CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Nalbufine HCl Orpha solution for injection 10 mg/ml
Orpha-Devel Handels und Vertriebs GmbH, Austria

nalbuphine (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/983/01/MR
Registration number in the Netherlands: RVG 30852

23 August 2010

Pharmacotherapeutic group:	opioids, morphinan derivatives
ATC code:	N02AF02
Route of administration:	parenteral
Therapeutic indication:	short-term relief of moderate to severe pain. It can also be used for pre- and postoperative analgesia.
Prescription status:	prescription only
Date of first authorisation in NL	23 March 2006
Concerned member states:	Mutual recognition procedure with AT, BE, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NO (withdrawn 1 February 2007), PL, PT, SE, SI, SK, and UK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 Nalbufine HCl Orpha solution for injection 10 mg/ml from Orpha-Devel Handels and Vertriebs GmbH, from Austria. The first date of authorisation was on 23 March 2006 in the Netherlands. The product is indicated for the short-term relief of moderate to severe pain. It can also be used for pre- and postoperative analgesia.

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

Nalbuphine hydrochloride is an opioid with kappa-agonistic and mu-antagonistic properties. Beside the essential agonistic (analgesic) effect this opioid has antagonistic effects of about a fourth of nalorfine and ten times of pentazocine.

This mutual recognition concerns a generic application claiming essential similarity with the innovator product Nubain Injection 10 mg/ml (RVG license 09778), which has been registered in the Netherlands by Bristol-Myers Squibb since 15 March 1986, but withdrawn from the market since 31 December 2004. In addition, reference is made to Nubain Injection 10 mg/ml authorisations in the individual member states.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. However, for several CMS (BE, DE, DK, EE, ES, FI, IE, IT, LT, LU, NO, PL, SE, SK and UK) reference is made to the European Reference Product (AT – Nubain 20 mg Ampullen / Torrex Chiesi Pharma GmbH: 1-19063).

This type of application refers to information that is contained in 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. For this kind of applications, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. No bioequivalence study was deemed necessary according to the *Note for Guidance on the investigation of bioavailability and bioequivalence*, as this product concerns a parenteral formulation with the same amount of active substance and the same excipients as its reference product. The current product can be used instead of its reference product.

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

No scientific advice has been given to the MAH with respect to the product, and no paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The RMS 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 nalbuphine hydrochloride, an established active substance not described in the European Pharmacopoeia (Ph.Eur. *). Nalbuphine hydrochloride is a white or almost white crystalline powder that is freely soluble in methanol and dimethylsulfoxide, soluble in water and sparingly soluble in ethanol. Nalbuphine hydrochloride is hygroscopic.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product and the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance use in the medicinal product.

Manufacture
A structural flowchart and a description of the synthesis were given in an acceptable way. The manufacturing process is described in a sufficiently detailed manner.

Specification
The active substance specification is considered adequate to control the quality and includes tests for appearance, IR, chloride, appearance of solution, acidity or alkalinity, specific optical rotation, related substances, water content, sulphated ash, heavy metals and assay. For the specification of the impurity β-Nalbuphine a toxicological justification is present. However, this provided toxicological justification was not considered sufficient by two of the CMS's (see post-approval commitments). Batch analytical data demonstrating compliance with this specification have been provided for 3 production scale batches.

Stability
Stability data on the active substance have been provided for 3 batches stored at 25ºC/60% RH (24 months), 30ºC/65% RH (24 months), and 40ºC/75% RH (6 months) in accordance with applicable European guidelines. No changes are seen in the stability results. Based on the data submitted, a retest period could be granted of 3 years without specific storage conditions. The retest period has been changed by a post approval type IB variation from 3 years to 4 years (see variation NL/H/0983/001/IB/005 in the 'steps taken after finalisation of the initial procedure' table at the end of this PAR).

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
Nalbufine HCl Orpha, solution for injection 10 mg/ml, is formulated as a solution for injection. The packaging is a colourless glass Type I, sealed stem with colour break point ampoule, which is in compliance with Ph.Eur. requirements. Each ampoule contains 2 ml liquid with 20 mg of the active ingredient Nalbuphine hydrochloride.

