CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Naloxon HCL B. Braun 0.4 mg/ml, solution for injection
B. Braun Melsungen AG, Germany

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/894/01/MR
Registration number in the Netherlands: RVG 33994

Date of first publication: 10 March 2009
Last revision: 23 August 2011

Pharmacotherapeutic group:	antidotes
ATC code:	V03AB15
Route of administration:	intramuscular; intravenous
Therapeutic indication:	complete or partial reversal of CNS and especially respiratory depression, caused by natural or synthetic opioids; diagnosis of suspected acute opioid overdose or intoxication; complete or partial reversal of respiratory and other CNS depression in the neonate whose mothers have received opioids.
Prescription status:	prescription only
Date of first authorisation in NL:	22 August 2004
Concerned Member States:	Mutual recognition procedure with AT, BE, DE, DK, EL, ES, FI, IE, IT, LU, NO, PT, SE, and UK.
Application type/legal basis:	Directive 2001/83/EC, Article 10a

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 Naloxon HCL B. Braun 0.4 mg/ml, solution for injection, from B. Braun Melsungen AG, Germany. The date of authorisation was on 22 August 2004 in the Netherlands.

The product is indicated for treatment of:
- Complete or partial reversal of CNS and especially respiratory depression, caused by natural or synthetic opioids.
- Diagnosis of suspected acute opioid overdose or intoxication.
- Complete or partial reversal of respiratory and other CNS depression in the neonate whose mothers have received opioids.

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

Naloxone hydrochloride, a semisynthetic morphine derivative (N-allyl-nor-oxymorphone), 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, such as pentazocine, for example, but also nalorphine. 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.

The marketing authorisation is granted based on article 10a of Directive 2001/83/EC, well-established use. This application concerns a bibliographical application based on well-established medicinal use of naloxone hydrochloride. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ‘‘Medicinal use’’ does not exclusively mean ‘‘use as an authorised medicinal product’’, so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

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

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.

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.). Naloxone hydrochloride 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 suitability 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.

Quality 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 additionally a limit for any other individual impurity of NMT 0.10% (according to the Ph. Eur. monograph “Substances for pharmaceutical use”) and additionally, depending on the source, diverging limits and methods for related substances and residual solvents according to the CEP’s. Batch analytical data demonstrating compliance with this specification have been provided for several batches from the manufacturers.

Stability of drug substance
From the manufacturers, stability data on the active substance have been provided for at least 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 60 months. Based on the data submitted, a re-test period could be granted of 4 years.

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

Medicinal Product

Composition
Naloxon HCL B. Braun 0.4 mg/ml, solution for injection contains as active substance 0.4 mg naloxone hydrochloride (as naloxone hydrochloride dihydrate) per 1 ml, and is a clear and colourless solution.

The solution for injection is packed in Type I clear glass ampoules.

The excipients are: water for injections, sodium chloride, hydrochloric acid, nitrogen.

Composition of the product is documented sufficiently. pH of the solution is 3.1-4.5, which is acceptable in view of the dosage form, and so is osmolality (270-310 mOsmol/kg). The specified pH (3.1 – 4.5) is in theory low for a solution for injection, especially when applied intramuscular. From the stability studies is seen that the pH tends to increase during storage. On the basis of the results of the development study on optimum pH concerning degradation (between 3.0 and 3.5), this pH has been chosen. The MAH has justified the pH regarding safety, tolerance etc. in the pre-clinical documentation.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Packaging is usual and suitable for the product at issue.

Excipients
The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph. Eur. monographs, except for hydrochloric acid, which complies with Pharmacopoeia Helvetica (Ph. Helv.*).

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 5 pilot-scale batches in accordance with the relevant European guidelines. Process validation for full-scale batches will be forwarded post authorisation.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on specific monographs in the Ph. Eur. and includes tests for appearance, extractable volume, identity, pH, osmolarity, related substances, assay, sterility, bacterial endotoxines and particulate matter. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided.
Batch analytical data of 3 pilot-scale batches from the proposed production site(s) have been provided, demonstrating compliance with the specification. The results of batch analysis of three production batches will be provided post-approval.
The drug product is a solution for injection, presented in a 1 ml colourless glass ampoule, and is administered as i.v. or i.m. injection or as i.v. infusion mixed with 0.9 % sodium chloride or 5 % glucose; infusion solutions which have proven to be compatible with the product.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches (25°C/60% RH and 40°C/75%RH) in accordance with applicable European guidelines demonstrating the stability of the product over 36 months. On basis of the data submitted, a shelf life of 3 years was granted when stored below 25ºC. The labelled storage conditions are: *“Keep the ampoules in the outer carton in order to protect from light”* and *“Store below 25ºC”*. Results of the 3 production batches covering the whole shelf life are submitted post-approval.

