

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Remifentanil hameln rds 1 mg, 2 mg and 5 mg, powder for
concentrate for solution for injection or infusion
hameln rds gmbh, Germany**

remifentanil (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/1532/001-003/DC
Registration number in the Netherlands: RVG 103427-103429**

8 March 2010

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| Pharmacotherapeutic group: | general anesthetics, opioid anesthetics |
| ATC code: | N01AH06 |
| Route of administration: | intravenous |
| Therapeutic indication: | induction and/or maintenance of general anaesthesia; provision of analgesia in mechanically ventilated intensive care patients 18 years of age and over. |
| Prescription status: | prescription only |
| Date of authorisation in NL: | 3 December 2009 |
| Concerned Member States: | Decentralised procedure with DE |
| 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 Remifentanil hameln rds 1 mg, 2 mg and 5 mg, powder for concentrate for solution for injection or infusion, from hameln rds gmbh. The date of authorisation was on 3 December 2009 in the Netherlands.

The product is indicated for:

- use during induction and/or maintenance of general anaesthesia as an analgesic agent.
- provision of analgesia in mechanically ventilated intensive care patients 18 years of age and over.

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

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

Assays of histamine in patients and healthy volunteers have shown no elevation in histamine levels after administration of remifentanil in bolus doses up to 30 $\mu\text{g}/\text{kg}$.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Ultiva Powder for concentrate for solution for injection or infusion which has been registered in many Member States by GlaxoSmithKline through Mutual Recognition procedure DE/H/106/01-03. In the Netherlands, the innovator product was first registered as Ultiva 1 / 2 / 5 mg on 15 October 1996 (NL License RVG 20601-20603). In addition, reference is made to Ultiva authorisations in the individual member states (reference product).

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

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 Remifentanil hameln rds 1 mg, 2 mg and 5 mg are products for parenteral use in aqueous solution, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of their reference products.

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 these products, and no paediatric development programme has been submitted, as this is not required for a generic application.

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 these product types 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 remifentanil hydrochloride, an established active substance not described in the European, British or US Pharmacopoeia (Ph.Eur.*). The active substance is a white to off-white powder which is freely soluble in water, soluble in methanol, sparingly soluble in ethanol and slightly soluble in acetone. Remifentanil hydrochloride does not exhibit stereo isomerism. Possible polymorphism is not described and is considered not relevant, as the drug substance is formulated as a solution.

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, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Remifentanil hydrochloride is manufactured in a 2 step reaction. Remifentanil hydrochloride is purified by recrystallisation. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

The drug substance specification is established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 5 full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for 3 full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH. The batches were adequately stored. At both conditions no changes are observed in the tested parameters. The proposed retest period of 36 months without additional storage conditions could therefore be granted.

**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

Each ml of Remifentanil hameln rds 1 mg/ 2 mg/ 5 mg contains 1 mg remifentanil when reconstituted as directed.

The product is a white to off-white or yellowish, compact powder.

The 1 mg powder for concentrate for solution for injection or infusion is packed in a 4 ml vial of colourless type I glass with bromobutyl rubber stopper and cap

The 2 mg powder is packed in a 6 ml vial of colourless type I glass with bromobutyl rubber stopper and cap.

The 5 mg powder is packed in a 10 ml vial of colourless type I glass with bromobutyl rubber stopper and cap.

The excipients are: glycine and hydrochloric acid (for pH-adjustment).

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the characterization of the originator product, compatibility studies with solutions for infusion and the freeze-drying process. A sterile filtration is necessary for sterility of the solution. Given the sensitivity of the drug substance to hydrolysis, the choice for sterile filtration as the sterilisation method of choice is sufficiently justified.

The choices of the packaging are also justified. The pharmaceutical development of the product has been adequately performed. Since the drug product is intended for parenteral use, no BE studies were required. The generic drug product was shown to be essentially similar to the originator product.

Manufacturing process

The manufacturing process consists compounding, pre-filtration, sterile filtration, filling and freeze-drying steps. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product has been presented for 3 production-scale batches.

Control of excipients

The excipients comply with the Ph.Eur. requirements. These specifications are acceptable.

Microbiological attributes

The drug product is manufactured under aseptic conditions (sterile filtration followed by aseptic filling into sterile vials). The sterility of the drug product is routinely controlled during release and stability testing. The release and stability data confirm the suitability and capacity of the aseptic manufacturing operations as well as the integrity and suitability of the container closure system to prevent microbial contamination.

Compatibility

The drug product formulations and packaging materials are identical to the currently marketed originator products, which is substantiated by comparison of analytical results of both products showing similarity. Therefore, the applicant concludes that remifentanyl can be considered to be compatible and stable with the same diluents under the same conditions as the originator product. Since the claims and the drug product composition are similar to the originator, this is acceptable.

The product is stable for 24 hours after reconstitution and dilution to concentrations from 20 to 250 µ/ml in the following diluents:

- Dextrose 5 % in sodium chloride 0.9 %
- Dextrose 5 % in water
- Sodium chloride 0.45 %
- Sodium chloride 0.9 %
- Sterile water for injections

Furthermore, a compatibility study has been performed which has proven these results.

An immediate administration of solutions diluted with Ringer-Lactate solution for infusion and Ringer-Lactate with 5 % Glucose solution for infusion is necessary, as these solutions were found to be not stable.

Quality control of drug product

The product specification includes tests for appearance (before and after reconstitution), identity, assay, uniformity of content, uniformity of dosage units, related substances, water content, sterility, sub-visible particles, pH and bacterial endotoxins. The release and shelf-life requirements are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 production-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on 3 production-scale batches of each strength, stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in colourless neutral Ph.Eur. type I glass vials, closed with a bromobutyl rubber stopper.