The current product Nalbufine HCl Orpha 20 mg/2 ml solution for injection contains the same amount of Nalbuphine HCl (i.e. 10 mg/ml) as the originator Nubain (Bristol-Myers Squibb), and contains the same excipients: sodium citrate (E331), citric acid (E330), hydrochloric acid (E507), sodium chloride and water.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
The product is based upon the innovator product. The development of the product is satisfactory performed and explained. The excipients used are common in the manufacture of injections. The packaging is usual and suitable for the product at issue.

Excipients
All excipients comply with their USP/Ph.Eur. monographs.

Manufacturing process and quality control of the medicinal product
The solution for injection is prepared by dissolving the ingredients in water for injections. Sufficient details on the manufacture are present. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 full scaled batches in accordance with the relevant European guidelines.

Product specification
The finished product specification controls the relevant parameters for the dosage form. The specification includes tests for appearance, identification of the drug substance, pH, extractable volume, particulate matter, assay, impurities, sterility and bacterial endotoxines. Limits in the specification have been justified and are considered appropriate to adequately control the quality of the product.
Satisfactory validation data for the analytical methods have been provided.
Batch analytical data for 2 full-scale batches from the proposed production site have been provided demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 full scale batches from the current drug substance supplier, stored at 25°C/60% RH (18 months), 30ºC/65% RH (12 months) and 40°C/75% RH (6 months). Most parameters like appearance and pH show stable results under long-term storage conditions. Under accelerated conditions, a decrease in assay is observed, whereas no increase is seen in total impurities. Based on the data submitted, a shelf-life was granted of 2 years when stored below 25ºC, the ampoules must be stored in the outer carton in order to protect from light. The shelf-life has been changed into 3 years by a post-approval type IB variation (see variation NL/H/0983/001/IB/006 in the ‘steps taken after finalisation of the initial procedure’ table at the end of this PAR).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present or used in the manufacture of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

Nalbuphine is a substance with a long-standing history of clinical use and a well-known safety profile. Relevant non clinical data have been summarised in the non clinical overview, as far as these data were publicly available. Additional data confirming the lack of genotoxic potential have been included in the non clinical report.

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 nalbuphine 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

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

No bioequivalence study was conducted as this concerns parenteral medication. A waiver for Bioavailability (BA) and Bioequivalence (BE) is applicable according to the Note for Guidance (NfG). Proof of “essential similarity” is furthermore given by the comparison of the impurity profiles of Nalbufine HCl Orpha and Nubain and analytical tests.

Risk Management Plan
Nalbuphine was first approved in 1986 and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of nalbuphine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post-authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The applicant has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Nubain Injection 10 mg/ml marketed by Bristol-Myers Squibb.

During the procedure one of the CMSs who did not have the innovator on their market raised a pharmocokinetic issue. They stated that in SPC section 4.5 the pharmacokinetic/metabolic interactions were completely missing, and demanded the text to be updated to contain this information or otherwise to be provided with a scientifical/clinical justification on why the pharmacokinetic or metabolic interactions would not have to be mentioned in the SPC and PIL.

To resolve this issue, the MAH has included the following statement in section 4.5 of the SPC "*There is no information available regarding the potential for pharmacokinetic interactions between nalbuphine and other medicinal products. Caution is therefore recommended if nalbuphine is combined with potent enzyme inhibitors or medicinal products with a narrow therapeutic range*."

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 (preliminary) test was performed with 10 participants, followed by two subsequent main stuy rounds, with 10 participants each.

The target group for the current medicinal product is all people irrespective of age, sex, level of education, etc. There were sufficient questions about the critical sections. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Modifications between Preliminary study and Main Study (Round 1) led to serious improvement of the PIL. Main Study Round 2 did not bring new or further results. The PIL-test is performed satisfactory.

Conclusions and recommendations
The patient information leaflet has been adapted sufficiently taking into account the results of the test(s), resulting in a sufficiently improved PIL.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nalbufine HCl Orpha, solution for injection 10 mg/ml is a generic form of Nubain. Nubain is a well-known medicinal product with an established favourable efficacy and safety profile.

The chemical-pharmaceutical documentation in relation to the proposed product is of sufficient high quality in view of the present European regulatory requirements.

Relevant non clinical and clinical data have been summarised in the non clinical and clinical overviews respectively, as far as these data were publicly available. No bioequivalence study was deemed necessary according to the Note for Guidance on the investigation of bioavailability and bioequivalence, as Nalbufine HCl Orpha concerns a parenteral formulation with the same amount of active substance and the same excipients as its reference product.

