holder: B.Braun Melsungen AG
- Date of authorisation: 22-08-2006

- Marketing authorisation granted by:
  - Member State (EEA) : Netherlands
    - MRP
- Marketing authorisation number: RVG 33994

Medicinal product authorised in the Community/Member State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Naloxon HCl B. Braun 0.4mg/ml, solution for injection
- Marketing authorisation holder: B.Braun Melsungen AG
- Date of authorisation: 16-07-2007
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - MRP
- Marketing authorisation number: 67923.00.00

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Naloxon HCl B. Braun 0.4mg/ml, solution for injection
- Marketing authorisation holder: B.Braun Melsungen AG
- Date of authorisation: 16-07-2007
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - MRP
- Marketing authorisation number(s): 67923.00.00

- Bioavailability study number(s): 2015-004493-15

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised

orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 November 2015. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: Juris Pokrotnieks

- The application was received by the EMA on 1 November 2016.
- The procedure started on 24 November 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 20 February 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 February 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 28 February 2017.
- During the meeting on 23 March 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 May 2017.
- The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:

  A GMP inspection at one site responsible for manufacture of the finished product located in USA performed at 19 June 2017. The outcome of the inspection carried out was issued on 04 September 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 June 2017.
- During the PRAC meeting on 06 July 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 20 July 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 31 August 2017.
- During the meeting on 14 September 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Nyxoid on 14 September 2017.

2. Scientific discussion

Problem statement

Naloxone is a widely accepted opioid antagonist used to reverse respiratory depression caused by opioid overdose. It has been used in emergency medicine since the 1970s. Naloxone is listed by World Health Organisation (WHO) as an "essential medicine" and is traditionally available in injectable forms. Parenteral (IV, IM or SC) naloxone is commonly used in the treatment of reversing opioid overdose with a dose range from 0.4 mg to 2 mg.

Naloxone is a μ-opioid competitive antagonist with affinity for μ-opioid receptor (and partly at the δ-opioid receptor) that competes with other drugs for this receptor thereby controlling this specific opioid receptor. Due to this property, naloxone is able to reverse the effects of opioids such as heroin by preventing their metabolites to influence the receptor's normal function. This reversal effect is very rapid.

About the product

Naloxone 1.8 mg nasal spray, solution is intended for immediate administration as emergency therapy for known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression.

The nasal spray has the potential to remove the psychological and policy barriers which can prevent availability of existing injectable forms of naloxone for emergency administration in the first minutes following an opioid overdose.

The rationale for the development of intranasal naloxone builds on the background of take home naloxone (THN) programmes and improves on current improvised IN naloxone use.

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that the Applicant did not demonstrate the unmet medical need.

2.1. Quality aspects

2.1.1. Introduction

The finished product is presented as nasal spray, solution in a single dose container containing 1.8 mg of naloxone (as hydrochloride dihydrate) as active substance.

Other ingredients are: trisodium citrate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide and purified water.

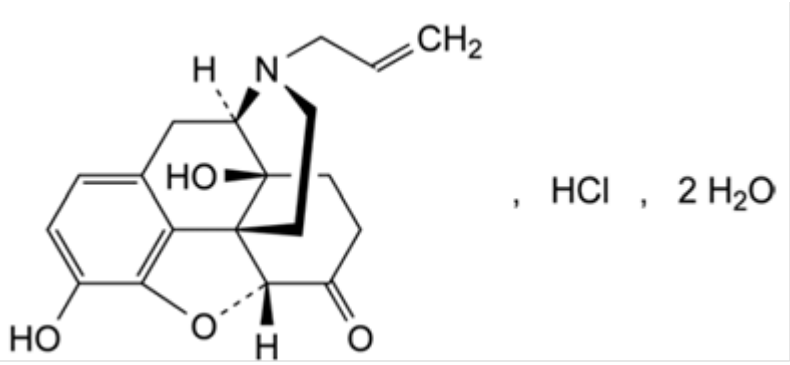
The product is available in a type I glass vial with siliconised chlorobutyl stopper containing 0.1 ml solution. The secondary packaging (actuator) is comprised of polypropylene and stainless steel, as described in section 6.5 of the SmPC.

2.1.2. Active Substance

General information

The chemical name of naloxone hydrochloride dihydrate is (5*R*,9*R*,13*S*,14*S*)-17-(prop-2-enyl)-3,14-dihydroxy-4,5-epoxymorphinan-6-one hydrochloride corresponding to the molecular formula C19H22ClNO4·2H2O. It has a relative molecular mass of 399.9 and the following structure:

Figure 1 – Structural formula of naloxone hydrochloride dihydrate



The active substance is a white or almost white, hygroscopic, crystalline powder, freely soluble in water, soluble in ethanol (96 per cent) and practically insoluble in toluene.

The structure of the molecule and its hydrate form have been characterised using common analytical techniques. Analysis has confirmed that naloxone hydrochloride used to manufacture Nyxoid is present in the dihydrate form.

The finished product contains the active substance in the form of a solution and consequently properties such as particle size distribution and polymorphism of the active substance of are of no relevance when it comes to clinical performance of the product.

Naloxone exhibits stereoisomerism due to the presence of four chiral centres; this is controlled routinely using standard techniques.

As there is a monograph of naloxone hydrochloride dihydrate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for naloxone hydrochloride dihydrate which has been provided within the current Marketing Authorisation Application.

The relevant information regarding proof of structure studies and physicochemical characterisation has been assessed by the EDQM before issuing the Certificate of Suitability.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification includes tests for: appearance (visual), identity (IR), identity of chlorides (Ph. Eur.), appearance of solution (Ph. Eur.), acidity or alkalinity (Ph. Eur.), specific optical rotation (Ph. Eur.), related substances (HPLC), water (Ph. Eur.), sulfated ash (Ph. Eur.), assay (Ph. Eur.) and residual solvents (GC).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph.

Batch analysis data (n=3, commercial scale) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. The re-test period of the active substance as stated in the Certificate of Suitability is 36 months if stored in two polyethylene bags placed in an opaque container.

Comparability exercise for Active Substance

Not applicable.

2.1.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as a nasal spray, solution in a single dose container containing 1.8 mg of naloxone (as hydrochloride dihydrate) as active substance. The solution is contained in a Type I clear glass vial, sealed with a chlorobutyl elastomer stopper/plunger that is fitted into a non-reusable, Unit Dose System

(UDS) nasal spray which delivers 100 µl of solution as a single dose. The finished product is comprised of two individually blister-packaged units of naloxone 1.8mg nasal spray contained in a single cardboard carton.

The aim of the pharmaceutical development was to develop a naloxone hydrochloride solution suitable for nasal administration.

The pharmaceutical development of the finished product contains Quality by Design (QbD) elements.

A process risk assessment was performed to identify any areas that require risk mitigation or further development activities prior to process validation and commercialization. This was made by identifying the product CQAs and the critical process parameters (CPP) with respect to the operations and activities of component supply, manufacturing process and packaging process. The methodology used for this purpose comprised a high-level and extended risk assessment leading to an integrated risk mitigation plan. None of the risks identified were assigned as high. The medium risks identified in the risk assessment were further assessed in an extended risk assessment and corresponding integrated risk mitigation plans were recommended.

Naloxone hydrochloride dihydrate is freely soluble in water and therefore is appropriate for delivery in an aqueous solution. As mentioned above, the particle size of active substance is not relevant for the performance of the nasal solution.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Compatibility of the active substance and the excipients was confirmed in the stability studies.

The pH of formulation is important in order to avoid irritation of the nasal mucosa and the pH of the solution has an impact on the product stability. Therefore, a buffer is included in the formulation to control the product pH.

The original indication claimed by the applicant included children of all ages including new-borns. However, the pharmaceutical development section of the dossier lacked a discussion on the suitability of the proposed product for the paediatric population, including a discussion on suitability of the tip of the nasal spray device (diameter of 1 cm) for the size of the nostrils/nasal cavity of the target age group(s). This constituted a major objection. In recognition of the lack of available data to support the original proposed indication including children, the applicant decided to revise the indication at the request of the CHMP to include adults and adolescents aged 14 and above only.

The nasal spray produces a fine mist of droplets. The spray is formed by the liquid exiting the device spray orifice and was characterised. Pump delivery, spray content uniformity and droplet size distribution were also measured and limits included in the finished product specification.

During pharmaceutical development of the finished product, the applicant assessed the impact of angle of orientation on the performance of the nasal spray, and submitted data concerning the effect of angle of orientation on pump delivery and droplet size distribution. The angle of actuation was found to have no impact on the volume of spray delivered (pump delivery). Droplet size distribution was measured by laser diffraction. Results showed d10, d50 and d90 were very similar with all angle orientations tested. These data confirmed that the spray characteristics and doses delivered were consistent and comparable for upright or angled spray delivery, and that the device performance was orientation independent.

The effect of dropping, vibration and shaking on device performance was also studied. Extractables and leachables from the primary container (vial, stopper/plunger and actuator) were also assessed. A discussion on potential delamination of glass vials was provided, being supported by long-term stability data.

Prior to use, the drug product solution is in contact with the vial and plunger. During use the drug product passes through the actuator with momentary contact. The tip of the nasal actuator temporarily comes in contact with the patient during use. Studies were performed to determine the potential extractables from each component with patient and product contact.

Controlled extraction studies targeting organic and inorganic compounds were performed on the polypropylene actuator, chlorobutyl elastomer stopper/plunger and Type I glass vial to determine the compounds which could potentially leach into the finished product from each component.

One lot of finished product was placed on stability for 36 months and will be monitored for the presence of organic and inorganic leachables using the same analytical procedures used for the extraction studies.

The finished product is supplied as a unit dose delivery system. The formulation contains no antimicrobial preservatives.

The container closure system is comprised of primary and secondary packaging. The primary packaging is a type I glass vial with siliconised chlorobutyl stopper containing 0.1 ml solution. The material complies with Ph. Eur. and EC requirements. The secondary packaging comprises a container holder, into which the primary container is seated, which is subsequently assembled with an actuator to form the secondary packaging. The finished product is individually packaged in a blister pack with peel-off backing. The blister is not intended to enhance the stability of the product and is used as protective package for storage and labelling purposes. Two individual blister packs are packaged in a cardboard outer carton to form the patient pack, in line with posology. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: component preparation, formulation, filling and bioburden reduction step, inspection and assembly, and packaging.

Major steps of the manufacturing process have been validated by a number of studies. The process is a standard manufacturing process, and the manufacturer is experienced in manufacturing nasal spray unit dose devices and its components.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description of product (visual), description of container (visual), pH (potentiometric, Ph. Eur.), identification (HPLC, UV), assay (HPLC), specified degradation products (HPLC), unspecified degradation products (HPLC), total degradation products (HPLC), spray content uniformity (HPLC), uniformity of dosage units (HPLC), microbial

limits (enumeration, Ph. Eur.), osmolality (osmometer, Ph. Eur.), pump delivery (weight), droplet size distribution (laser diffraction).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description of product, description of container, pH, identification, assay, specified degradation products, unspecified degradation products, total degradation products, spray content uniformity, uniformity of dosage units, microbial limits, osmolality, pump delivery, and droplet size distribution. The analytical procedures used are stability indicating. No significant changes were observed at any of the conditions tested

Forced degradation studies were performed using stressed conditions: heat, acid, base, oxidation and light. It was shown that the product is sensitive to oxidation and basic conditions.

In addition, a single batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples of the finished product solution were exposed to light in their primary container closure (vial and plunger stopper) and in their secondary container closure (container holder and actuator).

A study was performed according to Ph. Eur. 2.2.18 to determine the freezing point of the finished product solution. The freezing point was determined, which was the basis for assigning a special storage condition ‘do not freeze’.

Based on available stability data, the proposed shelf-life of 24 months and the storage precaution ‘do not freeze’ as stated in the SmPC (section 6.3) are acceptable.

Comparability exercise for finished medicinal drug product

Not applicable.

Adventitious agents

No excipients derived from animal or human origin have been used.

GMO

Not applicable.

2.1.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The active substance naloxone hydrochloride dihydrate is described in the European Pharmacopoeia. A valid CEP has been provided for the active substance.

The finished product is in the form of an aqueous solution for administration as a nasal spray.

Pharmaceutical development is well conducted taking in consideration the target population. The spray plume release in the nasal cavity has been demonstrated not to be significantly affected by the body position. The finished product contains well-known compendial excipients, widely used materials in pharmaceutical formulations, with a long history of safe use in pharmaceutical technology. All excipients in the formulation, as well as the amounts used, have been properly justified.

The manufacturing process is a standard process. Although this is not a sterile dosage form, it involves steps to keep bioburden low, which improves the stability of the finished product. Data concerning process development is considered acceptable. The manufacturing process critical steps, IPCs and finished product specification have been well identified and justified.

Stability studies were conducted according to the ICH recommendations, and data supporting the proposed shelf-life of 24 months with a special condition ‘do not freeze’ has been provided.

2.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.1.6. Recommendations for future quality development

Not applicable.

2.2. Non-clinical aspects

2.2.1. Introduction

This application was supported by the literature review and a number of studies performed by the Applicant, predominantly to support new administration route.

2.2.2. Pharmacology

When administered by IV, IM or SC routes, naloxone rapidly antagonises mild respiratory depression caused by small doses of opioids but the effect is temporary as it is extensively and rapidly metabolised. This results in a duration of action that is generally shorter than that of the opioid and as such, the effects of the opioid may return as the effects of naloxone dissipate, resulting in the requirement of additional doses of naloxone.

The intranasal route is one of the most permeable and highly vascularised sites for administration, ensuring rapid absorption and like the intravenous route, it by-passes the first pass metabolism. Naloxone injection kits are currently used off label with an improvised IN atomiser by some medical and trained professionals as a route of IN naloxone administration. However, the naloxone concentration of such preparations requires administration of a large volume that is not optimal for IN delivery; as the naloxone solution can also run out of the nasopharynx and can be swallowed which contributes very little to the overall absorption, due to the low oral bioavailability of naloxone. To maximise the bioavailability of naloxone, the Applicant has developed a proprietary intranasal product that contains an appropriate concentration of naloxone to provide an effective dose within the accepted volumes, suitable for administration in the nasal cavity.

The pharmacology associated with naloxone has been reported extensively in the literature and the Applicant's additional *in vitro* and *in vivo* studies are consistent with data reported previously. The pharmacodynamic profile of naloxone following intranasal administration is anticipated to be similar to the well-established profile following the injectable routes of administration such as IV and IM. The Applicant has not performed any further *in vivo* pharmacodynamic studies supporting the intranasal administration.

2.2.3. Pharmacokinetics

Following intranasal administration in the rat, naloxone is absorbed rapidly (within 1 minute) and the decline from the initial peak is equally rapid with plasma concentration of naloxone at six hours post-dose being minimal. Plasma concentrations of naloxone increase in a slightly less than dose proportional manner between the 4.9 and 19.4 mg/kg intranasal doses.

Following oral administration, the pharmacokinetic profile of naloxone in animals is characterised by a rapid absorption and low bioavailability due to an extensive first pass effect. Naloxone is predominantly and rapidly metabolised by conjugation pathways to form naloxone-3-glucuronide, which is the major metabolite detected in humans and in the animal species tested. Since naloxone-3-glucuronide is inactive, the duration of naloxone activity is very limited. Naloxone distributes to all tissues, nonetheless, it is characterised by a high brain to plasma concentration ratio due to its high lipid solubility.

