CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Nexodal, solution for injection 0.4 mg/ml
Orpha Devel Handels- und Vertriebs GmbH, Austria

naloxone (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1024/001/MR
Registration number in the Netherlands: RVG 30938

7 July 2010

Pharmacotherapeutic group:	antidotes
ATC code:	V03AB15
Route of administration:	intravenous
Therapeutic indication:	reversal of CNS depressive effects, especially respiratory depression, caused by natural or synthetic opioids and partial agonist/antagonist opioids; diagnosis of suspected acute opioid overdose or intoxication.
Prescription status:	prescription only
Date of first authorisation in NL:	20 December 2005
Concerned Member States:	Mutual recognition procedure with AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NO, PL, PT, RO, SE, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Nexodal, solution for injection 0.4 mg/ml, from Orpha Devel Handels- und Vertriebs GmbH. The date of authorisation was on 20 December 2005 in the Netherlands.

The product is indicated for:

- complete or partial reversal of central nervous system (CNS) depressive effects, especially respiratory depression, caused by natural or synthetic opioids and partial agonist/antagonist opioids.
- Diagnosis of suspected acute opioid overdose or intoxication.

A comprehensive description of the indications and posology is given in the SPC.

Naloxone hydrochloride is a specific opioid-antagonist that acts competitively at opioid receptors. It reveals very high affinity for the opioid receptor sites and therefore displaces both opioid agonists and partial antagonists.
Naloxone hydrochloride does not counteract central depression caused by hypnotics or other non-opioids and does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists. Even high doses of the drug (10 times the usual therapeutic dose) produce insignificant analgesia, only slight drowsiness, and no respiratory depression, psychotomimetic effects, circulatory changes, or miosis.
In the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity. Because naloxone hydrochloride, unlike nalorphine, does not exacerbate the respiratory depression caused by other substances, it can therefore also be used for differential diagnosis.

In other MRPs with NL as RMS article 10a applications (well established use) have been accepted for Naloxone HCl 0.4 mg/ml solution for injection in April 2007 in procedures NL/H/893/001 and NL/H/894/001 by many European countries. These procedures were based on the well established use of Narcan in Europe, whereas this mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Narcan injection 0.4 mg/ml (NL License RVG 07432) which was first registered in the Netherlands by Bristol-Myers Squibb B.V. in 31 August 1978. The product was however withdrawn from the Dutch market on 31 December 2005. The application is therefore based on the historical Dutch Narcan originator product. In addition, reference is made to Narcan authorisations in the individual member states (reference product). However, in some European countries no reference product or historical reference product is available. Therefore, the application for these CMSs is based on the European reference product Narcanti authorised in CMS Austria.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Nexodal, solution for injection 0.4 mg/ml is an aqueous product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its historical reference product.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for a generic medicinal product.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is naloxone hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The substance is a white or almost white crystalline powder.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements/tests for any other impurity, acetone and dimethylformamide. Batch analytical data demonstrating compliance with this specification have been provided for two batches. The MAH committed to submit new validation studies in order to demonstrate specificity and robustness of the in-house method for related substances.

Stability of drug substance
A re-test period of 4 years has been granted based on submitted long term and accelerated stability results. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Each ampoule of 1 ml Nexodal contains 0.4 mg naloxone hydrochloride (as naloxone hydrochloride dihydrate). It is a clear and colourless solution with a pH 3.0-4.0 and an osmolality 0.3 Osmol/kg.

The solution for injection is packed in type I clear, colourless glass ampoules.

The excipients are: sodium chloride, diluted hydrochloric acid (for pH adjustment), water for injections.

Pharmaceutical development
The development of the product is described. Both the product and the manufacturing process are simple. Process development focussed on maintaining a proper pH and achieving sterility. The pH is closely controlled (between 3.1 and 3.3) to assure the stability of the drug substance, which will hydrolyse at higher pH values. The solution has no significant buffering capacity. Test batches at laboratory scale were made and tested. No unexpected findings are reported. No overages are used. The product contains the same excipients as the innovator product. These comply with their Ph.Eur. specifications. The ampoules are similar to the ampoules of the innovator product.
The pharmaceutical development has been adequately described.

Manufacturing process
The manufacturing process has been adequately described. All steps take place under a laminar flow of sterile filtered nitrogen. All equipment in contact with the solution is sterilised by standard overkill processes before use. Aseptic precautions are observed. The bulk solution is homogenised, prefiltered and then filtered into the holding vessel of the ampoule filling machine, where it is filled into pre-sterilised and depyrogenised ampoules.
Process validation data on the product have been presented for two pilot-scale batches and one full-scale batch in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of drug product
The product specifications cover appropriate parameters for this dosage form. The specification includes tests for appearance, identification, pH, particles, assay, related substances, sterility, bacterial endotoxins and extractable volume. Suitable methods are applied. Batch analysis has been performed on five batches: three pilot-scale batches and two full-scale batches. The batch analysis results show that the finished product meets the proposed specifications.

Compatability/In-use stability
For i.v. infusion Nexodal 0.4 mg/ml can be diluted with sodium chloride 0.9% or glucose 5%. Nexodal is incompatible with formulations containing bisulphite, metabisulphite, “long-chain” or high molecular weight anions. The product is also incompatible with alkaline solutions.
Stability after dilution with standard infusion solutions has not been investigated. In-use storage times will normally not be longer than 24 hours at 2 to 8°.