In-use stability
Chemical and physical in-use stability data have been provided demonstrating that the product remains stable for 24 hours below 25°C. The stated storage conditions are the following: *“Store diluted solutions below 25°C”.*

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.

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

II.2 Non clinical aspects

The MAH provided an overview of published data. Briefly, in animals, naloxone, when administered alone, produced no respiratory depression in doses exceeding 100 times its effective dose; it exhibited no analgesic activity or other "agonistic" effects; and, in fact, in the absence of narcotics, had no demonstrable activity at all. Naloxone showed a relatively low acute toxicity and repeated dose toxicity data did not reveal additional effects that indicate a special hazard for humans. Naloxone was weakly positive in the Ames mutagenicity and *in vitro* human lymphocyte chromosome aberration tests and was negative in the *in vitro* Chinese hamster V79 cell HGPRT mutagenicity assay and in an *in vivo* rat bone marrow chromosome aberration study. Studies to determine the carcinogenic potential of naloxone hydrochloride have not been performed to date. Reproduction studies conducted in mice and rats at doses as high as 50 times the usual human dose (10 mg/day) demonstrated no impairment of fertility or teratogenic or embryotoxic effects. Yet, dose-dependent changes in the speed of postnatal neurobehavioral development have been reported in rats after in utero exposure. In addition, increases in neonatal mortality and reduced body weights have been described after exposure during late gestation in rats. Although these effects were observed in animals, in clinical practice these potential neonatal effects need to be weighed against the potential effects of opioids on the neonate, when these are not antagonised.

Environmental risk assessment
This application for marketing authorisation is a well-known substance application and the use of the active substance naloxone hydrochloride is common medicinal practice. Accordingly, the product being subject of this application may replace other naloxone hydrochloride products already marketed, but will not increase the overall use of such compounds to a relevant extent. Therefore, an environmental risk assessment is not deemed necessary.

II.3 Clinical aspects

No bioequivalence study was conducted for this solution for injection, which is acceptable. This application is based on literature data only.

The present application relies on well-established use for the registration of naloxone hydrochloride. Consequently, the documentation submitted is based on published studies and standard textbooks. Naloxone hydrochloride is a fast acting, rather safe, opioid antagonist, used as antidote. Naloxone was marketed in the Netherlands as Narcan® since 1978, but was withdrawn from the Dutch market on 31 December 2005 for commercial reasons. Its use is restricted to specialists care.

Pharmacology
Working mechanism and adverse reactions are derived from hand- and textbooks[1] [2, 3, 7, 15, 32, 36, 41, 54].
With regard to the pharmacokinetics, reference is made to several review articles. The provided expert report shortly summarises the pharmacokinetics.

Efficacy
For the indication '*Complete or partial reversal of CNS and especially respiratory depression caused by natural or synthetic opioids*', 4 references are submitted [2] [5, 8, 9, 22]. Two of them [5, 8] are random, active control studies in adult patients undergoing surgery. Both demonstrate the opioid antagonistic activity of naloxone hydrochloride i.v. on opioid induced respiratory depression, which was, amongst others, measured on the time to recurrence of normal respiratory rate (RR) within minutes after administration of the compound.
One study [22] demonstrates the efficacy of naloxone hydrochloride in fentanyl induced respiratory depression in a placebo and active control (3-way) controlled design in healthy volunteers. Efficacy was measured on the time to recurrence of normal RR.

One reference [9] gives an overview of studies in newborns and concludes that naloxone hydrochloride in newborns can only be used to antagonize respiratory depression due to narcotics given to the mother, but not for the treatment of otherwise induced respiratory distress.
For the indication *'Diagnosis of a suspected acute overdose with opiates'*, 2 references are submitted [3] [25, 38]. These references are concerned with reversal and treatment of opioid intoxication by naloxone hydrochloride.

Safety
The occurrence of adverse reactions is relatively low. Hypertension, pulmonary oedema, ventricular tachycardia and -fibrillation have been described.