2.2.4. Toxicology

The safety of intranasal administration, the intended human route, has been assessed in a single and a 7-day repeated study in male SD rats. Intranasal administration of naloxone for 7 days (up to 19 mg/kg/day) did not cause any mortality or any treatment related changes indicative of toxicity and 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 mid dose) 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.

In the rat, following a single intranasal administration, at the highest non-toxic dose tested, the plasma Cmax is 1327-fold greater than the plasma Cmax achieved following a single intranasal dose (4 mg) in human subjects and following a single intravenous dose (0.4 mg) in human subjects and is 7962-fold greater than a single intramuscular dose (0.4 mg) in human subjects. The plasma AUC0-∞ is 294-fold greater than the AUC0-∞ achieved following a single intranasal dose (4 mg) in human subjects and 1471-fold greater than the plasma AUC0-∞ achieved following a single intravenous dose or intramuscular dose (0.4 mg) in human subjects. These safety margins are considered adequate and satisfactory.

2.2.5. Ecotoxicity/environmental risk assessment

Substance (INN/Invented Name): naxolone / Nyxoid			
PBT screening	***Method***	***Results***	***Conclusion***
log K_{ow}	OECD 107 Shake Flask Method	log K_{ow} = 0.765 (pH 7) **≤ 4.5**	Potential PBT (**N**) reference to the study
PBT-assessment			
Parameter		***Results***	**Conclusion**
Bioaccumulation	log K_{ow}	-1.24 (pH 4) 0.765 (pH 7) 1.55 (pH 9)	**Not B**
Persistence	ready biodegradability	Not readily biodegradable	**P**
Toxicity (Fish, Early Life Stage Toxicity)	NOEC	9.9 mg/L (≤10 µg/L)	**Not T**
PBT-statement :	not considered as PBT		
Phase I			
Calculation	***Value***	***Unit***	***Conclusion***
$PEC_{surfacewater}$	0.02	µg/L	**≥0.01 threshold**
Other concerns (e.g. chemical class)			**N**
Phase II Physical-chemical properties and fate			
Study type	***Test protocol***	***Results***	***Remarks***
Determination of adsorption coefficient	OECD 106	Koc = 874.8 L/kg	**Koc ≤ 1000 L/kg**
Ready Biodegradability Test	OECD 301	----------	Waived by OECD 308
Aerobic Transformation in Aquatic Sediment systems	OECD 308	By day 100 % recovered 12.4 and 4.4 in the two systems Sediment phase: 71.0 – 72.3%	reference to the study Required a Sediment-Dwelling Midges test

		By day 14 Sediment phase: 55.5 – 81.7% - greater than 10%			
Phase II-A Effect studies					
Study type	***Test protocol***	***End point***	***value***	***Unit***	***Remarks***
Green alga, Growth Inhibition (GLP)	OECD 201	Yield and Growth rate NOEC	13	mg/L	*Pseudokirchneriella subcapitata* (72h) reference to the study
Daphnia sp. Reproduction Test	OECD 211	Survival EC50 Reproduction and grow NOEC	>48 21	mg/L	reference to the study
Fish, Early Life Stage Toxicity	OECD 210	NOEC	9.9	mg/L	**The most sensitive organism** reference to the study
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50}	≥1000	mg/L	reference to the study
Phase II-B Studies					
Sediment Dwelling Organism *(Chironomus riparius)*	OCDE 218	Development and emergence NOEC	100	mg/kg	reference to the study

In Phase I a PECsurfacewater of 0.02 µg/L was calculated for naloxone. As it exceeds the action limit of 0.01 µg/L, a Phase II fate and effects assessment were conducted.

The phase II studies comprised the determination of the adsorption coefficient, an aerobic transformation test in aquatic sediment systems as well as chronic toxicity studies in aquatic organisms and an activated sludge respiration test.

Naloxone is not PBT substance and the results of the water/sediment system demonstrated that it shifts significantly from the water phase to the sediment phase. The degradation products in sediment are ≤ 10 %. A further assessment of the sediment phase was provided in phase IIB with a chronic sediment toxicity study.

A new adsorption/desorption test for naloxone using 3 different soil samples should be performed and the predicted environmental concentrations in sediment recalculated. Regarding the results, the possible effect of naloxone into the terrestrial environment should be discussed.

The applicant has committed to provide this adsorption/desorption test as a post-approval measure.

2.2.6. Discussion on non-clinical aspects

Naloxone has been used in opioid overdose management for over 40 years to reverse respiratory depression and is available in injectable forms in doses ranging from 0.4 mg to 2 mg. When administered by IV, IM or SC routes, naloxone rapidly antagonises mild respiratory depression caused by small doses of opioids but the effect is temporary as it is extensively and rapidly metabolised. This results in a duration of action that is generally shorter than that of the opioid and as such, the effects of the opioid may return as the effects of naloxone dissipates, resulting in the requirement of additional doses of naloxone.

The pharmacology and safety pharmacology associated with naloxone has been reported extensively in the literature. Additional proprietary studies from the Applicant confirm the pharmacology and safety pharmacology data available in the literature. Similarly, the pharmacokinetic profile of naloxone has been widely reported in the literature. The Applicant has a limited number of proprietary GLP toxicokinetic studies with naloxone (administered by oral or intravenous routes) that again support the data available in the literature. Furthermore, the Applicant has conducted a short-term (up to 7 days) Good Laboratory Practice (GLP) intranasal toxicity study in the rat with associated toxicokinetic evaluation at Day 1.

The nonclinical studies performed with naloxone hydrochloride (administered by oral or intravenous routes) not only confirm the data already available in the literature (general toxicity) but also provide additional new information, including genotoxicity and carcinogenicity studies, reproductive and developmental studies. Intranasal administration of naloxone for up to 7 days (up to 19 mg/kg/day, the highest dose tested) in the rat, does not cause any local irritation at the highest doses tested and does not cause any additional toxicity to that observed with oral and intravenous administration nor are any target organs of toxicity identified (in rodents and dogs). Based on the nonclinical data generated from studies conducted with naloxone, no new or unexpected toxicities are anticipated with the intranasal naloxone product. The nonclinical data support the conclusion that intranasal naloxone is safe for its intended use in the treatment of opioid agonist overdose.

With regards to ecotoxicity, the available data do not allow to conclude definitively on the potential risk of naloxone to the environment. A new adsorption/desorption test for naloxone using 3 different soil samples should be performed and the predicted environmental concentrations in sediment recalculated. Regarding the results, the possible effect of naloxone into the terrestrial environment should be discussed. The Applicant has committed to provide this data as a post-approval measure.

2.2.7. Conclusion on the non-clinical aspects

The applicant presented non-clinical arguments that support the Marketing Authorisation application for intranasal naloxone.

2.3. Clinical aspects

2.3.1. Introduction

This MAA draws on the availability of published data supporting the use of naloxone in this indication covering efficacy and safety data for the use of naloxone:

- In the treatment of opioid overdose.
    - As part of take home naloxone (THN) programmes.

- For intranasal administration.

In addition, a comparative Phase I study was presented. This was a 5-part, open-label, randomised, single dose, crossover study in healthy subjects to compare the pharmacokinetics (PK) of a single dose of naloxone nasal spray (1 mg, 2 mg and 4 mg naloxone hydrochloride) and the reference product given as a 0.4 mg intramuscular and 0.4 mg intravenous dose. Data from the study has been used to demonstrate how IN use in the claimed indication is justified considering the performance of the IN formulation against the IM reference product.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

2.3.2. Pharmacokinetics

Study MR903-1501 A 5-part, open-label, randomised, single dose, crossover study in healthy subjects to compare the pharmacokinetics of a single dose of intranasal MR903 (1 mg, 2 mg and 4 mg) and naloxone hydrochloride given as a 0.4 mg intramuscular and 0.4 mg intravenous dose.

Methods

The primary objectives were; to assess the pharmacokinetics of IN MR903 1 mg, 2 mg and 4 mg compared with 0.4 mg naloxone given as an IM and IV dose and, to compare the early partial exposure to naloxone, measured by the area under the plasma concentration-time curve calculated from the time of dosing to the median time to maximum observed plasma concentration (tmax) of the IM reference treatment (AUCp), following IN and IM administration, with the aim of showing that the AUCp for IN administration was non-inferior to the AUCp for IM administration. A secondary PK objective was to determine the absolute bioavailability of naloxone when administered via the IN route, by comparison of the dose-adjusted AUC values following IN and IV administration. Exploratory objectives were to assess the relative onset and duration of action of the different routes of administration by comparison of the exploratory parameters, time taken to reach 50% of maximum observed plasma concentration (Cmax), (t50) and half-value duration (HVD). Also, to assess the relative time taken to reach peak concentrations following IN and IV administration, by comparing IN time to maximum observed plasma concentration (tmax) with IV tmax+time to cannulate subjects (tcan).

No formal assessment of bioequivalence was planned, however, assuming moderate variability for the PK parameters AUCt and Cmax (i.e. a SD of 0.35 to 0.4 for the period differences on log scale), and a true ratio of 1, a sample size of 28 subjects for each comparison would provide 80% to 90% chance for observing a 90% confidence interval which lies entirely between 80% and 125%). Assuming that 20% of subjects would not provide valid PK data for a comparison of interest, 35 subjects were to be randomised to the study.

A total of 89 subjects were enrolled into the study and 38 were randomised and received IMP. The PK population included all 38 healthy subjects who were randomised and received IMP. 6 subjects discontinued from the study; one subject due to an unrelated AE, 1 subject due to subject's choice and 4 subjects were excluded due to a positive result in the drugs of abuse test. Subjects were between 20 and 54 years old. The mean age of subjects was 32.4 years. Twenty-seven (71.1%) subjects were male and 11 (28.9%) were

female. The mean (SD) weight at screening was 72.40 (9.173) kg (median 71.55 kg) and mean height was 175.5 (8.02) cm (median 177.0 cm).

Subjects received a single dose of study drug on Day 1 of each study period randomised across five study periods as follows:

Study Medication/IMP	Overall Dose	Dosing Frequency	Mode of Administration
MR903 (naloxone hydrochloride solution 10 mg/mL)	1 mg	Single dose (one 0.1 mL actuation in one nostril)	Intranasal
MR903 (naloxone hydrochloride solution 20 mg/mL)	2 mg	Single dose (one 0.1 mL actuation in one nostril)	Intranasal
MR903 (naloxone hydrochloride solution 20 mg/mL)	4 mg	Single dose (one 0.1 mL actuation (2 mg) in each nostril)	Intranasal
Naloxone hydrochloride solution for injection	0.4 mg	Single dose	Intramuscular
Naloxone hydrochloride solution for injection	0.4 mg	Single dose	Intravenous

Each administration was performed after a fasting period of at least 8 h and fasting was maintained for at least 4 hours after dosing. There was a minimum of 4 days between dosing in each study period.

Blood samples for PK assessments were drawn at pre-dose, and at 1, 2, 4, 6, 8, 10, 12.5, 15, 30, 45 minutes and 1, 1.5, 2, 4, 6, 8, 10 and 12 hours after dosing (19 samples per study period).

Blood samples, 6 mL each, were drawn into tubes containing K2EDTA anticoagulant. Samples were centrifuged within 30 minutes of collection. Following centrifugation (1500 g, 4°C, 15 minutes) the plasma was transferred via pipette into two labelled 3 mL polypropylene tubes and stored at -20°C within 1 hour of collection. The plasma samples were analysed by liquid chromatography tandem mass spectrometry (LC-MS/MS) methodology using validated bioanalytical assays for naloxone and naloxone-3-glucuronide.

Safety was assessed by documentation of adverse events, clinical laboratory results, vital signs, physical examinations, and electrocardiograms (ECGs) and recorded on the standard electronic Case Report Form (eCRF) pages and Serious Adverse Event (SAE) data form.

Results

Mean observed plasma concentration-time curves for naloxone and Naloxone-3-glucuronide are presented on a linear scale in the following Figures:

Figure 4. Mean Naloxone Plasma Concentration versus Time by Treatment (linear scale)

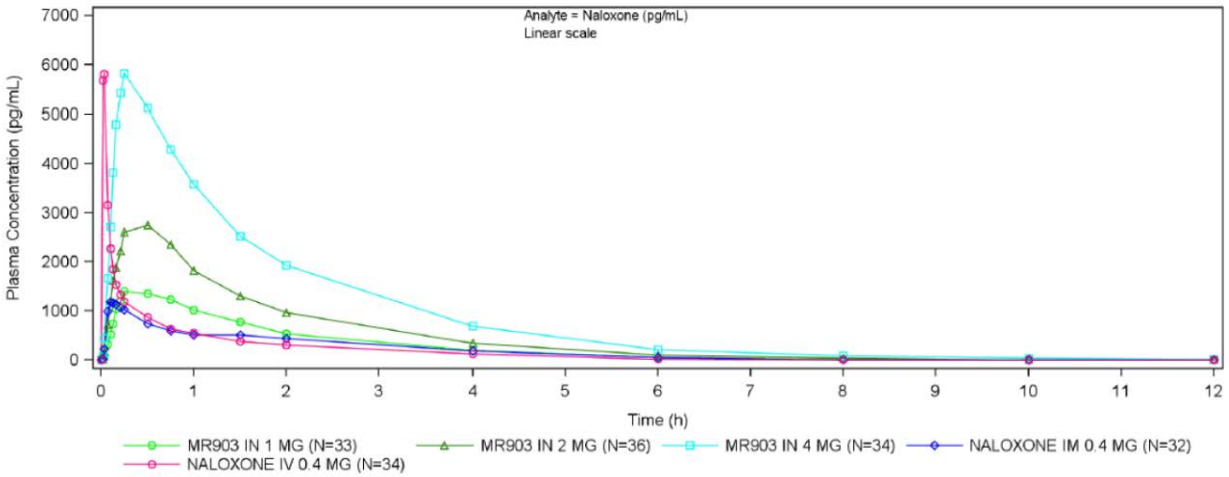
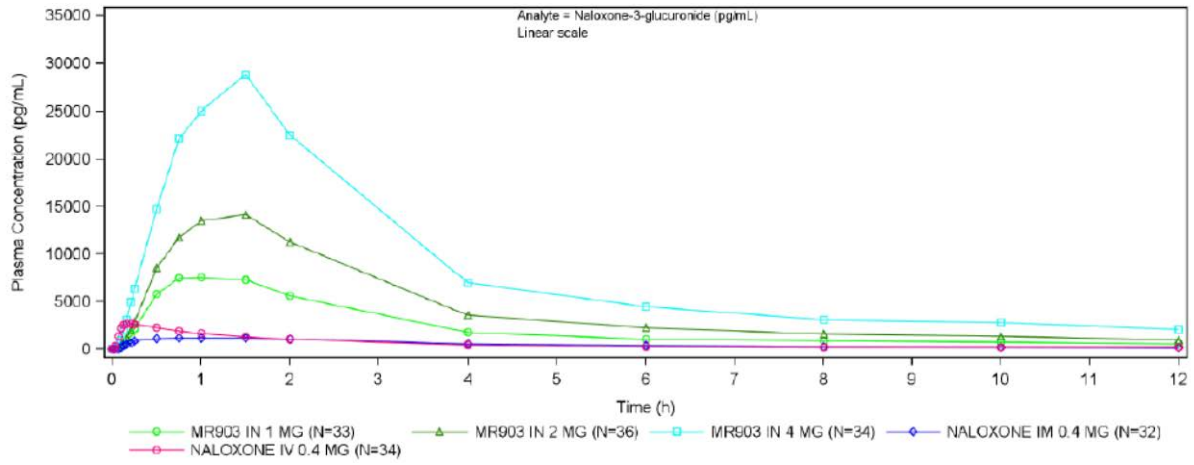


Figure 5. Mean Naloxone-3-glucuronide Plasma Concentration versus Time by Treatment



The following table presents the PK summary statistics for naloxone.