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

The content of the SPC is in accordance with that accepted for the reference product Nubain Injection 10 mg/ml marketed by Bristol-Myers Squibb.

The Board followed the advice of the assessors. Nalbufine HCl Orpha was authorised in the Netherlands on 23 March 2006.

The MEB recommended granting a Marketing Authorisation for Nalbufine HCl Orpha 10 mg/ml solution for injection to the CMSs in view of the quality, the non clinical and the clinical data presented.

However, Nalbuphine is a new active substance for some of the CMSs, which raised concerns of preclinical and clinical potential serious risks to public health. For these CMSs the clinical and preclinical assessment reports submitted by the RMS were too limited to allow a secondary assessment. Their assessment regarding the clinical and preclinical data on Nalbuphine was therefore based on the respective Expert reports, submitted references and additional published data.

Preclinical issues that were considered to constitute potential serious risks to public health included the lack of complete genotoxicity and reproductive toxicity testing.

The clinical data submitted were also regarded insufficient to assess the safety and efficacy of product. The clinical potential serious risks to public health concerned the decreased efficacy when Nalbuphine is used in patients already treated with mu-agonistic opioids, since the reversal of a respiratory depression by Nalbuphine can lead to the break through of pain perception (both are mediated via mu-receptors). Moreover, the clinical potential serious risks to public health that were raised also included gender differences in treatment response but also an analgetic ceiling for Nalbuphine, whereby the analgetic effect does not increase with increasing doses at the higher dosing spectrum, showing that analgesia may be antagonised at the higher dose and resulting in inadequate pain relief in some patients. Finally, from a pharmacokinetic point of view, it was considered that the use of Nalbuphine in paediatrics and in impaired organ function had not been sufficiently addressed, nor had potential drug-drug interactions or issues regarding the elimination of the drug and the resulting metabolites.

While addressing these concerns it was recognized that Nalbuphine is a new active substance on some MS markets but nonetheless not new to the European Market. According to the Directive 2004/27/EC article 10 it is acceptable to refer to a European Reference Product in case the product is not registered in the respective Member State of the European Union. In addition, the marketing experience within the European Union dates back to 1986 and the product is on the market for more than 15 years now without any serious hazard observed and with positive assessment from patients and health personnel. Furthermore, the efficacy and safety of the product was proven by the literature provided in the expert

reports while additional data was provided by the Reference Member State. Therefore, further preclinical studies were not considered necessary.

As regards the decreased efficacy of Nalbuphine when combined with other mu-agonistic opioids it was taken into account that Nalbuphine is comparable to Naloxone as far as the reversal of a respiratory depression is concerned. However Nalbuphine, contrary to Naloxone, is as much unique as it also provides analgesia via kappa receptor agonism and hence can reduce the break trough pain or completely suppress it. In terms of safety when no (postoperative) monitoring is possible, any mild pain (if it might happen) is preferable to severe respiratory depression and death. The molecule is the only mixed opioid antagonist/agonist currently available. The literature references discussed in the expert report describe excellent efficacy and safety results for the product covering 30 years of experience.

Furthermore, several comments on the SPC were also addressed and the SPC was amended as requested. With regards to the issues concerning the use of Nalbuphine Hydrochloride in paediatrics and patients with impaired organ function the SPC was changed to take these special groups into consideration. The concomitant use of other opioids, the interaction with other medicinal products and the decrease of efficacy of more potent opioids as well as the ceiling effect were also described in the SPC. Regarding the pharmacokinetic/metabolic interactions several literature searches showed no pharmacokinetic interactions for Nalbuphine.

In light of this information the concerns raised about the preclinical and clinical potential serious risks to public health where withdrawn and all the member states mutually recognised the RMS' evaluation of the marketing authorisation. The mutual recognition prcedure was finished on 14 June 2007.

Braille
Nalbuphine HCl Orpha, solution for injection 10 mg/ml will only be used by health care professionals (in hospital use). Hence, the requirements regarding "Braille" can be waived.

The PSUR submission cycle is 3 years. The first PSUR was submitted in June 2008 (DLP 15 May 2008) as agreed during the procedure. The next PSUR will be submitted having a DLP 15 May 2010 taking the Harmonised Birth Date into consideration.