Conclusion on clinical aspects
Naloxone hydrochloride 0.4 mg/ml can be administered intravenously (i.v.) or intramuscularly (i.m.). The innovator product Narcan was only used for intravenous administration. I.v. administration is preferred for the fast onset of effect. Naloxone hydrochloride, i.m. is less rapid in action, but longer lasting. Literature data substantiated the acceptance of the i.m. route of administration.
However, the subcutaneous route of administration was also requested, but was not approved since literature provided was not considered convincing. Sufficient information is available to justify i.m. use of naloxone next to i.v. use in adults and children/ neonates.

Risk management plan
Naloxone hydrochloride was first approved in April 1975, and there is now more than 10 years post-authorisation experience with the active substance. In view of the existing knowledge and experience with the active substance naloxone hydrochloride the available data and the known risk benefit profile it is accepted that the MAH will perform the standard pharmacovigilance activities as described in volume 9 of *The rules governing medicinal products in the European Union*. An additional Risk Management Plan and Risk Minimisation Plan are not required at the moment. If, in future, new data suggest otherwise, the submission of a Risk Management Plan and a Risk Minimisation Plan can be necessary.

Product information

SPC
The SPC is based on the former Dutch Narcan SPC. Additional information on i.m. route of administration and dosing in neonates is included in the SPC of Naloxon HCL B. Braun 0.4 mg/ml.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. A first pilot test was performed with an adapted PIL with 2 participants. The PIL section 1, 2, 3 and 4 were changed according to the preliminary comments made. Two further test rounds of 10 test persons were performed (diagnostic and scoring) There were sufficient questions (15 as well as 3 open questions) about the critical sections including questions on comprehensibility and applicability, also testing traceability as well as technical readability aspects. The second round resulted in 98% answers found and 97% correct answers. The leaflet was thus found readable and understandable according to the predefined limits (>90% of the subjects could find the information asked for and >90% there of was able to understand it once found). The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The MEB, on the basis of the data submitted, considered that Naloxon HCL B. Braun 0.4 mg/ml solution for injection demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation. Intravenous or intramuscular administration of Naloxon HCL B. Braun 0.4 mg/ml was considered acceptable, whereas the subcutaneous route of administration was not approved, since the literature provided was not considered convincing.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The Board followed the advice of the assessors. Naloxon HCL B. Braun 0.4 mg/ml, solution for injection was authorised in the Netherlands on 22 August 2004.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The mutual recognition procedure was finished on 24 April 2007. The other member states mutually recognised the Dutch evaluation for the marketing authorisation.

The SPC is based on the former Dutch Narcan SPC. Additional information on i.m. route of administration and dosing in neonates is included in the SPC of Naloxon HCL B. Braun 0.4 mg/ml.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from 26 August 2006 to 25 August 2009.

The date for the first renewal will be: 24 April 2012.

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

Quality - medicinal product

- Manufacturing process: the MAH has committed to submit results of validation on the first three commercial scale batches in due time, according to the submitted process validation scheme.
- Batch analysis: the MAH has committed provide the results of batch analysis of three production batches as soon as available.
- Stability: the MAH has committed to submit the results of the first three production batches covering the whole shelf life when available.

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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
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
Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance. From a manufacturer currently approved.	NL/H/0894/ 001/IA/001	IA	14-10-2008	28-10-2008	Approval	N
Identification of a specific impurity and inclusion of the impurity in the release and shelf-life specification.	NL/H/0894/ 001/II/002	II	22-2-2009	24-4-2009	Approval	N
Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance. From a manufacturer currently approved.	NL/H/0894/ 001/IA/003	IA				
Repeat-use procedure with IS.	NL/H/894/ 001/E/001	E	8-7-2010	8-7-2010	Approval	Y, Annex I

Annex I – Repeat-use procedure (NL/H/894/001/E/001)

The Repeat use procedure started on 11 April 2011. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state, Iceland, on the basis of the data submitted, considered that Naloxon HCL-hameln 0.4 mg/ml solution for injection demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation. Intravenous or intramuscular administration of Naloxon HCL-hameln 0.4 mg/ml was considered acceptable, whereas the subcutaneous route of administration was not approved, since the literature provided was not considered convincing.
The repeat use procedure was finished on 27 July 2011.

The date for the first renewal will be 24 April 2012.

The PSUR submission cycle is 3 years with harmonised PSUR Data Lock Point April 2013.

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

Quality – medicinal product

- Process validation results of the next two commercial batches will be provided when available.
- Batch analysis results of the next two commercial batches will be provided when available.
- Stability results of three production batches under long-term conditions covering the whole shelf-life will be submitted when available.

These commitments will be answered as a common package together with the application for renewal which will be submitted October 2011.