Table 5. Naloxone Summary Statistics of Plasma PK Parameters by Treatment

PK Parameter	Statistics	MR903 IN 1mg (N=33)	MR903 IN 2 mg (N=36)	MR903 IN 4 mg (N=34)	Naloxone IM 0.4 mg (N=32)	Naloxone IV 0.4 mg (N=34)
AUCt (pg*h/mL)	n (n*)	33 (33)	36 (36)	34 (34)	32 (32)	34 (34)
	Geometric Mean	2561.10	4858.94	10006.97	2005.65	2006.34
	CV (%)	43.2	39.4	35.8	17.7	22.5
	SD, SE	1179.596 , 205.341	2002.042 , 333.674	3450.464 , 591.750	353.572 , 62.503	443.792 , 76.110
	Median	2627.53	5345.30	9996.98	2064.50	1997.27
	Min, Max	1152.6, 5783.1	2334.8, 11227.5	3961.5, 21076.3	1307.2, 2915.9	998.1, 3122.6
AUCINF (pg*h/mL)	n	33	36	33	32	33
	Geometric Mean	2690.78	4965.00	10070.19	2118.03	2100.32
	CV (%)	40.5	38.5	35.8	16.6	21.1
	SD, SE	1165.692 , 202.921	2005.661 , 334.277	3490.884 , 607.685	348.690 , 61.640	431.419 , 75.100
	Median	2704.21	5413.59	9912.32	2160.19	2069.71
	Min, Max	1225.9, 5877.9	2438.5, 11345.8	4054.3, 21169.7	1374.9, 3046.5	1064.4, 3348.9
AUCp (pg*h/mL)	n	33	36	34	32	34
	Geometric Mean	51.78	109.82	265.94	114.00	440.24
	CV (%)	112.2	105.1	98.6	67.9	56.2
	SD, SE	51.737 , 9.006	121.720 , 20.287	297.452 , 51.013	67.551 , 11.941	235.056 , 40.312
	Median	56.69	112.59	324.51	135.94	441.16
	Min, Max	3.8, 205.0	13.6, 561.5	39.5, 1518.8	28.4, 279.5	73.9, 1120.1

PK Parameter	Statistics	MR903 IN 1mg (N=33)	MR903 IN 2 mg (N=36)	MR903 IN 4 mg (N=34)	Naloxone IM 0.4 mg (N=32)	Naloxone IV 0.4 mg (N=34)
Cmax (pg/mL)	n (n*)	33 (33)	36 (36)	34 (34)	32 (32)	34 (34)
	Geometric Mean	1512	2867	6019	1273	5943
	CV (%)	50.2	49.6	54.5	55.8	92.9
	SD, SE	706.13 , 122.92	1464.7 , 244.12	4030.2 , 691.17	571.58 , 101.04	5965.1 , 1023.0
	Median	1630	2880	6210	1465	5350
	Min, Max	423, 3490	1240, 7500	1720, 24600	347, 2380	1170, 21900
LambdaZ (h^{-1})	n	33	36	33	32	33
	Arithmetic Mean	0.5516	0.5300	0.4412	0.5349	0.5702
	SD, SE	0.11516 , 0.02005	0.11803 , 0.01967	0.12186 , 0.02121	0.10995 , 0.01944	0.09329 , 0.01624
	Median	0.5583	0.5223	0.4366	0.5419	0.5793
	Min, Max	0.266, 0.746	0.182, 0.771	0.280, 0.771	0.365, 0.839	0.405, 0.827
t1/2Z (h)	n	33	36	33	32	33
	Arithmetic Mean	1.329	1.405	1.692	1.347	1.248
	SD, SE	0.3765 , 0.0655	0.5078 , 0.0846	0.4690 , 0.0816	0.2651 , 0.0469	0.2100 , 0.0366
	Median	1.242	1.327	1.587	1.279	1.196
	Min, Max	0.93, 2.61	0.90, 3.81	0.90, 2.48	0.83, 1.90	0.84, 1.71
HVD (h)	n	33	36	34	32	34
	Arithmetic Mean	1.3173	1.2671	1.2461	1.0864	0.1292
	SD, SE	0.66335 , 0.11548	0.55432 , 0.09239	0.63846 , 0.10949	1.11845 , 0.19772	0.19194 , 0.03292
	Median	1.1371	1.2137	1.1842	0.5297	0.0543
	Min, Max	0.529, 3.623	0.387, 2.682	0.326, 2.633	0.201, 4.486	0.018, 1.053

PK Parameter	Statistics	MR903 IN 1mg (N=33)	MR903 IN 2 mg (N=36)	MR903 IN 4 mg (N=34)	Naloxone IM 0.4 mg (N=32)	Naloxone IV 0.4 mg (N=34)
t50 (h)	n	33	36	34	32	34
	Arithmetic Mean	0.1726	0.1560	0.1506	0.0659	0.0204
	SD, SE	0.07963 , 0.01386	0.07236 , 0.01206	0.08353 , 0.01433	0.02355 , 0.00416	0.01791 , 0.00307
	Median	0.1528	0.1372	0.1254	0.0595	0.0152
	Min, Max	0.069, 0.403	0.067, 0.341	0.059, 0.456	0.036, 0.150	0.009, 0.100
tmax (h)	n	33	36	34	32	34
	Arithmetic Mean	0.4464	0.4417	0.4150	0.2137	0.0439
	SD, SE	0.27562 , 0.04798	0.23224 , 0.03871	0.23640 , 0.04054	0.25786 , 0.04558	0.04170 , 0.00715
	Median	0.2539	0.5000	0.2518	0.1675	0.0347
	Min, Max	0.168, 1.000	0.135, 1.000	0.168, 1.000	0.067, 1.500	0.018, 0.251
tcan (h)	n	0	0	0	0	34
	Arithmetic Mean					0.0255
	SD, SE					0.01247 , 0.00214
	Median					0.0167
	Min, Max					0.000, 0.050
tmax+tcan (h)	n	0	0	0	0	34
	Arithmetic Mean					0.0694
	SD, SE					0.04292 , 0.00736
	Median					0.0521
	Min, Max					0.018, 0.268

Statistical results on the bioavailability of treatments with respect to naloxone are displayed in the Table below (primary PK parameters dose adjusted):

Table 6. Naloxone bioavailability comparison

Parameter	Treatment group	N	n	Ratio (%) (Test/Reference)	90% CI of Ratio
AUCt/D (pg.h/mL)	NALOXONE IM 0.4 MG	32	32	98.84	(92.55, 105.55)
	NALOXONE IV 0.4 MG*	34	32		
	MR903 IN 1 MG	33	33	106.06	(94.80, 118.66)
	MR903 IN 2 MG*	36	33		
	MR903 IN 4 MG	34	33	102.71	(90.07, 117.11)
	MR903 IN 2 MG*	36	33		
AUCp/D (pg.h/mL)	NALOXONE IM 0.4 MG	32	32	25.30	(19.77, 32.38)
	NALOXONE IV 0.4 MG*	34	32		
	MR903 IN 1 MG	33	33	93.19	(74.97, 115.84)
	MR903 IN 2 MG*	36	33		
	MR903 IN 4 MG	34	33	124.68	(88.68, 175.28)
	MR903 IN 2 MG*	36	33		
Cmax/D (pg.h/mL)	NALOXONE IM 0.4 MG	32	32	21.08	(15.76, 28.20)
	NALOXONE IV 0.4 MG*	34	32		
	MR903 IN 1 MG	33	33	107.00	(92.15, 124.25)
	MR903 IN 2 MG*	36	33		

The parameter for the early partial exposure (AUCp) was based on the AUC measured up to the median tmax of the IM reference, which was 0.1675 hours. When the AUCp was compared between the IN and IM reference treatment, the 2 mg IN demonstrated very similar exposure with a bioavailability ratio of 98.07%,

90% CI ranged from 73.15% to 131.48%. For the 1 mg and 4 mg IN treatments the ratios were 46.09% and 266.58% respectively, reflecting the differences in administered IN doses.

Considering the overall exposure, the comparative dose-adjusted AUCt ratio of 50.81% for the IN 1 mg to the IM 0.4 mg reference is supportive of the assumption of a 2:1 availability ratio (IN:IM) between the two routes of administration. The non-dose-adjusted ratio was 127.04% and for the IN 2 mg 235.42%. For the highest IN dose the overall exposure ratio to IM was 483.39%. Bioavailability ratios for the IN treatments relative to IV 0.4 mg were similar to when the IM was used as reference, at 125.56%, 234.20% and 481.07% for the ascending doses. The dose adjusted bioavailabilities of the IN treatments compared with the IM treatment ranged from 47.08% (for the IN 2 mg) to 50.81% (for the IN 1 mg). Likewise, the dose-adjusted absolute bioavailability results using the IV as reference ranged from 46.84% (for the IN 2 mg) to 50.22% (for the IN 1 mg).

Cmax ratios ranged from 121.77% to 491.27% for the IN treatments compared with the IM reference and, when adjusted for dose, from 45.05% for the IN 2 mg to 49.13% for the IN 4 mg. When compared with the IV reference, Cmax ratios ranged from 25.67% to 99.13% and dose adjusted Cmax ratios ranged from 9.30% for the IN 2 mg to 10.27% for the IN 1 mg.

Exploratory analysis comparing AUCt for the IV and IM treatments demonstrated overall exposure to be similar, with a bioavailability ratio of 98.84%. The IN doses were also shown to be dose proportional, with an AUC ratio of 106.06% for the 1 mg compared with 2 mg and 102.71% for the 4 mg compared with 2 mg and 90% CIs falling within 80 to 125%.

The partial areas were roughly comparable between the IN 1 and 2 mg when adjusted for dose, with a ratio of 93.19%, but dose-adjusted exposure was slightly higher for the 4 mg dose, with a bioavailability ratio of 124.68% compared with the IN 2mg. Dose-adjusted Cmax ratios were similar for the 1 mg and 4 mg IN doses compared with the 2 mg at 107% and 106.58%.

HVD was shortest from the IV 0.4 mg at 0.1292 h, followed by the IM 0.4 mg at 1.0864 and was longest for the IN treatments at 1.2461, 1.2671 and 1.3173 hours for the IN 4 mg, 2 mg and 1 mg treatments respectively.

Naloxone-3-glucuronide to naloxone ratios were similar across the three intranasal treatments at 11.23, 11.27 and 10.48 for the 1 mg, 2 mg and 4 mg dose levels respectively. Ratios for the IM and IV treatments were also similar, 3.062 for the IM and 3.333 for the IV.

2.3.3. Pharmacodynamics

Mechanism of action

No PD data has been produced by the Applicant.

Naloxone is a μ-opioid competitive antagonist. It has an affinity for the μ-opioid receptor and works by competing with other relevant drugs for a space on the receptor. Due to its ability to compete and control the specific opioid receptors, naloxone can reverse the effects (e.g. respiratory depression) that were caused by heroin (or another opioid) by preventing heroin metabolites from exercising influence on the receptor's normal functioning. Reversal is a fairly rapid event at the μ-opioid receptor, and partly at the δ-opioid receptor, the main instigators of respiratory depression in opioid consumption.

2.3.4. Discussion on clinical pharmacology

The aim of the biopharmaceutical development program was to develop an intranasal naloxone formulation that was accessible and easy to administer by non-healthcare professionals in a life-threatening situation. Nyxoid has been tested in one pivotal bioavailability study, MR903-1501, which examined three IN dose strengths alongside IM and IV reference treatments, with the aim of matching MR903 to the early exposure from the standard of care IM 0.4 mg dose.

The bioavailability for all the MR903 doses was around 50%, higher than what is described in some literature for this route of administration (4%). This may be due to the much higher concentration of the formulation, reducing the swallowing of the naloxone. The intended dose is not formally bioequivalent to the reference IM 0.4mg dosage. Cmax and AUC are substantially higher (roughly equivalent to a 1 mg IM for the 2 mg IN dose). However, early partial AUC are similar. Early concentrations from 0-6 minutes are also generally similar between the IM 0.4 mg and IN 2 mg naloxone.

Studies were conducted in healthy non-drug using subjects. In drug abusers, there can be nose mucosal differences from the general population and the applicant provided an extensive discussion on this topic. Several alterations exist that may impact the absorption of IN naloxone, such as vasoconstriction or non-allergic rhinitis which may indeed influence the rate and extent of absorption.

With regards to the absorption area reduction, typically the area of septic perforation constitutes around 8% of the total available area for absorption, which indicates that this is of no major concern. As the applicant acknowledged, there may be an impact of rate and extent of absorption on IN Naloxone for the patients that may not be fully characterized by studying the PK of IN naloxone in healthy subjects. However, septum perforations occur in a small number of subjects in the target population and there is an increasing amount of literature evidence that IN naloxone is of use in the intended patient population. In addition, given the significantly higher systemic availability of 2 mg Nyxoid versus the 0.4 mg i.m. reference product, this is not likely to result in lack of effect.

Regarding the recommended administration in the supine position, this was also the position used in the PK study and similar to what is expected to be the most common position of the patients suffering from an overdose.

The Applicant has not performed any *in vivo* pharmacodynamic studies to support the intranasal administration, arguing that the delivery by intranasal route is anticipated to be similar to the pharmacodynamic profile established following IV and IM administration. However, the proof of concept was not provided under conditions in which naloxone is clinically administrated: respiratory depression and the consequent pulmonary oedema. Under these conditions, the mixture of pulmonary oedema fluids and air in the lungs increases as the respirations and heartbeat slow down, exuding from the mouth and nostrils as a characteristic “foam cone”.

The occurrence of a foam cone may result in diminished absorption of intranasal administered naloxone due to drug running from the nose together with the foam cone as well as due to hypertrophy of the mucosa. As a result of the significantly higher systemic availability of intranasal administered Nyxoid 2 mg compared to the 0.4 mg intramuscular administered naloxone reference product, it could potentially still result in clinically effective systemic availability depending on the extent of the foam cone.

Clearing the nares and removing the foam cone prior to intranasal administration of Nyxoid may potentially limit the diminished contact time with the mucosa and increase the efficacy of Nyxoid. Therefore, it is

recommended to inspect and clear the nasal airway immediately prior to administration. The SmPC has been updated to reflect this recommendation in section 4.2.

No multiple dose studies were presented. Instead, repeated administration of the 2 mg IN dose have been simulated using the data from MR903-1501 and the principle of superposition in order to demonstrate the likely plasma profiles following subsequent doses of IN and IM naloxone. The plasma profile of the 2 doses, separated by 3 minutes apart is not much different from the single 4mg dose profile in study MR903-1501. It is also clear that that the titration that is possible to be obtained with the IM administration is not at all viable with the current IN formulation. However, it can be considered that the obtained profiles is inside the expected profiles in reversal of acute opioid overdose for the IM route of administration.