The date for the first renewal submission will be: 14 June 2010 (in line with the next PSUR submission).

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

<u>Quality – Active substance</u>

- The provided toxicological justification for the ß-nalbuphine impurity was not considered sufficient by two of the CMS's. Therefore, the MAH committed to perform additional toxicological studies on the impurity ß-nalbuphine. The results will be forwarded as soon as available. Furthermore, the MAH commited that the product will not be marketed in these two CMS's before the positive outcome of the study.

<u>Quality – Drug product</u>

- According to the request from the French authority the MAH committed to perform a comparative study of the physico-chemical characteristics and impurities profile between the proposed generic product and the reference product marketed in France. The results will be provided within 6 months after the end of the procedure.
  The MAH committed not to market the product in France before sending the required data.

- The MAH commited to demonstrate the stability of standard and sample solutions in order to complete the validation data. The data showing the stability of the solutions will be available within 6 months after the end of the procedure.

These committents have been fulfilled post-approval, see Annex I.

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
DLP	Data Lock Point
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
Withdrawal of the marketing authorization in Norway.	NL/H/983/01/MR	Withdrawal	1-2-2007	---	Approval	N
Change in batch size of the active substance or intermediate. Up to 10-fold compared to the original batch size approved at the grant of the marketing authorization	NL/H/0983/001/IA/001	IA	17-9-2007	1-10-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.	NL/H/0983/001/IA/002	IA	17-9-2007	1-10-2007	Approval	N
Change in the name and/or address of a manufacturer of the finished product.	NL/H/0983/001/IA/003	IA	19-2-2008	4-3-2008	Approval	N
Change in the name of the medicinal product.	NL/H/0983/001/IB/004	IB	19-2-2008	3-6-2008	Approval	N
Change in the re-test period of the active substance	NL/H/0983/001/IB/005	IB	1-7-2008	31-7-2008	Approval	N
Change in the shelf-life of the finished product as packaged for sale, from 24 to 36 months.	NL/H/0983/001/IB/006	IB	6-3-2009	6-4-2009	Approval	N
To add an alternative manufacturer for the finished product responsible for bulk production, primary and secondary packaging, batch control and batch release.	NL/H/0983/001/II/007	II	17-6-2009	13-10-2009	Approval	N

Annex I to the PAR – Fulfilment of post approval commitments

I Scope

The marketing authorisation holder (MAH) has provided answers to the three post approval commitments that resulted from the MRP procedure.

II Scientific discussion

Post approval commitment 1
According to the request from two CMSs, suitable toxicological studies need to be performed in order to demonstrate the safety of the impurity ß-nalbuphine. However, at least 6 months will be necessary to obtain the results of these studies. The results will be forwarded as soon as available.
Furthermore, the MAH committed not to market the product in both CMSs before the positive outcome of the study demonstrating safety of ß-nalbuphine. If the studies do not show safety of this related substance the MAH will tighten the limits in the specification below 0.15 % to fulfil all requirements.

Response and assessment
The DMF holder has provided four arguments which sufficiently justifiy the limit of NMT 0.5% of β-Nalbuphine.

Post approval commitment 2
As requested by a CMS the MAH committed to perform a comparative study of the physico-chemical characteristics and impurities profile between the proposed generic product and the reference product marketed in the respective CMS. The results will be provided within 6 months after the end of the procedure. The MAH committed not to market the product in that CMS before sending the required data.

Response and assessment
Since the MAH was not in the position to obtain samples of the reference product in the respective CMS, it was agreed with that CMS and RMS that as the reference product has been withdrawn from the market in the CMS, this commitment could be dropped.

Post approval commitment 3
The MAH committed to demonstrate the stability of standard and sample solutions in order to complete the validation data. The data showing the stability of the solutions for "*few hours after the preparation*" will be available within 6 months after the end of the procedure.

Response and assessment
The report on stability of nalbuphine test solution in assay and related substances HPLC analysis has been provided. It is concluded that test solutions of nalbuphine HCl raw material and finished product (20 mg/ml injectable solution) can be considered stable up to 48 hours from preparation in the common condition of use: volumetric flask or autosampler vial at both room temperature and refrigerator (2-8°C). Therefore, this point is considered resolved.

III Overall Conclusion

Based on the review of the data on quality, the Member States consider that the response related to the post approval commitments is approvable. The commitments have been fulfilled.