IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Remifentanil Noridem 5 mg powder for concentrate for solution for injection or infusion
Remifentanil
PA1122/014/003

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/2861/001-003/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 22nd October 2018 under procedure number IE/H/0710/001-003/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1122/014/001-003
Marketing Authorisation Holder: Noridem Enterprises Ltd

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

On 24 October 2011, Austria, Germany, Greece, Ireland, Spain and the UK agreed to grant Marketing Authorisations (MAs) to Ranbaxy (UK) Limited for the medicinal products Noridem Enterprises Limited Remifentanil/Noridem 1 mg, 2mg and 5 mg Powder for Injection. The MAs were granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (RMS UK/H/2861/01-3/DC). After the national phase, MAs were granted in the UK on 6 December 2011 (PL 24598/0025-27). These products are prescription-only medicines.

These are generic applications for Remifentanil/Noridem 1 mg, 2mg and 5 mg Powder for Injection submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applications refer to the EEA reference products Ultiva for Injection 1, 2 and 5 mg, which were first authorised in the UK on 30 October 1996 to Glaxo Group Limited (PL 14213/0002 - 4). Following a change of marketing authorisation holder, the product was authorised on 3 April 2000 to Elan Pharma International Limited (PL 16804/0009 – 11). After a second change of marketing authorisation holder, the product was authorised on 1 May 2004 to GlaxoSmithKline UK Limited (PL 194949/0026 – 28).The reference products have been registered in the EEA for more than 10 years, hence the period of data exclusivity has expired.

Remifentanil is a selective μ-opioid agonist with a rapid onset and very short duration of action. The μ-opioid activity, of remifentanil, is antagonised by narcotic antagonists, such as naloxone.

Remifentanil is indicated as an analgesic agent for use during induction and/or maintenance of general anaesthesia.

Remifentanil is indicated for provision of analgesia in mechanically ventilated intensive care patients 18 years of age and over.

The indications applied for are identical to the indications approved for the reference product.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years. A bioequivalence study is not necessary to support these applications for parenteral products.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns

requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market.

II. QUALITY ASPECTS

II.1 Introduction

The proposed product is presented as a sterile, endotoxin-free, preservative-free, white to off-white, powder for concentrate for solution tor injection or infusion. The medicinal product is supplied in a lyophilised form in a glass vial containing, 1 mg, 2mg or 5 mg of remifentanil base (as remifentanil hydrochloride). When reconstituted as directed, solutions of the proposed product are clear and colourless and contain 1 mg/mL remifentanil hydrochloride.

Other ingredients consist of, glycine and hydrochloride acid (for pH adjustments). Both the excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for both excipients. Appropriate justification for the inclusion of each excipient has been provided. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in, or used in the manufacturing process for the proposed product. Furthermore, no genetically modified organisms are used in the manufacture of glycine and hydrochloride acid.

The finished products are licensed for marketing in colourless, glass vials (Ph.Eur, type I) vials, closed with bromobutyl rubber (Ph.Eur, type I) stoppers and sealed with aluminium caps which have a plastic flip-off cover. The vials are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons and are packaged in pack sizes of 5 vials.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. The glass vials and rubber stoppers comply with Ph Eur requirements and are suitable for contact with parenteral solution products.

II.2 Drug Substance

Remifentanil Hydrochloride

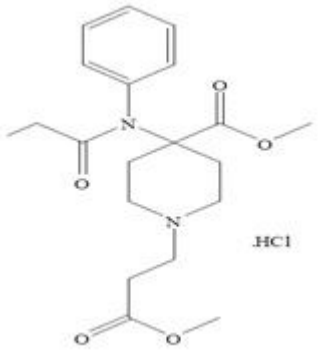
rINN name: Remifentanil Hydrochloride

Chemical name: 3-(4-Methoxycarbonyl-4-((1-oxopropyl)phenylamino)-1-piperidine)propanoic acid, methyl ester hydrochloride

Molecular formula: $C_{20}H_{28}N_2O_5HCl$

Molecular weight: 412.9

Structure



General properties

Description: White to off-white crystalline solid

Solubility: Freely soluble in water, sparingly soluble in ethanol, very slightly soluble in methyl isobutyl ketone and slightly soluble in isopropyl alcohol.

The active substance, remifentanil hydrochloride, is the subject of a European Pharmacopoeia (EP) monograph.

Manufacture
Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for all working standards.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product
Pharmaceutical development
The aim of the pharmaceutical development programme was to produce a stable, robust, reproducible lyophilised finished product that could be considered a generic medicinal product of Ultiva for Injection 1 mg, 2 mg and 5 mg (GlaxoSmithKline UK Limited). Suitable pharmaceutical development data have been provided for this application.

The physico-chemical properties of the drug product have been compared with the reference product. These data demonstrate that the proposed product can be considered a generic medicinal product of Ultiva for Injection 1 mg, 2 mg and 5 mg (PL 19494/0026-28) licensed to GlaxoSmithKline UK Limited.

Impurity Profiles
Comparative impurity data were provided for the test and reference products. The impurity profiles were found to be similar, with all impurities within the specification limits.