2.3.5. Conclusions on clinical pharmacology

The presented clinical pharmacology data is sufficient to support this application.

2.4. Clinical efficacy

Literature review

The Applicant did not perform any efficacy studies but referred to data available for the reference product. Moreover, the efficacy of THN and IN naloxone has been established in a number of published studies which are listed below.

Table 7. Published Efficacy Data

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Barton *et al.* (2005)	Efficacy	NLX IN, 2mg; followed by NLX IV if needed	n=95	open-label	6 months	52 patients responded to NLX, 43 patients (83%) to IN versus 9 patients (17%) to IV	Barton, E. D. et al. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. J. Emerg. Med. 29, 265–271 (2005).
Kelly *et al.* (2005)	Efficacy	NLX IN, 2mg	n=84	open-label, randomised	2 years	The IM group had more rapid response than the IN group, and were more likely to have more than 10 spontaneous respirations per minute within 8 minutes (82% vs 63%; p=.0173). No statistically significant difference between the IM and IN groups for needing rescue naloxone (13% IM vs 26%	Kelly, A. M. *et al.* Randomised trial of intranasal versus intramuscular

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
		NLX IM, 2mg	n=71			IN, P=.0558. No major adverse events. IN naloxone was sufficient to reverse opiate toxicity in 74%. *IN Naloxone NOT as effective as IM naloxone.*	naloxone in pre-hospital treatment for suspected opioid overdose. *Med. J. Aust.* 182, 24–27 (2005).
Beltz *et al.* (2006)	Efficacy	NLX IV (66%); IV+IM (17%); IM (11%): IN (1%); IM+IN (.5%)	n=164	Retrospective review of series of emergency treated opioid overdose	1 year	There were 75 patients (46%) initially unresponsive to painful stimulus. Respiratory rate was <10 breaths/min in 79 (48%). Death occurred in 36 (22%) at the scene or during trans- port. A full or partial response to naloxone occurred in 119 (73%). Recognized adverse reactions were limited to agitation / combativeness in 25 (15%) and emesis in six (4%). Aver- age EMT arrival time was 5.9 minutes. Average paramedic arrival time was 11.6 minutes in most cases and 16.1 minutes in 46 cases (28%) in which paramedics were requested by EMTs at the scene. *No particular data on IN formulation*	Belz, D., Lieb, J., Rea, T. & Eisenberg, M. S. Naloxone use in a tiered-response emergency medical services system. Prehospital Emerg. Care 10, 468–471 (2006).

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Robertson *et al.*	Efficacy	NLX IV	n=100	Retrospective review of series of emergency treated opioid overdose	17 months	Clinical response was noted in 33 (66%) and 58 (56%) of the IN and IV groups, respectively (p = 0.3). The mean time between naloxone administration and clinical response was longer for the IN group (12.9 vs. 8.1 min, p = 0.02). However, the mean times from patient contact to clinical response were not significantly different between the IN and IV groups (20.3 vs. 20.7 min, p = 0.9). More patients in the IN group received two doses of naloxone (34% vs. 18%, p = 0.05), and three patients in the IN group received a subsequent dose of IV or IM naloxone.	Robertson, T. M., Hendey, G. W., Stroh, G. & Shalit, M. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. *Prehospital Emerg. Care* 13, 512–515 (2009).
		(2009) NLX IN	n=50				
Kerr *et al.* (2009)	Efficacy	NLX IM, 2mg	n=89	Open-label, randomised	29 months	Rates of response within 10 minutes were similar: i.n. naloxone (60/83, 72.3%) compared with i.m. naloxone (69/89, 77.5%) [difference: -5.2%, 95% confidence interval (CI) -18.2 to 7.7]. No difference was observed in mean response time (i.n.: 8.0, i.m.: 7.9 minutes; difference 0.1, 95% CI -1.3 to 1.5). Supplementary naloxone was	Kerr, D., Kelly, A. M., Dietze, P., Jolley, D. & Barger, B. Randomized controlled trial comparing the effectiveness

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
		NLX IN, 2mg	n=83			administered to fewer patients who received i.m. naloxone (i.n.: 18.1%; i.m.: 4.5%) (difference: 13.6%, 95% CI 4.2–22.9)	and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction 104, 2067–2074 (2009). ACTRN: 12606000322538
Merlin *et al.* (2010)	Efficacy	NLX IV	n=55	Retrospective review of series of emergency treated opioid overdose	3 years	Of confirmed opioid overdoses, change in RR was 6 for the IV group and 4 for the IN group (P = .08). Change in GCS was 4 for the IV group and 3 for the IN group (P = .19). Correlations between RR and GCS for initial, final, and change were significant at the 0.01 level (ρ = 0.577, 0.462, 0.568, respectively).	Merlin, M. A. et al. Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. Am. J. Emerg. Med. 28, 296–303 (2010).
		NLS IN	n=38				
Sabzghabaee *et*	Efficacy	NLX IV, 0.4mg	n=50	Open-label, randomised, phase II	3 months	Patients who had been administered IN naloxone demonstrated significantly higher levels of consciousness than those in the IV	Sabzghabaee, A. M., Eizadi-Mood, N.,

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
al. (2014)		NLX IN, 0.4mg	n=50			group using both descriptive and GCS scales (p < 0.001). There was a significant difference in the heart rate between IN and IV groups (p = 0.003). However, blood pressure, respiratory rate and arterial O2 saturation were not significantly different between the two groups after naloxone administration (p = 0.18, p = 0.17, p = 0.32). There was also no significant difference in the length of hospital stay between the two groups (p = 0.14).	Yaraghi, A. & Zandifar, S. Naloxone therapy in opioid overdose patients: Intranasal or intravenous? A randomized clinical trial. Arch. Med. Sci. 10, 309–314 (2014). https://clinicaltrials.gov/show/NCT01293058
Krieter *et al.* (2016)	Pharmacokinetics	NLX IN, 2mg, single dose, one nostril	n=29	Open-label, randomised, 5-period, 5-treatment, 5-sequence, crossover, phase I	3 months	The present study compared the pharmacokinetic properties of intranasal naloxone (2 to 8 mg) delivered in low volumes (0.1 to 0.2 mL) using an Aptar Unit-Dose device to an approved (0.4 mg) intramuscular dose. A parallel study assessed the ease of use of this device in a simulated overdose situation. All doses of intranasal naloxone resulted in plasma concentrations and areas under the curve greater than those observed following the intramuscular dose; the time to reach	Krieter, P. *et al.* Pharmacokinetic Properties and Human Use Characteristics of an FDA Approved Intranasal Naloxone Product for the
		NLX IN, 4mg, single dose, each nostril	n=29				

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
		NLX IN, 4mg, single dose, one nostril	n=29			maximum plasma concentrations was not different following intranasal and intramuscular administration. Plasma concentrations of naloxone were dose proportional between 2 and 8 mg and independent of whether drug was administered to 1 or both nostrils. In a study using individuals representative of the general population,>90% were able to perform both critical tasks (inserting nozzle into a nostril and pressing plunger) needed to deliver a simulated dose of naloxone without prior training. Based on both pharmacokinetic and human use studies, a 4-mg dose delivered in a single device (0.1 mL) was selected as the final product.	Treatment of Opioid Overdose. *J. Clin. Pharmacol.* (2016). doi:10.1002/jcph.759 https://clinicaltrials.gov/show/NCT02572089
		NLX IN, 8mg, single dose, each nostril	n=29				
		NLX IM, 0.4mg	n=29				
Dettmer *et al.* (2001)	Efficacy of THN	NLX IM	not stated	Report of Berlin and Jersey Take-Home NLX Projects	not stated	The first published report of lives saved directly by the provision of take home naloxone. The drug was generally used appropriately. In only one case out of 34 was its use inappropriate, with two of doubtful benefit. No unexpected adverse effects were reported.	Dettmer, K., Saunders, B. & Strang, J. Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes. *Bmj* 322, 895–896 (2001).

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Doe-Simkins *et al.* (2009)	Efficacy of THN	NLX IN	n=385	Report of Boston Take-Home NLX Project	15 months	After 15 months, the program provided training and intranasal naloxone to 385 participants who reported 74 successful overdose reversals. Problems with intranasal naloxone were uncommon. Overdose prevention education with distribution of intranasal naloxone is a feasible public health intervention to address opioid overdose.	Doe-Simkins, M., Walley, A. Y., Epstein, A. & Moyer, P. Saved by the nose: Bystander-administered intranasal naloxone hydrochloride for opioid overdose. *Am. J. Public Health* 99, 788–791 (2009).

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Strang *et al.* (2013)	Efficacy of THN	NLX	N/A	Pilot Phase of N-ALIVE trial	N/A	The naloxone investigation (N-ALIVE) randomized trial commenced in the UK in May 2012, with the preliminary phase involving 5,600 prisoners on release. The trial is investigating whether heroin overdose deaths post-prison release can be prevented by prior provision of a take-home emergency supply of naloxone. The subsequent full N-ALIVE trial (contingent on a successful pilot) will involve 56,000 prisoners on release, and will give a definitive conclusion on lives saved in real-world application.	Strang, J., Bird, S. M. & Parmar, M. K. B. Take-home emergency naloxone to prevent heroin overdose deaths after prison release: Rationale and practicalities for the N-ALIVE randomized trial. J. Urban Heal. 90, 983–996 (2013).

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Bird *et al.* (2015)	Efficacy of THN	NLX	N/A	Protocol for Scotland's Public Health Policy Evaluation	N/A	Evidence-synthesis of prospectively monitored small-scale THN schemes led to a performance indicator for distribution of THN-kits relative to opiate-related deaths. Next, we explain the primary outcome and statistical power for Scotland's before/after monitoring. Results: Fatality-rate at opiate overdoses witnessed by THN- trainees was 6% (9/153, 95% CI: 2–11%). National THN-schemes should aim to issue 20 times as many THN-kits as there are opiate-related deaths per annum; and at least nine times as many. Primary outcome for evaluating Scotland's THN policy is reduction in the percentage of all opiate-related deaths with prison-release as a 4-week antecedent. Scotland's baseline period is 2006–10, giving a denominator of 1970 opiate-related deaths. A priori plausible effectiveness was 20–30% reduction, relative to baseline, in the proportion of opiate-related deaths that had prison-release as a 4-week antecedent. A secondary outcome was also defined.	Bird, S. M., Parmar, M. K. B. & Strang, J. Take-home naloxone to prevent fatalities from opiate-overdose: Protocol for Scotland's public health policy evaluation, and a new measure to assess impact. Drugs Educ. Prev. Policy 22, 66–76 (2015).

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Dwyer *et al.* (2015)	Efficacy of THN and overdose education (OE+THN vs OE)	NLX	N=415	Survey	14 months	A total of 415 ED patients received OE or OEN between January 1, 2011 and February 28, 2012. Among those, 51 (12%) completed the survey; 37 (73%) of those received a naloxone kit, and 14 (27%) received OE only. Past 30-day opioid use was reported by 35% OEN and 36% OE, and an overdose was reported by 19% OEN and 29% OE. Among 53% (27/51) of participants who witnessed another individual experiencing an overdose, 95% OEN and 88% OE stayed with victim, 74% OEN and 38% OE called 911, 26% OEN and 25% OE performed rescue breathing, and 32% OEN (n=6) used a naloxone kit to reverse the overdose. We did not detect statistically significant differences between OEN and OE-only groups in opioid use, overdose or response to a witnessed overdose.	Dwyer, K. et al. Opioid Education and Nasal Naloxone Rescue Kits in the Emergency Department. West. J. Emerg. Med. 16, 381–384 (2015).

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Strang *et al.* (2015)	NLX efficacy.	NLX IN; SL; BC	N/A	Systematic Review	N/A	Methods: A three-stage analysis of candidate routes of administration was conducted: (1) Assessment of all 112 routes of administration identified by FDA against exclusion criteria. (2) Scrutiny of empirical data for identified candidate routes, searching PubMed and WHO International Clinical Trials Registry Platform using search terms "naloxone AND [route of administration]". (3) Examination of routes for feasibility and against the inclusion criteria. Results: Only three routes of administration met inclusion criteria: nasal, sublingual and buccal. Products are currently in development and being studied. Pharmacokinetic data exist only for nasal naloxone, for which product development is more advanced, and one concentrated nasal spray was granted licence in the US in 2015. However, buccal naloxone may also be viable and may have different characteristics. Conclusion:	Strang, J. et al. Naloxone without the needle - systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal. Drug Alcohol Depend. (2015). doi:10.1016/j.drugalcdep.2016.02.042

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Strang *et al.*, editor (2015)	Efficacy of THN	NLX IM; IN	N/A	Systematic Review EMCDDA	N/A	Systematic review of the available studies on take-home naloxone to reverse opioid overdose and included 21 studies for analysis (with various study designs). There is evidence from one interrupted time-series study, involving 2 912 opioid users at risk of overdose in 19 communities followed up for seven years, that educational and training interventions complemented by take-home naloxone decrease overdose-related mortality. There is weaker, but consistent, evidence that similar interventions for opioid-dependent patients and their peers effectively improve knowledge while forming positive attitudes to the correct use of naloxone and the management of witnessed overdoses.	EMCDDA. Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone. (2015).

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Strang *et al.* (2016)	Aims: To consider provision of improvised nasal naloxone in clinical practice; to search for evidence for pharmacokinetics and effectiveness (versus injection).	NLX IN	N/A	Systematic Review	N/A	Methods (1) To document existing nasal naloxone schemes and published evidence of pharmacokinetics (systematic search of the CINAHL, Cochrane, EMBASE and MEDLINE databases and 18 records included in narrative synthesis). (2) To analyse ongoing studies investigating nasal naloxone (WHO International Clinical Trials Registry Platform and USNIH RePORT databases). Results: (1) Multiple studies report overdose reversals following administration of improvised intranasal naloxone. (2) Overdose reversal after nasal naloxone is frequent but may not always occur. (3) Until late 2015, the only commercially available naloxone concentrations were 0.4mg/ml and 2 mg/2 ml. Nasal medications are typically 0.05–0.25 ml of fluid per nostril. The only published study of pharmacokinetics and bioavailability finds that nasal naloxone has poor bioavailability. Questions	Strang, J., McDonald, R., Tas, B. & Day, E. Clinical provision of improvised nasal naloxone without experimental testing and without regulatory approval: imaginative shortcut or dangerous bypass of essential safety procedures? Addiction 574–582 (2016). doi:10.1111/add.13209
Strang et al., editor (2016)	Efficacy of THN	NLX IM; IN	N/A	Guidelines EMCDDA	N/A	Comprehensive Presentation of current knowledge around THN and its use so far.	EMCDDA. Preventing opioid overdose deaths with take home naloxone. (2016).