Microbiological Attributes
The product is for single use. No preservatives are added. Sterility is achieved by filtration. The MAH justified this choice: autoclaving is not possible due to the instability of naloxone. A low initial (pre-filtration) level of contamination with endotoxins and viable micro organisms is achieved by using microbiologically pure materials, controlled conditions, and limited process and holding times.

Stability tests on the finished product
Stability data on the product have been provided for five batches in accordance with the ICH stability guideline. The batches were stored at 25±2°C / 60±5% RH (24 months), 40±2°C / 75±5% RH (6 months), and 30±2°C / 65±5% RH (12 months).
Based on the results provided, the proposed shelf-life of 24 months when stored below 25°C could be granted. After finalisation of the MRP, on 4 December 2008, the shelf life was extended to 36 months through variation NL/H/1024/001/IB/003 (see page 9 of this report).
The MAH committed to place the first three production batches and one batch annually on stability testing.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a generic formulation of Narcan, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of naloxone released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Naloxone is a well-known active substance with established efficacy and tolerability.

Nexodal, solution for injection 0.4 mg/ml is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the historical reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Nexodal 0.4 mg/ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk management plan

Naloxone was first approved in 1975, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of naloxone can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Pharmacovigilance system

The MAH committed to provide additional information regarding Pharmacovigilance prior to placing the product on the market (see Post-approval commitments below). An updated Pharmacovigilance plan (dated 22 April 2008) was provided to all CMSs and the issue was solved.

Product information

SPC

The SPC is based on the former Dutch Narcan SPC with some updates in accordance with the current QRD template and MeDRA terminology. Furthermore, sections 4.6, 4.8 and 5.3 were adapted according to the SPC of MRP NL/H/893-894/001, based on more recent information on disturbance of neonatal development.

Readability test

The package leaflet ha-s been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 10 participants, followed by two rounds with 10 participants each. The German language version of the PIL was used. Test persons were adequately selected according to age, gender, education and experience with readability testing. There were sufficient questions (14 as well as 8 open questions) about the critical sections including questions on comprehensibility and applicability, testing traceability as well as technical readability aspects.
Following the pilot test, several amendments were made to the PIL, in accordance with the test results and comments made in this round. The first round of the actual readability test did not result in further adaptations. The readability test resulted in 90% to 100% answers found in both rounds together and 90% to 100% correct answers. There were no changes to the PIL after the second test round.
The leaflet was found readable and understandable according to the predefined limits. On request of the RMS, the use of the term "heroin" was changed into "morphine" as an example of opioids to address the indications claimed. Furthermore the MAH has changed the PIL into QRD format and provided an adequate statement that the readability test is still valid for this adapted PIL.
The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nexodal, solution for injection 0.4 mg/ml has a proven chemical-pharmaceutical quality and is a generic form of Narcan injection 0.4 mg/ml. Narcan is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The MAH committed to provide additional information regarding Pharmacovigilance prior to placing the product on the market (see Post-approval commitments below).

The SPC is based on the SPC of the historical reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other naloxone containing products.

The Board followed the advice of the assessors. Nexodal, solution for injection 0.4 mg/ml was authorised in the Netherlands on 20 December 2005. The mutual recognition procedure started on 21 December 2007.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Nexodal, solution for injection 0.4 mg/ml with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 20 March 2008.

A European harmonised birth date has been allocated (14 April 1975) and subsequently the first data lock point for naloxone is April 2010. The first PSUR will cover the period from March 2008 to April 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 1 January 2011.

The following post-approval commitments have been made during the procedure:

<u>Quality - active substance</u>

- The MAH committed to submit new validation studies in order to demonstrate specificity and robustness of the in-house method for related substances. This commitment has been fulfilled.

<u>Quality - medicinal product</u>

- The MAH committed to complete the validation of the manufacturing process. The product will not be marketed in the UK and France until this commitment has been fulfilled.
- The MAH committed to provide validation data of HPLC testing within 6 months after closure of the procedure. This commitment has been fulfilled.
- The MAH committed to place the first three production batches and one batch annually on stability testing.
- The MAH committed to submit a variation in order to change the name of a manufacturer of the finished product. This commitment has been fulfilled (variation NL/H/1024/001/IA/001, see table below).

<u>Pharmacovigilance</u>

- The MAH committed to provide the following information regarding Pharmacovigilance prior to placing the product on the market:
    - ⇒ updated version of the description of the Pharmacovigilance system, in which the responses are embedded (listing the SOPs, briefly describing some issues in the main text, etc).
    - ⇒ Written procedures covering the following issues will be provided: signal generation, detection of duplicate reports.

An updated Pharmacovigilance plan (dated 22 April 2008) was provided to all CMS and the commitment was fulfilled.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CNS	Central Nervous System
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the name and/or address of a manufacturer of the finished product.	NL/H/1024/ 001/IA/001	IA	7-8-2008	21-8-2008	Approval	N
Addition of a secondary packaging site of the finished product.	NL/H/1024/ 001/IA/002	IA	7-8-2008	21-8-2008	Approval	N
Change in the shelf-life of the finished product: from 24 months to 36 months.	NL/H/1024/ 001/IB/003	IB	4-12-2008	3-1-2009	Approval	N
Submission of an updated Ph. Eur. Certificate of Suitability for an active substance in the manufacturing process of the active substance from a manufacturer currently approved.	NL/H/1024/ 001/IA/004	IA	8-10-2009	22-10-2009	Approval	N