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted on three batches of each strength and are satisfactory. The validation data demonstrated consistency of the manufacturing process. All results comply with the process validation protocol and presented specifications.

Finished Product Specification
Finished product specifications are provided for both release and shelf-life, and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Stability of the Product
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life for Remifentanil/Noridem 1, 2 and 5 mg Powder for Solution for Injection or Infusion of 18 months, 2 years and 3 years respectively has been approved. Storage conditions are "Do not store above 25^{o}C. Keep the vial in the outer carton protected from light".
Finished product stability studies have been carried out after reconstitution in water as well as after dilution in an appropriate diluent. For storage conditions in both cases see Section 6.3 of the Summary Product Characteristics (SmPC).

Bioequivalence Study
The product is formulated for administration as a solution by the intravenous route. Hence there is no requirement for a bioequivalence study.

Quality Overall Summary
A satisfactory quality overall summary is provided and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

MAA Forms
The MAA forms are pharmaceutically satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of Remifentanil Noridem 1 mg, 2 mg and 5 mg Powder for Concentrate for Solution for Injection or Infusion from a non-clinical point of view.

III. NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of remifentanil are well-known. Therefore, no further studies are required and the applicant has provided none.

The non-clinical overall summary was written by a suitably qualified person and is satisfactory. The *curriculum vitae* of the expert has been provided.

III.2 Pharmacology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
No formal Environmental Risk Assessment has been provided. The applicant has justified the absence adequately. As a generic product, the use of this product is not expected to increase the overall use of remifentanil and so no additional increase in environmental risk has been identified.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs)
The SmPCs are satisfactory from a non-clinical viewpoint and is consistent with that for the reference products.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of Remifentanil Noridem 1 mg, 2 mg and 5 mg Powder for Concentrate for Solution for Injection or Infusion from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction
Remifentanil is indicated as an analgesic agent for use during induction and/or maintenance of general anaesthesia.

Remifentanil is indicated for provision of analgesia in mechanically ventilated intensive care patients 18 years of age and over.

POSOLOGY AND METHOD OF ADMINISTRATION

Remifentanil should be administered only in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by persons specifically trained in the use of anaesthetic drugs and the recognition and management of the expected adverse effects of potent opioids, including respiratory and cardiac resuscitation. Such training must include the establishment and maintenance of a patent airway and assisted ventilation.

Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY
The toxicology of remifentanil are well-known. No new data have been submitted and none are required for these types of applications.

CLINICAL PHARMACOLOGY
The clinical pharmacology of remifentanil is well-known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for these applications.

IV.2 Pharmacokinetics
Remifentanil Noridem 1 mg, 2 mg and 5 mg Powder for Concentrate for Solution for Injection or Infusion are generic versions of Ultiva for Injection 1, 2 and 5 mg. The use of the reference products is well-established in the UK. Both the reference and proposed products contain the same quantitative and qualitative composition of the active ingredient, remifentanil

According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

IV.3 Pharmacodynamics
No new data have been submitted and none are required for an application of this type.

IV.4 Clinical efficacy
No new data have been submitted and none are required for an application of this type.

IV.5 Clinical safety
No new safety data have been submitted or required for this generic application. As remifentanil is a well-known product with an acceptable adverse event profile, this is satisfactory.

Expert Report
A satisfactory clinical overall summary is provided, and has been prepared by an appropriately qualified physician. The *curriculum vitae* of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPCs and PIL are medically acceptable, and consistent with those for the reference product. The labelling is medically acceptable and in-line with current requirements.

MAA form
The MAA forms are medically satisfactory.

IV.7 Discussion on the clinical aspects
There are no objections to approval of Remifentanil Noridem 1 mg, 2 mg and 5 mg Powder for Concentrate for Solution for Injection or Infusion from a clinical point of view.

V. OVERALL CONCLUSIONS

V User consultation
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. The language used for the purpose of user testing the package leaflet was English.

The results 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*.

VI Overall conclusion, benefit/risk assessment and recommendation

Quality

The important quality characteristics of Remifentanil Noridem 1 mg, 2 mg and 5 mg Powder for Concentrate for Solution for Injection or Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

The applicant's Remifentanil Noridem 1 mg, 2 mg and 5 mg Powder for Concentrate for Solution for Injection or Infusion has been demonstrated to be generic versions of the reference products Ultiva for Injection 1, 2 and 5 mg (GlaxoSmithKline UK Limited).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs and PILs are acceptable, and consistent with those for the reference product. The labelling is acceptable and in-line with current requirements.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's Remifentanil Noridem 1 mg, 2 mg and 5 mg Powder for Concentrate for Solution for Injection or Infusion and the reference products Ultiva for Injection 1, 2 and 5 mg (GlaxoSmithKline UK Limited), are interchangeable. Extensive clinical experience with remifentanil is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk is, therefore, considered to be positive.

VI. REVISION DATE

May 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/2861/001-003/DC to IE/H/0710/001-003/DC	N/A	N/A	N/A	Approved 22/10/2018