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Walley *et al.* (2013)	To evaluate the impact of state supported overdose education and nasal naloxone distribution (OEND) programs on rates of opioid related death from overdose	N/A	N/A	Interrupted time series analysis year strata with high and low rates of OEND implementation to those with no implementation	Self-report: IN (327); interrupted time-series analysis	Among these communities, OEND programs trained 2912 potential bystanders who reported 327 rescues. Both community-year strata with 1-100 enrolments per 100 000 population (adjusted rate ratio 0.73, 95% confidence interval 0.57 to 0.91) and community-year strata with greater than 100 enrolments per 100 000 population (0.54, 0.39 to 0.76) had significantly reduced adjusted rate ratios compared with communities with no implementation. Differences in rates of acute care hospital utilization were not significant.	Walley A.Y et al., Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ, 2013; 346 doi: 10.1136/bmj.f174

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Weber *et al.* (2012)	Safety and efficacy of nebulised naloxone	N/A	N/A	Retrospective analysis	N/A	Out of 129 cases, 105 met the inclusion criteria. Of these, 23 (22%) had complete response, 62 (59%) had partial response, and 20 (19%) had no response. Eleven cases (10%) received rescue naloxone, no case required assisted ventilation, and no adverse events occurred. The kappa score was 0.993. Conclusion: nebulised naloxone is a safe and effective needleless alternative for prehospital treatment of suspected opioid overdose in patients with spontaneous respirations	Weber J.M et al., Can nebulised naloxone be used safely and effectively by emergency medical services for suspected opioid overdose? Prehospital emergency care. April/June 2012 Volume 16 Number 2 doi: 10.3109/10903127.2011.640763

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Rando *et al.* (2015)	Efficacy of IN administration by police	N/A	247 eligible for study inclusion	Prospective intervention study	January 2011 – October 2014	Of the 67 participants who received naloxone by police officers, 52 (77.6%) survived, and 8 (11.9%) were lost to follow-up. In conclusion, this study showed that intranasal naloxone administration by police first responders is associated with decreased death rates of opioid overdose victims	Rando J. et al., Intranasal naloxone administration by police first responders is associated with decreased opioid overdose deaths. American Journal of Emergency Medicine 33 (2015) 1201-1204 DOI: http://dx.doi.org/10.1016/j.ajem.2015.05.022

Author (date)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Clark *et al.* (2014)	Effectively of literature on community-based opioid overdose prevention programs (OOPPs)	n/a	19 articles met the criteria	Systemic review	n/a	Non-randomised studies suggests that bystanders (mostly opioid users) can and will use naloxone to reverse opioid overdoses when properly trained, and that this training can be done successfully through OOPPs	Clark A.K et al., A systemic review of community opioid overdose prevention and naloxone distribution programs. J Addict Med. Volume 8, 2014 DOI: 10.1097/ADM.0000000000000034

Abbreviations: IN = intranasal, IV = intravenous, IM = intramuscular.

Summary of key literature

Take Home Naloxone

The concept of 'take-home naloxone' (THN), initiated by Strang et al. (1992; 1993) in the 1990s, is now well accepted and large initiatives have emerged quickly over recent years in various regions of the world. Globally, there is increasing introduction of pre-provision of an emergency supply of naloxone (to heroin users themselves, their family and friends, and also to people who work with those at risk of opioid overdose), which is an approach advocated by the United Nations and World Health Organisation.

Prenoxad® (an IM injection kit) is now approved for emergency use in a non-medical setting in several European countries, although currently only available in the UK. There are, however, some barriers to use of the injectable medication:

- Some people do not feel comfortable performing an injection, or fear needle-stick injuries in this high-risk patient population for blood-borne diseases (Open Society Public Health Program, Public Health Fact Sheet, 4th Nov 2012).
- Furthermore, injectable naloxone requires a certain level of skill and training in order to ensure successful administration by non-health care professionals.

Based on the rationale that more opioid-overdose deaths could be prevented if people who witness overdoses recognised the danger in which the victims are and were able to administer the overdose-reversal drug, 'take-home' naloxone programmes have been developed to increase the availability of the antidote in places where overdoses are especially likely to occur. Under these programmes, an emergency supply of naloxone is given out, together with instructions about its administration, to drug users and their close friends, partners and families, as well as other individuals likely to witness overdoses, so that, in the event of an opioid overdose, naloxone is readily available and can be administered to the overdose victim before the arrival of an ambulance.

Maxwell et al., 2006

The first US-based THN programme in Chicago reported 319 overdose reversals between 2001 and 2006 (Maxwell et al., 2006). The authors stated that a steady increase in heroin overdose deaths was noticed since 1991, with a four-fold increase between 1996 and 2000. This trend reversed in 2001 when the THN programme was initiated, with a 20% decrease in 2001 and 10% decreases in 2002 and 2003.

EMCDDA, 2016

The first programmes in the United States and Europe began distributing naloxone in 1996 and a report on outcomes in European sites — Berlin, Germany, and Jersey, Channel Islands — was published in 2001 (Dettmer et al., 2001). Further naloxone initiatives in Europe have been implemented in Catalonia (Spain), Denmark, Estonia, Italy and Norway. A number of other European countries are currently considering THN initiatives to prevent drug-related deaths (EMCDDA, 2016).

EMCDDA, 2015b

Evidence about naloxone programmes has grown. Since 2005, several studies have been published addressing different aspects of these programmes. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) recently reviewed the effectiveness of education and training interventions complemented by take-home naloxone, including 21 studies, and found evidence that these programmes decrease overdose-related mortality (EMCDDA, 2015b).

In January 2011, Scotland introduced THN as a funded public health policy. The Scottish National Naloxone Programme (SNNP) gives naloxone kits to people at high risk of heroin overdose both in the community and on release from prison. Since the start of the programme, the number of heroin-related deaths within four weeks of prison release has fallen each year. Wales announced a similar intention for a THN programme in May 2011 after a one year demonstration project. In England the N-ALIVE trial commenced in prisons in May 2012. (Strang et al., 2013). It was a large prison-based randomised controlled trial designed to test the effectiveness of giving naloxone-on-release to prisoners with history of heroin use, to prevent fatal opiate overdoses. Prisoners taking part in the trial were randomly assigned either to treatment-as-usual or to treatment-as-usual plus a supply of take-home emergency naloxone. The preliminary phase involved 5,600 prisoners on release and was completed in 2015.

Bird et al. 2015

A publication by Bird et al. (2015) summarises the background and rigorous set-up for before/after monitoring to assess the impact on high-risk opiate-fatalities. Evidence-synthesis of prospectively monitored small-scale THN schemes led to a performance indicator for distribution of THN-kits relative to opiate-related deaths. They found that the fatality-rate at opiate overdoses witnessed by THN trainees was 6% (9/153, 95% CI: 2–11%). Based on their findings, Bird and colleagues determined that, for THN to be available at every witnessed opiate-overdose, a national THN-policy should aim to issue to at-risk clients around 20 times as many (and at the least, nine times as many) THN-kits as there are opiate-related deaths (ORDs) per annum.

Dettmer et al., 2001

Early implementation pilots provided the first data on the safety of THN provision. In the first published Europe-based THN pilot, conducted in Berlin (Germany) and in Jersey (Channel Islands), the researchers (Dettmer et al., 2001) reported 34 peer rescues from overdose in Berlin and found naloxone administration to be inappropriate in only one case (a cocaine overdose). All overdose victims were successfully revived. No increased use of heroin or occurrence of adverse effects (other than withdrawal symptoms) was observed. Among the five overdose reversals reported in Jersey, none involved adverse events. This study was the first published report of lives saved directly by the provision of THN The range of doses given raises the possibility that naloxone was being titrated to effect resuscitation without provoking withdrawal. The authors concluded that in future, family members may be trained to give emergency naloxone, and for them non-intravenous administration would be more realistic.

Doe-Simkins et al., 2009

Expanded access to naloxone for home use has occurred to date, by prescribing IM naloxone or by off-label use of naloxone injection by combining a prefilled syringe with a mucosal atomisation device for intranasal spraying. A publication by Doe-Simkins et al., (2009) describes how, in August 2006, the Boston Public Health Commission (BPHC) passed a public health regulation that authorised an opioid overdose prevention program that included IN naloxone education and distribution of the IN spray to potential bystanders of patients experiencing opioid overdose. Participants were taught by trained non-medical needle exchange staff. Over 15 months, the program provided training and IN naloxone to 385 potential bystanders, who reported 74 successful overdose reversals. Problems with IN naloxone were uncommon. The BPHC naloxone distribution program demonstrates that overdose prevention education with distribution of IN naloxone is a feasible public health intervention to address opioid overdose. The Massachusetts Department of Public Health has identified overdose prevention as a major focus area for new public health initiatives and has

expanded the program to 5 additional sites that target needle exchange participants, staff at substance abuse treatment programs, homeless shelters, and families and friends of opioid users.

Dwyer and colleagues, 2015

Emergency departments (EDs) may be effective (high-yield) venues for addressing numbers of opioid deaths if they combine education about overdose prevention with education on appropriate actions in a witnessed overdose. In addition, the ED has the potential to equip patients with nasal naloxone kits as part of this effort. In view of this, Dwyer and colleagues (2015) evaluated the feasibility of an ED-based overdose prevention program and described the overdose risk knowledge, opioid use, overdoses, and overdose responses among participants who received overdose education and naloxone rescue kits (OEN) and participants who received overdose education only (OE). Program participants were surveyed by telephone after their ED visit about their substance use, overdose risk knowledge, history of witnessed and personal overdoses, and actions in a witnessed overdose including use of naloxone.

A total of 415 ED patients received OE or OEN between January 1, 2011 and February 28, 2012. Among those, 51/415 (12%) completed the survey; 37/415 (73%) of those received a naloxone kit, and 14/415 (27%) received OE only. Past 30-day opioid use was reported by 35% OEN and 36% OE, and an overdose was reported by 19% OEN and 29% OE. Among 27/51 (53%) of participants who witnessed another individual experiencing an overdose, 95% OEN and 88% OE stayed with victim, 74% OEN and 38% OE called 911, 26% OEN and 25% OE performed rescue breathing, and 32% OEN (n=6) used a naloxone kit to reverse the overdose. Furthermore, the researchers did not detect statistically significant differences between OEN and OE-only groups in opioid use, overdose or response to a witnessed overdose.

Walley et al., 2013a

Walley et al. (2013a) conducted an interrupted time series analysis of opioid-related overdose death and acute care utilisation rates from 2002 to 2009, comparing community-year strata with high and low rates of Overdose Education and Naloxone Distribution (OEND) implementation to those with no implementation. The study included the 19 Massachusetts communities (geographically distinct cities and towns) with at least five fatal opioid overdoses in each of the years 2004 to 2006. The OEND programs were implemented among opioid users at risk for overdose, social service agency staff, family, and friends of opioid users. The OEND programs equipped people at risk for overdose and bystanders with IN naloxone rescue kits and trained them how to prevent, recognize, and respond to an overdose by engaging emergency medical services, providing rescue breathing, and delivering naloxone. Among these communities, OEND programs trained 2912 potential bystanders who reported 327 rescues. Both community-year strata with 1-100 enrolments per 100 000 population (adjusted rate ratio 0.73, 95% confidence interval 0.57 to 0.91) and community-year strata with greater than 100 enrolments per 100 000 population (0.54, 0.39 to 0.76) had significantly reduced adjusted rate ratios compared with communities with no implementation. Differences in rates of acute care hospital utilisation were not significant.

No deaths were reported. Of 327 rescue attempts using naloxone reported by 212 individuals, 87% (286/327) were reported by users. Most rescue attempts occurred in private settings. Naloxone was successful in 98% (150/153) of the rescues attempts. For the three rescue attempts where naloxone was not successful, the people who overdosed received care from the emergency medical system and survived. In conclusion, opioid overdose death rates were reduced in communities where OEND was implemented. This study provides observational evidence that by training potential bystanders to prevent, recognise, and respond to opioid overdoses, OEND is an effective intervention (Walley et al, 2013a).

Clark and colleagues, 2014

Clark and colleagues (2014), conducted a systematic review which describes the current state of the literature on community-based opioid overdose prevention programs (OOPPs), with particular focus on the effectiveness of these programs. The authors used systematic search criteria to identify relevant articles, which were abstracted and assigned a quality assessment score. Nineteen articles evaluating OOPPs met the search criteria for this systematic review. Principal findings included participant demographics, the number of naloxone administrations, percentage of survival in overdose victims receiving naloxone, postnaloxone administration outcome measures, OOPP characteristics, changes in knowledge pertaining to overdose responses, and barriers to naloxone administration during overdose responses. The current evidence from non-randomised studies suggests that bystanders (mostly opioid users) can and will use naloxone to reverse opioid overdoses when properly trained, and that this training can be done successfully through OOPPs (Clark et al, 2014).

IN naloxone

Barton et al., 2005

In the US, Narcan as an initial injectable formulation was commonly used in patients suffering from a suspected opioid overdose. These patients often have limited peripheral venous access, making the intranasal route potentially very advantageous. Barton et al. (2005), investigated the use of improvised IN Narcan by paramedics to assess its efficacy and safety as an alternative (needleless) medication delivery route in pre-hospital settings. They conducted a study using a prospective, non-randomised trial over a 6-month period, in which IN naloxone was administered by paramedics to patients with suspected opiate overdoses. All adult patients were encountered in the pre-hospital setting as altered mental status (AMS), 'found down' (FD) or suspected opiate overdose (OD), patients who met the criteria for naloxone administration and thus were included in the study. The standard protocol called for these patients to have an IV line placed and to receive IV naloxone (1-2 mg) based on the paramedic's assessment of a possible overdose. However, for this study protocol, the patients initially had 2 mg of intranasal naloxone administered using a disposable Mucosal Atomiser Device (MAD®). One mL of the 1 mg/mL naloxone solution was administered into each naris (by inserting the MAD® approximately ¼ to ½ inch), providing a total volume of 2 mL. Immediately after IN naloxone administration, the standard protocol (including airway management, IV line placement and IV medications) was followed. The standard protocol was discontinued only if the patient responded and no further treatment was required.

The main outcome measures were: times of initial patient encounter, IN naloxone administration, IV insertion, IV naloxone administration, and patient response. In addition, paramedics were asked to report any obvious abnormalities noted in the patient's nasal mucosa (such as bleeding, deformity, mucus, etc.) at the time of IN drug administration. The naloxone solution administered in the described study was less concentrated than the MR903 formulation and consequently a larger volume was administered than in MR903-1501 to achieve a 2 mg dose. It can be assumed, based on both historic published and in house data (Dowling et al 2008 and OXN1001), that the solution administered using MAD had a lower absolute bioavailability than MR903, and will therefore have resulted in lower plasma naloxone concentrations than those recorded for MR903 2 mg.

Ninety-five patients met the study criteria and thus received IN naloxone. Fifty-two of these patients responded to either IN or IV naloxone, with 43 (83%) responding to the IN naloxone alone, before the paramedics could administer the IV naloxone. Seven patients (16%) in the IN naloxone response group required additional doses of IV naloxone after initial response due to "recurrent somnolence" or "slow

response," whereas 36 patients (84%) required no further naloxone therapy. In conclusion, this study demonstrates the effectiveness of naloxone, and indicates that it delivered an 83% response rate when used intranasally. It is reasonable to expect that this response rate might increase for MR903 due to the anticipated superior bioavailability of MR903 compared with the MAD-administered product.

Merlin et al., 2010

Another study, conducted by Merlin et al. (2010) in the US, proposed that IN naloxone administration is preferable to IV naloxone when administered by emergency medical services for opioid overdoses. Merlin et al. performed this study using a retrospective chart review of pre-hospital advanced life support patients on confirmed opioid overdose patients. The intent of this study was to investigate whether IN naloxone was non-inferior when compared to IV naloxone in increasing respiratory rates (RR) and mental status in patients presenting with suspected opioid overdose in the pre-hospital setting. The primary outcome measures were changes in Glasgow Coma Scale (GCS) and unassisted RRs recorded by paramedics after administration of IN and IV naloxone. GCS and unassisted RRs were thus used as indicators of naloxone effectiveness. The median changes in RR and GCS were determined. Three hundred forty-four patients who received naloxone by paramedics from January 1, 2005, until December 31, 2007, were evaluated. Of the confirmed opioid overdoses, the change in RR was 6 for the IV group and 4 for the IN group (P = .08). Change in GCS was 4 for the IV group and 3 for the IN group (P = .19). Correlations between RR and GCS for initial, final, and change were significant at the 0.01 level (ρ = 0.577, 0.462, 0.568, respectively).

Table 8. Comparison of response to naloxone by route of administration

		Route of administration, median (95% CI[a])		Difference estimation (95% CI[a])	P of comparison[b]
		IV (n=55)	IN (n=38)		
RR, per min	Initial	10 (6-12)	10 (6-12)	0 (-2 to 4)	.60
	Final	18 (16-18)	16 (12-16)	4 (2 to 6)	.001
	change	6 (4-10)	4 (2-6)	2 (-0.001 to 5)	.08
GCS score	Initial	4 (3-9)	3 (3-6))	0 (0 to 1)	.37
	Final	15 (14-150	12 (8-14)	1 (0 to 3)	.01
	Change	4 (3-8)	3 (0-5)	1 (-0.001 to 3)	.19

[a] The confidence interval for the medium is slightly greater than 95%, as there is no assumption of distribution.

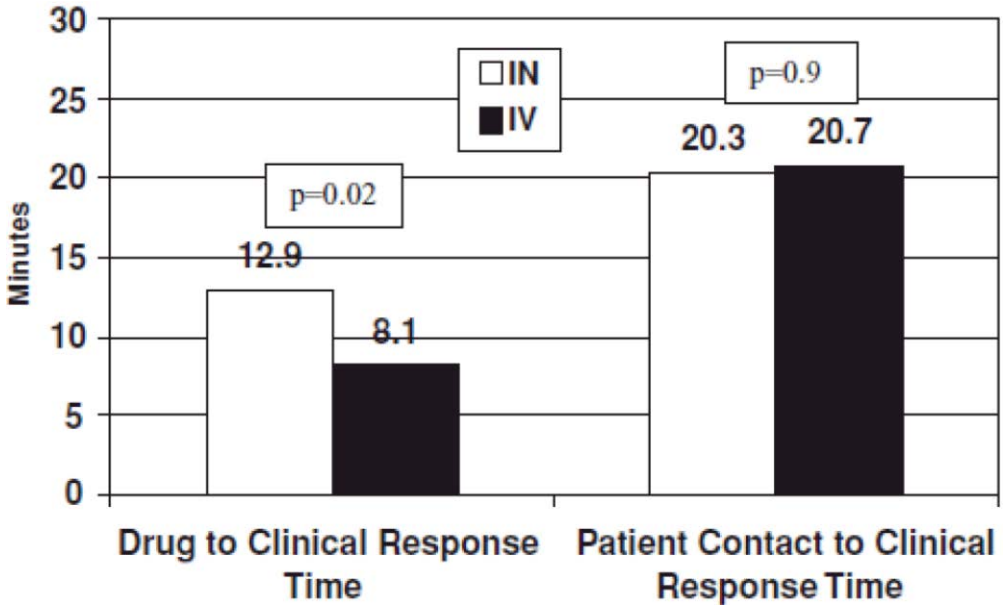
[b] By Wilcoxon rank sum test.

Merlin et al. (2010) concluded that IN naloxone is as effective as IV naloxone at reversing the central nervous system-depressing effects caused by opioids.

Robertson et al., 2009

Robertson et al. (2009), conducted a study to compare the IV and IN routes of naloxone administration with respect to the time from patient contact and medication administration to clinical effect in patients with suspected narcotic overdose. The researchers performed a retrospective review of emergency medical services (EMS) and hospital records, before and after implementation of a protocol for administration of intranasal naloxone by the Central California EMS Agency. Patients with suspected narcotic overdose treated in the pre-hospital setting over 17 months, between March 2003 and July 2004, were included in this study. Paramedics documented dose, route of administration, and positive response times using an electronic record. Clinical response was defined as an increase in RR (breaths/min) or GCS score of at least 6. Main outcome variables included time from medication to clinical response and time from patient contact to clinical response. Secondary variables included numbers of doses administered and rescue doses given by an alternate route. Between-group comparisons were accomplished using t-tests and chi-square tests as appropriate. One hundred fifty-four patients met the inclusion criteria, including 104 treated with IV and 50 treated with IN naloxone. A clinical response was noted in 33 (66%) and 58 (56%) of the patients in the IN and IV groups, respectively (p = 0.3). The mean time between naloxone administration and clinical response was longer for the IN group (12.9 vs. 8.1 min, p = 0.02). However, the mean times from patient contact to clinical response were not significantly different between the IN and IV groups (20.3 vs. 20.7 min, p = 0.9). This is shown in Figure 2. In the IN group, 17/50 patients were given a second dose of naloxone, while in the IV group 19/104 required a second dose (34% vs. 18%, p = 0.05), and three patients in the IN group received a subsequent dose of IV or IM naloxone.

Figure 6. Time intervals in minutes. IN = Intranasal; IV = intravenous



It was found that although IN naloxone had a slower onset of action than the IV route, the overall time from patient contact to clinical effect was the same. Intranasal naloxone represents a more gradual and potentially safer way to reverse the effects of opioid overdose. The researchers showed that intranasal naloxone is a useful alternative in patients with suspected narcotic overdose in the pre-hospital setting and it potentially offers a decreased risk to the EMS providers caring for patients with difficult IV access and a relatively high prevalence of blood-borne pathogens. It is important to note that in this study, IN naloxone was administered by EMS (EMT) providers. MR903 is intended to be used by anyone who may witness an overdose, such as

peers, friends and family of drug users. As such, it will also be able to be administered in the vital minutes immediately following an overdose, before EMS providers can arrive.

In relation to the post-hoc analysis of rate of naloxone absorption, the data reported by Robertson et al provide reassurance that there will be no clinically relevant difference in the onset of efficacy between IN and IM administration, especially with an IN formula of the appropriate concentration. The time from patient contact to administration of therapy for IM is unlikely to be as long as for IV administration, but is likely to be longer than for IN administration. The 5 minute difference reported here in the time from drug administration to clinical response was compensated for by the ease of IN administration. It is reasonable to assume that the ease of administration of IN would also compensate for the slight difference in the rate of naloxone absorption between IN and IM administration.

Beltz et al, 2006

Beltz et al (2006) conducted a study in the US to examine the delivery and effect of naloxone in 164 patients. Respiratory rate was < 10 breaths/min in 79 (48%). The most frequent initial dose of naloxone was 1mg (range 0.2 – 2 mg). Total doses administered ranged from 0.2 to 4 mg. Death occurred in 36 (22%) patients at the scene or during transport.A full or partial response to naloxone occurred in a total of 119 patients (73%). In terms of adverse reactions, naloxone-associated violence such as agitation/combativeness or vomiting, occurred in 25 cases (15%) and emesis was identified in six (4%). No violence occurred in 127 cases (77%) and it could not be determined whether violence occurred in 12 cases (7%). Average EMT arrival time was 5.9 minutes and the average paramedic arrival time was 11.6 minutes in most cases and 16.1 minutes. To conclude, no serious side effects of naloxone were recognised in this study. Training to manage the agitation and combativeness seen in 15% of cases is useful as part of any program training EMTs to administer naloxone. However, nasal administration compared with parenteral administration has been shown to have a lower incidence of agitation, possibly due to slower absorption (Barton et al, 2005). Therefore, it can be seen that simplicity, efficacy and safety, as well as the time factors associated with the arrival of EMTs and paramedics, can be improved with significantly earlier delivery of naloxone to patients in opioid overdose if EMTs (and others if those likely to witness an overdose could be enabled to deliver naloxone to save lives when opioid overdose is suspected, something that an IN naloxone formulation is more likely to achieve.

Sabzghabaee et al, 2014

Sabzghabaee et al (2014) conducted a randomized clinical trial study in the Department of Poisoning Emergencies at Noor and Ali Asghar (PBUH) University Hospital in Iran. This study was designed to compare the effects of IN and IV administration of naloxone in patients who had overdosed on opioids. One hundred opioid overdose patients were assigned by random allocation software into two study groups (n = 50). Both groups received 0.4 mg naloxone: one group IN (diluted down to a 2 ml nasal spray, 1ml per nostril0 and the other IV. The primary outcome measure included change in the level of consciousness (measured using a descriptive scale and the GCS). The secondary outcomes were time to response, vital signs (blood pressure, heart rate and respiratory rate), arterial blood oxygen (O2) saturation before and 5 minutes after naloxone administration, side-effects (e.g. agitation) and the duration of hospital stay. Patients who had been administered IN naloxone demonstrated significantly higher levels of consciousness than those in the IV group using both descriptive and GCS scales ($p < 0.001$). This can be seen in Table 5. This finding may be because of direct transportation of naloxone to the central nervous system across the olfactory mucosa. In addition, there was a significant difference in the heart rate between IN and IV groups ($p = 0.003$). However, blood pressure, respiratory rate and arterial O2 saturation were not significantly different between the two

groups after naloxone administration (p = 0.18, p = 0.17, p = 0.32). There was also no significant difference in the length of hospital stay between the two groups (p = 0.14).

Table 9. Level of consciousness in opioid overdose patients before and after naloxone administration

Level of consciousness	Before naloxone	After naloxone
Intranasal administration, n (%)		
Coma	12 (24)	0
Stupor	24 (48)	0
Obtundation	14 (28)	0
Lethargic	0	28 (56)
Conscious	0	22 (44)
Intravenous administration, n (%):		
Coma	10 (20)	0
Stupor	28 (56)	0
Obtundation	12 (24)	20 (40)
Lethargic	0	18 (36)
Conscious	0	12 (24)

In conclusion, this study shows that IN naloxone is as effective as IV naloxone in reversing both respiratory depression and the depressive effects on the central nervous system caused by opioid overdose. It is therefore suggested to use the IN route for administration of naloxone in opioid overdose patients to reverse clinical manifestations of overdose, with less severe withdrawal, especially in patients with a history of previous addiction.

Rando and colleagues, 2015

Rando and colleagues (2015) assessed IN naloxone administration by police first responders in the US. Data from 247 individuals were eligible for study inclusion. Opioid overdose deaths increased significantly before initiation of the police officer naloxone prescription programme (NPP) with average deaths per quarter of 5.5 for 2011, 15.3 for 2012, and 16.3 for the first 9 months of 2013. After initiation of the police officer NPP, the number of opioid overdose deaths decreased each quarter with an overall average of 13.4. Of the 67 participants who received naloxone by police officers, 52 (77.6%) survived, and 8 (11.9%) were lost to follow-up. In conclusion, this study showed that IN naloxone administration by police first responders is associated with decreased death rates of opioid overdose victims.

Weber and colleagues, 2012

Weber and colleagues (2012) conducted a study to determine whether nebulised naloxone can be used safely and effectively by prehospital providers for patients with suspected opioid overdose. The author performed a

retrospective analysis of all consecutive cases administered nebulised naloxone from January 1 to June 30, 2010, by the Chicago Fire Department. All clinical data were entered in real time into a structured EMS database and data abstraction was performed in a systematic manner. Included were cases of suspected opioid overdose, altered mental status, and respiratory depression; excluded were cases where nebulised naloxone was given for opioid-triggered asthma and cases with incomplete outcome data. The primary outcome was patient response to nebulised naloxone. Secondary outcomes included need for rescue naloxone (IV or IM), need for assisted ventilation, and adverse antidote events. Kappa interrater reliability was calculated and study data were analysed using descriptive statistics.

Out of 129 cases, 105 met the inclusion criteria. Of these, 23 (22%) had complete response, 62 (59%) had partial response, and 20 (19%) had no response. Eleven cases (10%) received rescue naloxone, no case required assisted ventilation, and no adverse events occurred. The kappa score was 0.993. It was concluded that nebulised naloxone is a safe and effective needleless alternative for prehospital treatment of suspected opioid overdose in patients with spontaneous respirations (Weber et al, 2012).

2.4.1. Discussion on clinical efficacy

The applicant has not performed any efficacy trials in the target population.

Efficacy is discussed based on:

a) the evidence that naloxone, when administered IM by HCP is efficacious in reverting respiratory depression (literature and Naloxon® data);

b) that a trial on healthy volunteers has shown similar PK parameters between IN and IM administration (Applicant data provided);

c) that IN administration is similarly effective (albeit no non inferiority or equivalence study has formally been performed) to IM or IV administration on opioid users when administered by HCP (literature);

d) THN programs have been effective in countries where they have been effectively implemented (literature);

e) lay persons and HCP preference to administer naloxone IN rather than IM (no comprehensive study to support this has been provided).

It is clear that naloxone is an effective mode of reverting opioid respiratory depression, with post marketing data available for about 30 years in Europe. Yet, its efficacy has been mainly demonstrated with the use of IM and IV administration by HCP in patients with CNS / respiratory depression either with illicit, accidental or clinical use of opioids.

IN route of administration of naloxone has been used to treat opioid induced respiratory depression with success by HCP, although available literature data is of poor quality, not allowing confirming non inferiority as compared to IM or IV route. There is insufficient evidence that opioid overdose patients respond similarly to IN administration of naloxone as they respond to other route of administration. This lack of evidence is due to: a) small sample sizes; b) differences in the amount of respiratory or CNS recovery magnitude (GCS 15 vs 12, smaller respiratory rate (Merlin et al., 2009); c) more frequent need to administer a second dose of naloxone (up to 2 to 4 times more frequent with IN administration than with IM or IV administration

(Robertson *et al*., 2009, Kerr *et al.,* 2009), making it more risky to be left with no more naloxone to revert a repeated respiratory depression when the first treatment of naloxone wears off).

THN programmes have shown that lives have been saved with the use of IM naloxone kits, to be administered by observers of respiratory depressed patients who are known users of opioids. These programmes are strongly dependent on the education of lay persons to administer the product.

The Applicant has provided a PK study, which provided data on the Cmax / Tmax, showing that in normotensive non opioid treated healthy volunteers 2 mg of IN naloxone is similar in achieving Tmax and Cmax as compared to 0,4 mg of IM naloxone. However, no clinical non-inferiority study has been performed to prove that the efficacy of the IN route is equivalent to that of the IM route.

Data has also not been provided to confirm that lay persons can be acquainted with the device and mode of administration of Nyxoid, as compared to the THN programmes with IM naloxone, which results in further uncertainty over the proper utilisation in the real world setting.

To address these concerns, the Applicant has agreed to establish a training program for patients and carers and to perform a PAES to provide information on real-world use of Nyxoid.

Dosing recommendations cannot be extrapolated between adults and younger children. In addition, the device is not appropriate to be used in small (child) nostrils. Consequently, the indication needs to be limited to patients aged 14 years old and over.

2.4.2. Conclusions on the clinical efficacy

The Applicant has provided a set of data with literature evidence of efficacy of IM naloxone in opioid overdose with respiratory depression, both when administered by HCP and when administered by lay people who have undergone dedicated educational programs.

The applicant has also provided PK data to support naloxone use of IN as compared to IM route in healthy volunteers, and literature data to support the use of IN naloxone administered by HCP in opioid overdose to revert respiratory depression.

The CHMP considers the following measures necessary to address issues related to efficacy:

The Applicant will establish a training program, specifying that the training and supply of educational material for patients and carers will be conducted by Health Care Professionals (HCPs) in the health care setting relevant for individual countries.

The Applicant will conduct a PAES to investigate the effectiveness of Nyxoid in the real-life conditions of use.

2.5. Clinical safety

This application is supported by safety data from the PK studies and literature review. No patients have been exposed to Nyxoid.

The safety of intranasal naloxone has been established in a large number of published studies which are listed below.

Table 10. Published Safety Data Supporting Intranasal Naloxone

Author (or code)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Kelly et al. (2005)	Pharmacokinetics, Safety	NLX IN, 2mg NLX IM, 2mg	n=84 n=71	A single-centre, open-label, randomized, 4-way crossover, phase 1	up to 45 days	There were no major adverse events. For patients treated with IN naloxone, this was sufficient to reverse opiate toxicity in 74%.	Kelly, A. M. *et al.* Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *Med. J. Aust.* 182, 24–27 (2005).
Kerr et al. 2009	Effectiveness and safety	2 mg/ml IN naloxone 2 mg/ml IM naloxone	n=89 n=83	open-label, randomised	29 months	A total of 172 patients were enrolled into the study. Median age was 29 years and 74% were male. Rates of response within 10 minutes were similar: i.n. naloxone (60/83, 72.3%) compared with i.m. naloxone (69/89, 77.5%) [difference: -5.2%, 95% confidence interval (CI) -18.2 to 7.7]. No difference was observed in mean response time (i.n.: 8.0, i.m.: 7.9 minutes; difference 0.1, 95% CI -1.3 to 1.5). Supplementary naloxone was administered to fewer patients who received i.m. naloxone (i.n.: 18.1%;	Kerr, D., Kelly, A. M., 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 104, 2067–2074 (2009). ACTRN: 12606000322538

Author (or code)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
						i.m.: 4.5%) (difference: 13.6%, 95% CI 4.2–22.9)	
Middleton et al. (2011)	Effectively and safety	Compared IN doses of buprenorphine and naloxone [crushed buprenorphine (2 mg and 8 mg), crushed buprenorphine/naloxone (2/0.5 mg and 8/2 mg)] with an IV dose (0.8 mg buprenorphine/0.2 mg naloxone)	n=10	A randomised, double-blind, placebo-controlled, cross-over study.	3 weeks	No serious adverse events occurred. Side effects reported/observed after active drug administration included vomiting during (n = 4) and after (n = 5) a test session, constipation (n = 5) and headache during (n = 4; three during an active drug session and one after placebo) and after (n = 7; five after an active drug session and two after placebo) a test session. One subject reported blurry vision during session after an active dose.	Middleton L.S et a. The pharmacodynamic and pharmacokinetic profile of intranasal crushed buprenorphine and buprenorphine/naloxone tablets in opioid abusers. Addiction,(2011) 106, 1460-1473 doi:10.1111/j.1360-0443.2011.03424.x
Belz et al. (2006)	Effectively and safety	n/a	n=164	Case series of all (EMS)-treated cases of opioid overdose,in which naloxone	N/A	Naloxone-associated violence, such as agitation, combativeness, or vomiting, occurred in 25 cases (15%). No violence occurred in 127 cases (77%), and it could not be determined whether violence occurred in 12 cases (7%). The 25 cases associated with post-treatment violence were made up	Belz D. Et al. Naloxone use in a tierd-response emergency medical services system. (2006), Volume 10 Number 4

Author (or code)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
				was administered by paramedics during 2004		of agitation/combativeness in 21 cases (13%) and vomiting in six cases (4%). In all cases of vomiting, the patient was either alert post-treatment or had an intact gagreflex documented.	doi: 10.1080/10903120600885134
Sabzghabae et al, (2014)	Effectivity and safety	0.4 mg IN naloxone: one 0.4 mg IV naloxone	N=100	This randomised trial study		The study design focused particularly on agitation as a side effect, with 12 patients in the IV group, but no patient in the IN group, observed to become agitated after naloxone administration, initially of 0.4 mg naloxone diluted down to a 2 mL nasal spray (1 mL into each nostril) or dose of 0.4 mg IV by bolus, with further dose after 5 minutes if patient had failed to respond	Sabzghabaee A.M et al. Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomised clinical trial
Kim et al. (2009)	Safety and efficacy	n/a	n/a	Pilot programms	n/a	Complications such as seizures and arrhythmia have been reported after naloxone administration on very rare occasions. However, their links to naloxone have been questioned in the medical literature, and, even if there is a connection, it constitutes a risk only for patients with pre-existing heart disease	Kim D. et al., Expanded access to nalozone: option for critical response to the epidemic of opioid overdose mortality. American Journal of Public health (2009) Vol 99, No.3

Author (or code)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Beletsky et al. (2012)	Prevention and safety	n/a	n/a	Manuscript	n/a	The absence of naloxone formulations for non-injectable administration may actually be limiting its use by laypersons and presents a twofold barrier. On a clinical level, a layperson who witnesses an overdose may be less likely to intervene and administer an injection for fear of needle-stick injury or due to lacking familiarity with needle-and-syringe assembly	Beletsky L et al. Prevention of fatal opioid overdose. JAMA. (2012) 14;308*18): 1863-1864 doi:10.1001/jama.2012.14205.
Krieter et al. (2016)	Pharmacokinetics	NLX IN, 2mg, single dose, one nostril NLX IN, 4mg, single dose, each nostril NLX IN, 4mg, single dose, one nostril NLX IN, 8mg, single dose, each nostril NLX IM, 0.4mg	N= 29 N=29 N=29 N=29 N=29	open-label, randomised, 5-period, 5-treatment, 5-sequence, crossover, phase I	3 months	There were no differences in the safety profile of IN naloxone compared to IM dosing. No significant erythema, edema, erosion, or other signs were observed in the nasal cavity prior to or after administration of IN naloxone. Few adverse events (AEs) associated with the nasalmucosa were reported; all were mild (grade 1), transient, and with no clear relationship to dose. Vital signs, ECG, and clinical laboratory parameters did not reveal any clinically significant changes or evidence of QTcF prolongation after naloxone administration. Two additional AEs were reported with IN	Krieter, P. *et al.* Pharmacokinetic Properties and Human Use Characteristics of an FDA Approved Intranasal Naloxone Product for the Treatment of Opioid Overdose. *J. Clin. Pharmacol.* (2016). doi:10.1002/jcph.759

Author (or code)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
						administration: 1 for nasal pain after the 2-mg dose and 1 for headache after the 8-mg dose. Based on the selectivity of naloxone for opiate receptors and the human use characteristics described here, this product can be used safely with no prior training to provide an important and potentially life-saving intervention for the treatment of opioid overdose.	
Doe Simkins et al. (2012)	Efficacy and safety of NLX	NLX IN	N=385	Report of Take home NLX project	15 months	The first US-based take-home naloxone programme in Chicago reported 319 overdose reversals between 2001 and 2006 (Maxwell et al., 2006). Adverse events included one death and two cases of severe adverse reactions; however, the latter were likely to have been associated with polydrug use. A recent evaluation of the Massachusetts-based take-home naloxone programme reported that average heroin use in the previous 30 days among a subsample of programme participants (n = 325) who participated in a pre–post survey was not affected by naloxone availability	Doe-Simkins, M., Walley, A. Y., Epstein, A. & Moyer, P. Saved by the nose: Bystander-administered intranasal naloxone hydrochloride for opioid overdose. *Am. J. Public Health* 99, 788–791 (2009).

Author (or code)	Focus	Formulation	Population	Design	Duration	Main Findings	Full Citation
Rando et al., (2015)	Naloxone prescriptio n programme (police officers)	n/a	N=247	Prospective intervention study	2011-2014	The study found that intranasal naloxone administration by police first responders is associated with decreased deaths in opioid overdose victims, with limited safety issues. It is also noted that there is more general uptake and willingness to carry and administer naloxone where an alternative administration route to injecting is available including police.	Rando J. et al. Intranasal nalocone administration by police first responders is associated with decreased opioid overdose deaths. American Journal of Emergency Medicine 33 (2015) 1201-1204 http://dx.doi.org/10.1016/j.ajem.2015.05.022

Key studies conducted with IN formulation are summarised below.

Kelly et al, 2005

Kelly and colleagues (2005) conducted a prospective, randomised unblinded study comparing 2 mg IM naloxone with 2 mg/5 ml IN naloxone given by a mucosal atomiser. A total of 182 patients were enrolled, of whom 155 were evaluable. The patients ranged in age from13–57 years (average 28 years) and 72% were male. The primary outcome measure was the response time, defined as the time to regain a respiratory rate greater than 10 per minute. Secondary outcomes were the proportion of patients with respiratory rate greater than 10 per minute at 8 minutes, the proportion of patients with GCS score greater than 11 to 8 minutes, the proportion requiring rescue naloxone, and the rate of adverse events.

Patients who received IM naloxone responded faster than the IN group with respect to time until respirations greater than 10 per minute (mean of 6 minutes [95% CI, 5-7 min] to response for IM versus mean of 8 minutes [95% CI, 7-8 minutes] to response for IN, p = 0.006). Time to Glasgow Coma Scale greater than 11 was not significantly different.

There were no major adverse events for either group, but those who received IM naloxone were more likely to experience a minor adverse effect of treatment than those who received IN treatment (21% for the IM group v 12% for the IN group; P = 0.1818). The difference in agitation/irritation between the groups was particularly notable (13% for the IM group v 2% for the IN group; P = 0.0278). Sixty-two of the 84 patients allocated to the IN group (74%) did not require additional therapy. Adverse events (described as mild) are listed in Table below.

Table 11. Adverse Events after Naloxone 2 mg by intramuscular (IM) or intranasal (IN) routes

Adverse Event	No. in intramuscular naloxone group	No. intranasal naloxone group
Agitation and/or irritation	10	2
Nausea and/or vomiting	4	6
Headache	2	0
Tremor	1	1
Sweating	0	1

Kerr and colleagues, 2009

In a follow up to the study by Kelly and colleagues (2005), Kerr and colleagues (2009) compared safety and effectiveness of a specially prepared concentrated naloxone formulation (2 mg/ml) given via the IN versus IM routes in a randomized, controlled, open-label trial. The primary outcome was the proportion of patients who responded within 10 minutes of naloxone administration. Response was defined as effective and spontaneous respirations at a rate of ≥ 10 per minute and/or GCS ≥ 13. Patients who received a supplementary dose were classified automatically as not achieving an adequate response within 10 minutes. This endpoint was chosen to be consistent with current ambulance practice guidelines, where secondary naloxone is recommended for inadequate response after a 10-minute period. Secondary outcomes included time to adequate response, hospitalization, adverse event rate and requirement for 'rescue' naloxone due to inadequate primary response as judged by the treating paramedics. Adverse events were grouped into three categories including drug related (vomiting, nausea, seizure, sweating, tremor, acute pulmonary oedema, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, cardiac arrest, agitation and paraesthesia), administration-related (nasal obstruction, nasal deformity) and study-related (epistaxis, ruptured septum, spitting, coughing, leakage of solution from nasal passages).

A total of 172 patients were enrolled into the study with suspected of heroin overdose were treated by emergency medical personnel: 83 received 1 mg/0.5 ml into each nostril (2 mg total) and 89 patients received 2 mg/ml IM naloxone. The median age was 29 years, and 74% were male. Minor adverse events were similar between the two groups (IN: 19.3%, IM.: 19.1%; difference 0.2% 95% CI -11.6, 11.9), as were hospitalisation rates (IN: 28.9%, IM: 25.8%; difference 3.1% 95% CI -10.3, 16.4). No difference was

observed in agitation and/or violence (IN.: 6.0%, IM: 7.9%), nausea and/or vomiting (IN: 8.4%, IM: 7.9%) and headache (IN: 4.8%, IM: 3.3%) after naloxone treatment.

Krieter and colleagues, 2016

Krieter and colleagues (2016) compared the pharmacokinetic properties of intranasal naloxone (2 to 8 mg) delivered in low volumes (0.1 to 0.2 mL) using an Aptar Unit-Dose device to an approved (0.4 mg) intramuscular dose. There were no differences in the safety profile of IN naloxone compared to IM dosing. No significant erythema, edema, erosion, or other signs were observed in the nasal cavity prior to or after administration of IN naloxone. Few adverse events (AEs) associated with the nasalmucosa were reported; all were mild (grade 1), transient, and with no clear relationship to dose. Vital signs, ECG, and clinical laboratory parameters did not reveal any clinically significant changes or evidence of QTcF prolongation after naloxone administration. Two additional AEs were reported with IN administration: 1 for nasal pain after the 2-mg dose and 1 for headache after the 8-mg dose.

Table 12. Nasal Mucosal Adverse Events Following IN Naloxone

Treatment	Erythema[a]	Edema[b]	Other[a,b]	Total[a]
20 mg (20 mg/mL, 1 spray)	3	3	1	7
4 mg (20 mg/mL, 2 sprays)	1	1	0	1
4 mg (40 mg/mL, 1 spray)	1	1	0	3
8 mg (40 mg/mL, 2 sprays)	0	0	0	1

[a] All AEs were grade 1.

[b] Nasal pain.

Middleton et al, 2011

Middleton and colleagues (2011), reported no SAEs during a clinical study in opioid abusers that compared IN doses of buprenorphine and naloxone [crushed buprenorphine (2 mg and 8 mg), crushed buprenorphine/naloxone (2/0.5 mg and 8/2 mg)] with an IV dose (0.8 mg buprenorphine/0.2 mg naloxone) (Middleton et al, 2011). Side effects included constipation, vomiting, and headache. One subject reported blurry vision after an active dose. Thus in conclusion, the formulations were safely tolerated with minimum effects on oxygen saturation and respiratory rate (Middleton et al, 2011).

Sabzghabaee et al, 2014

Sabzghabaee and colleagues (2014) conducted a randomised clinical trial to compare the effects of IN and IV administration of naloxone in patients who had overdosed on opioids. The study design focused particularly on agitation as a side effect, with 12 patients in the IV group, but no patient in the IN group, observed to become agitated after naloxone administration, initially of 0.4 mg naloxone diluted down to a 2 mL nasal spray (1 mL into each nostril) or dose of 0.4 mg IV by bolus, with further dose after 5 minutes if patient had failed to respond (Sabzghabaee et al, 2014).

Belz et al, 2006

In 2006, Belz and colleagues, retrospectively reviewed case reports of 164 patients who received naloxone. These included 2 patients who received solely IN naloxone and one patient who received IN and IM naloxone. Other routes of administration included solely IM naloxone (18 patients) solely IV naloxone (108 patients)

and a combination of IM and IV naloxone (29 patients). The total naloxone dose ranged from 0.2 to 4 mg. Adverse reactions were limited to agitation/combativeness in 25 patients (15%) and emesis in 6 patients (4%).

2.5.1. Discussion on clinical safety

In an opioid overdose, the primary cause of a fatal outcome is respiratory depression and the resulting cardiac arrest. There are numerous risk factors influencing the likelihood of an overdose, including, but not limited to, the type of opioid, its strength, the amount that is absorbed into the blood and the recipient ADME status. Indeed individual factors, such as tolerance, current health status, duration of use and genetic influences, among others, add to the intricacy and complexity surrounding opioid overdose.

Widespread use of naloxone allows concluding that it is a generally safe and effective antidote especially for the respiratory-depressant effects of heroin and other opioids. It works best in reversing the effects of a heroin or morphine overdose, but, depending on dose and route of administration, it also works to reverse respiratory depression caused by other opioids, including methadone. The short duration of action of naloxone means that repeated doses may be required for full effectiveness at reversing respiratory depression.

Since the applicant has not provided a single study of intranasal naloxone, but has committed to produce a PAES in a real-world setting in EU MS, the study will also produce safety data that will mitigate the lack of information for the use of this formulation in the planned population.

2.5.2. Conclusions on the clinical safety

The applicant has provided published literature data on safety of naloxone, administered via various routes and in a range of doses. Given the well-known safety profile of naloxone, the presented evidence has been found to be sufficient.

The CHMP considers the following measures necessary to address issues related to safety:

The Applicant has committed to conduct a PAES that will also provide safety data in a real-world setting in EU.

The frequency of PSUR has been agreed to be every 6 months.

2.6. Risk Management Plan

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 reactions Decreased response due to impaired nasal mucosa

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies in the Pharmacovigilance Plan.

Risk minimisation measures

Safety Concern	**Routine Risk Minimization Measures**	**Additional Risk Minimization Measures**
Important Identified Risks		
Recurrence of respiratory depression	Wording in EU SmPC section 4.4, 4.7; PL section 2,3 Quick Start Guide (QSG) in the back of the blister	Patient information card to ensure awareness of signs and symptoms suggestive for respiratory depression
Precipitation of acute opioid withdrawal effects	Wording in EU SmPC section 4.4, 4.6, 4.8; PL section 2, 4 QSG in the back of the blister	Patient information card to ensure awareness of signs and symptoms suggestive for withdrawal effects
Important Potential Risks		

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Lack of efficacy due to medication errors	Wording in EU SmPC section 4.2; PL section 3 QSG will detail the method of administration	Patient information card to ensure awareness of the method of administration of Nyxoid
Missing Information		
Pregnancy and breast feeding	Wording in EU SmPC section 4.6; PL section 2	Not applicable
Use in elderly patients	Not applicable	Not applicable
Use in patients with hepatic impairment	Not applicable	Not applicable
Use in patients with renal impairment	Not applicable	Not applicable
Administration site reactions	Not applicable	Not applicable
Decreased response due to impaired nasal mucosa	Wording in EU SmPC section 4.4	Not applicable

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Based on the new form of administration, the CHMP is of the opinion that a separate entry in the EURD list for Nyxoid is needed, as it cannot follow the already existing entry for naloxone. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Naloxone is a medicinal product which is globally approved for the partial or complete reversal of opioid overdose. Injectable naloxone administered by the IV or IM route in doses from 0.4 mg to 2 mg is currently the standard treatment for opioid overdose.

3.1.2. Available therapies and unmet medical need

Naloxone became standard clinical practice in opioid overdose treatment more than three decades ago, having been discovered in the early 1960s and then approved as an opioid antagonist for IV, IM and SC administration in the 1970s. The clinical efficacy of naloxone in reversing opioid overdose has been demonstrated in numerous studies (Belz et al. 2006, Barton et al. 2002; Barton et al. 2005; Merlin et al. 2010; Robinson 2014) by showing a high proportion (82%) of patients achieve successful reversal of opioid overdose. In 2014 the WHO strongly recommended that naloxone should be available to people likely to witness opioid overdose (WHO, 2014). In many parts of the world, naloxone is already available for overdose treatment in a pre-hospital setting, including the EU, USA, Canada, Australia (EMCDDA, 2014). The first US-based take-home naloxone programme in Chicago reported 319 overdose reversals between 2001 and 2006 (Maxwell et al 2006). The author stated that a steady increase in heroin overdose deaths was noticed since 1991, with a fourfold increase between 1996 and 2000. This trend reversed in 2001 when take-home naloxone programme was initiated, with a 20% decrease in 2001 and 10% decreases in 2002 and 2003.

As an example, the distribution of naloxone in the UK for use by non-medically trained administers was suggested as early as 1992 as a potentially life-saving intervention (Strang & Farrell, 1992; Strang, 1993). Several THN schemes have now occurred in the UK. In Wales THN kits are available to all individuals at risk of opioid poisoning (Public Health Wales, 2015), and have reportedly been used successfully in 632 overdose cases since 2009. According to data from the Office for National Statistics published on 3rd of September 2015, the number of deaths from drug misuse in Wales has decreased by 16% on the previous year, with a total of 113 deaths. This continues a downward trend observed over the last five years, and since 2008 deaths from drug misuse have decreased by 30 per cent. Bennett et al have recommended that THN programmes are rolled out nationwide and have highlighted the value of naloxone in these circumstances as reliable, effective and safe (Bennett & Holloway, 2011). The provision of emergency take-home IM naloxone kits in Scotland for just 3 years has already substantially reduced deaths in the high risk group of recently

released ex-prisoners. In 2012 and 2013, the percentage of opioid-related deaths occurring four weeks of prison release (5.5% and 4.7%, respectively) was lower than when compared to the 2006-10 Baseline Indicator (9.8%) (NHS Scotland, 2014). A large-scale randomised trial of take-home IM naloxone N-ALIVE study provided to prisoners on their release in the UK recently completed the pilot phase after recruitment of 1,685 subjects (Strang, personal communication Aug 2015). The use of naloxone for overdose treatment in a pre-hospital setting is now endorsed by UK clinical guidelines (Dept. of Health England and devolved administrations, 2007).

In January 2015, EMCDDA published a systematic review of the effectiveness of these THN programmes which combine the distribution of naloxone kits with overdose education and training interventions (EMCDDA, 2015b). Relevant outcomes were: overdose-related knowledge; naloxone-related attitudes; naloxone use during witnessed overdose; naloxone induced adverse events; and overdose deaths. A total of 21 studies (1 RCT, 3 case-series, 17 pre-post studies) were identified, included in the analysis and evaluated, using a qualitative synthesis method. Results of the analysis showed that educational and training interventions with provision of THN decrease overdose-related mortality. Naloxone was used in a median of 67% of overdose witnessed (self-reported data of those returning for naloxone refills), and adverse events beyond naloxone-induced withdrawal symptoms were rare (≤ 13% cases of vomiting, ≤ 9% agitation, ≤ 1% seizures).

Increased availability of naloxone take-home antidote has not been shown to encourage people to use opioids more dangerously (Bazazi et al, 2010), in fact providing take-home kits has been shown to almost halve opioid related deaths from 9.8% in 2006-2010 to 4.7% in 2013 (NHS National Services Scotland, 2014).

Prenoxad (an IM injection kit) is now approved in the UK for emergency use in a non-medical setting. There are, however, some barriers to use of the injectable medication. Some people do not feel comfortable performing an injection, or fear needle-stick injuries in this high-risk patient population for blood-borne diseases. (Open Society Public Health Program, Public Health Fact Sheet, 4 Nov 2012) An injectable naloxone requires a certain level of skill and training in order to ensure successful administration by non-health care professionals. An intranasal formulation could facilitate an effective administration by non-health care professionals and could remove possible fear for needle stick injuries. A study among 99 injecting drug users in Melbourne, Australia found that three quarters (74%) would prefer IN naloxone to other administration methods, including IM or IV (Kerr et al., 2008). The higher concentration IM formulation containing 1 mg/mL naloxone is currently being used in ambulance care with an improvised IN atomiser (off-label) by some medical and trained professionals (NHS Highland, 2012).

3.1.3. Main clinical studies

There have been no efficacy or safety trials conducted with intranasal naloxone. Instead, the Applicant referred to efficacy of the reference product and published literature. The pivotal bridging bioavailability study, MR903-1501 examined three IN dose strengths alongside IM and IV reference treatments, with the aim of matching MR903 to the early exposure from the standard of care IM 0.4 mg dose.

3.2. Favourable effects

The main benefit of naloxone is the reversion of the opioid induced CNS / respiratory depression. Naloxone has been shown to revert respiratory depression when administered via IM, IV or IN route.

In study MR903-1501 the bioavailability for all the MR903 doses was around 50%, higher than what was described in some literature for intranasal administration for different formulations. Cmax and AUC were

substantially higher (roughly equivalent to a 1 mg IM for the 2 mg IN dose). Early concentrations from 0-6 minutes are also generally similar between the IM 0.4 mg and IN 2 mg naloxone, thus demonstrating sufficient plasma levels of naloxone can be achieved following IN administration.

The summary of literature has also demonstrated that IN naloxone can be an effective treatment in reversing respiratory depression in patients suffering an opioid overdose.

3.3. Uncertainties and limitations about favourable effects

Although there is evidence that naloxone IN is a good agent to revert respiratory depression in opioid overdose, there is a number of uncertainties regarding the proposed IN formulation: Nyxoid has only be studied in healthy subjects. The literature data has limitations and features IN formulations of different concentrations. Nevertheless, it suggests that the magnitude of effect on reversal of respiratory depression may be slightly lower than the injectable routes with which no clinical non-inferiority study has been performed. In addition, the number of responders to the first administration was lower with IN route and the need for a second naloxone administration has been shown to be up to 4x higher for some IN formulations.

Data has also not been provided to confirm that lay persons can be acquainted with the device and mode of administration of Nyxoid, as compared to the THN programmes with IM naloxone, which results in further uncertainty over the proper utilisation in the real world setting.

3.4. Unfavourable effects

As observed for the reference medicinal product, the most common adverse drug reaction seen with naloxone administration is nausea. Typical opioid withdrawal syndrome may be caused by the abrupt withdrawal of opioid in persons physically dependent on them.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile of naloxone is widely known. A single administration like the proposed indication is devoid of long-term or chronic effects. Uncertainties are therefore few.

The cultural and social setting of illicit opioid use may lead to the use of Nyxoid as a punishing agent, inducing opioid withdrawal syndrome in chronic opioid users if administered in non CNS depressed patients (e.g. by the illegal drug dealers). To decrease this risk, this product should be subject to controlled distribution.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Favourable effects are clear for the drug substance. The Applicant has also provided literature data supporting the intranasal administration and a PK study to demonstrate that naloxone plasma levels following Nyxoid administration are comparable to standard of care IM injection, hence bridging to efficacy data from the reference IM formulation.

Unfavourable effects are of much less magnitude. Adverse event profile of naloxone is well known. The risk of illicit use of IN naloxone can be managed by controlled distribution.

3.6.2. Balance of benefits and risks

Widespread use of naloxone allows concluding that it is a safe and effective antidote for the respiratory-depressant effects of heroin and other opioids. The short duration of action of naloxone means that repeated doses may be required for full effectiveness at reversing respiratory depression.

Administration of drugs by standard conventional routes (intravenous, intramuscular and subcutaneous) to populations such as injecting drug users carries some risk. Injecting drug users are often infected with blood-borne viruses such as human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV), and in spite of best practice guidelines designed to minimise needle-stick injury among health workers, needle-stick injuries occur, allowing for the possibility of blood-borne virus transmission. Among health care workers, 4% of HIV infections and 40% of HBV and HCV infections occur after occupational exposure. The benefits of incorporating intranasal naloxone for opioid overdose, include ease of access, rapid reversal of opioid overdose in high risk patients with a good overall effectiveness and safety and thus reduced needle-stick injury risk and the potential for peer and non-health professional administration.

The absence of naloxone formulations for non-injectable administration may be limiting its use by laypersons. On a clinical level, a layperson who witnesses an overdose may be less likely to intervene and administer an injection for fear of needle-stick injury or due to lacking familiarity with needle-and-syringe assembly. Therefore, availability of intranasal formulation has potential to address these concerns.

The ease of administration needs to be balanced by sufficient evidence that it will produce at least the same efficacious response in respiratory depressed patients due to opioid overdose when administered by lay people and HCPs. Otherwise, this new product could falsely give the impression that it is at least as good as the alternatives available in the market, but require needle use. Most people are expected to prefer a non-invasive procedure when there is evidence that the non-invasive procedure is as good as the invasive one. As such there might be patients whose death would be avoided if they had been administered IM naloxone instead of IN naloxone.

To address this uncertainty, the Applicant will establish a training program, specifying that the training and supply of educational material for patients and carers will be conducted by Health Care Professionals (HCPs) in the health care setting relevant for individual countries. Moreover, the effectiveness of Nyxoid in the real-world setting will be further investigated in a non-interventional Post Authorisation Efficacy Study. This study will also address the safety concerns “recurrence of respiratory depression”, “precipitation of opioid withdrawal effects” and “lack of efficacy due to incorrect administration” (leading to no or insufficient reversal of life-threatening effects of an opioid overdose) as well as collect data on adequateness of training users and effectiveness of training/educational material.

3.7. Conclusions

The overall B/R of Nyxoid is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Nyxoid is favourable in the following 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information

being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Nyxoid in each Member State the Marketing Authorisation Holder must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each MS where Nyxoid is marketed, all relevant health care professionals (HCP) who are expected to prescribe and/or supply Nyxoid are provided with:

- HCP Guidance Document with training delivery instructions
- The patient/carer information card
- Access to a video on how to use Nyxoid

The HCP Guidance Document should include:

- A brief introduction on Nyxoid
- A list of the educational material included in the training program
- Details of what information needs to be shared when training the patient/carer
    - how to manage a known or suspected opioid overdosed and how to properly administer Nyxoid
    - how to minimise the occurrence and severity of the following risks associated with Nyxoid: reappearance of respiratory depression, precipitation of acute opioid withdrawal effect and lack of efficacy due to medication error
- Instructions that the HCP has to provide the patient/carer with the PIC and to make sure that the patients/carers will have access to the video (either through the PIC or memory stick) and are encouraged to read the quick starting guide (QSG) and package leaflet included in the medicinal product outer carton.

The Patient Information Card should include:

- Information about Nyxoid and the fact that it cannot replace provision of basic life support
- Identification of signs of suspected opioid overdose, especially respiratory depression and information on how to check the airways and breathing
- Emphasis on the need to make an immediate emergency call for an ambulance
- Information on how to use the nasal spray to correctly administer Nyxoid
- Information on placing the patient into recovery position and administering the second dose, if required, in this position
- Information on how to manage and monitor the patient until the emergency medical assistance arrives
- Awareness of possible important risks such as opioid withdrawal symptoms and recurrence of respiratory depression

- Reference to the QSG on the back of the product immediate packaging

The Video should include:

- Steps detailing management of a patient which are aligned with information in PIC and package leaflet
- It should be available as
    - A link for online access in the HPD and PIC
    - Memory stick for HCP use to train, if WiFi not accessible

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Postauthorisation efficacy study (PAES): The Effectiveness of Nyxoid (intranasal naloxone) Administration by Lay People in Reversing Opioid Overdose.	Q4 2022

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.