At accelerated conditions (40°C/75% RH) after 6 months an out of specification was observed. At both other storage conditions no significant changes were observed. Light stability was tested on one batch, in accordance with the requirements of the NfG on Photostability Testing of New Active Substances and Medicinal products, with samples packed in the immediate pack and a dark control. There are no significant differences in the analytical results of the irradiated to the un-irradiated samples; therefore protection from light is not necessary.

The proposed shelf life of 24 months is justified with the storage requirement: *Do not store above 30°C. Do not refrigerate or freeze.*

However, the MAH preferred to include the following storage conditions, in line with the innovator product: *Do not store above 25°C. Do not refrigerate or freeze.* The MAH committed to continue the ongoing stability studies on the drug product up to the proposed shelf life of 24 months.

Chemical and physical in-use stability has been demonstrated for 24 hours at 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.

II.2 Non clinical aspects

These products are generic formulations of Ultiva Powder for concentrate for solution for injection or infusion, 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 remifentanil 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

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

Remifentanil hameln rds 1 mg, 2 mg and 5 mg, powder for concentrate for solution for injection or infusion are parenteral formulations and therefore fulfil 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 currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Remifentanil hameln rds 1 mg, 2 mg and 5 mg 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 products can be used instead of its reference product.

Risk management plan

Remifentanil was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of remifentanil 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. The MAH 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

There was general consensus regarding the two main indications between the SPC of the Innovator in different member states, and the use in children and cardiovascular surgery. In some member states, specific restrictions (e.g. induction of anaesthesia is not recommended for paediatric patients or cardiovascular surgery; the maximal application period of 72 h for ventilated post-operative adult ICU patients) are included in section 4.1, whereas in the SPC versions of other members similar restrictions are worded in section 4.2 of the Innovator SPC.

Some member states did however not include the indication general anaesthesia in spontaneous breathing patients in the Innovator SPC. In the opinion of the RMS, the benefit of using remifentanil in spontaneous breathing painful procedures is that profound analgesia can be achieved rapidly without large effect on cognitive function, with a more rapid recovery afterwards compared to other opioids. In low doses, remifentanil suppressed reflexes when spontaneous breathing patients were intubated or underwent bronchoscopy, thereby facilitating these procedures.

Bolus doses in spontaneous breathing patients should however not be given for safety reasons, and this is well addressed in the SPC. In several studies in different centres it has been shown that remifentanil can be safely used in spontaneous breathing patients (see summary of literature above), in doses between 0.025-0.1 µg/kg/min without bolus.

However, like all opioids, remifentanil can reduce respiration and blood pressure. Therefore, mechanical ventilation equipment (a laryngeal mask is usually sufficient) and a trained staff to handle respiratory or cardiac failure should always be available during spontaneous breathing procedures, for safety reasons. In the SPC section 4.2, this condition is clearly worded in bold: 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.

In the Innovator SPC of some member states, dosing advices for Target Controlled Infusion (TCI) are not included. However, in a randomised head-to-head comparative study between manual and TCI administration of remifentanil, the use of TCI significantly reduced the incidence of hypotensive episodes during surgery and the need for beta-blockers post-operative, whereas the need for propofol and morphine (post-operative) was similar between these two groups. Therefore, recommended to include TCI dosing schedules were included in the SPC.

TCI of remifentanil is not indicated for spontaneously breathing patients (for safety reasons) and mechanically ventilated post-operative patients (due to lack of data), but this is adequately addressed in the SPC.

Section 4.1: Mechanically ventilated intensive care patients

Two member states requested to add a specification for age (18 years and older) for the indication “mechanically ventilated intensive care patients”. This has been implemented by the MAH.

Section 4.2: Spontaneous ventilated patients

Two member states noted that this indication needs further specification, i.e. that anaesthesia in spontaneously breathing patients with remifentanil should only take place in patients with a secured airway (e.g. laryngeal mask anaesthesia), as respiratory depression is likely to occur in this kind of procedures. One CMS also proposed to include the risk of muscular rigidity. The MAH has included the proposed changes.

Section 4.2: Guidelines for discontinuation/continuation during immediate postoperative period IN ADULTS

One CMS objected to this wording, as continuation of remifentanyl post-operatively may be dangerous if the patient is transferred from a setting with strict monitoring of ventilation to a less equipped environment. Another CMS proposed to add a warning that postoperative continuation should only take place under monitoring and ventilatory support by trained personnel. It was decided to include the proposed warning.

Section 4.2: Cardiac Surgery

One of the CMSs requested to add that remifentanyl is not recommended for use during cardiac surgery in patients with poor left ventricular (LV) function (ejection fraction (EF) less than 0.35) and children/adolescents, because of the lack of experience in these groups.

The MAH indicated that based on data from the literature remifentanyl can be safely used in cardiac surgery in patients with a poor LV function. Several publications are available confirming that remifentanyl could be safely used in patients with weak LV function undergoing cardiac surgery.

Furthermore, it can not be maintained that there are no data that address the safety of paediatric patients and patients with poor left LV function. Based on data from literature, it can be concluded that remifentanyl can be safely used in children and patients with weak LV function undergoing cardiac surgery.

It was decided not to include the proposed warning also for reasons of harmonisation.

Furthermore the final agreed SPC is in line with the SPC of the innovator Ultiva, as approved via MRP.

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. Two stages of testing were performed, each involving 10 subjects, preceded by a preliminary round of testing with three subjects. The participants were questioned about the leaflet in an evaluation and problem-seeking test. The report details the demographic data of the volunteers by age, gender, social grade and education.

The questionnaire for this user test consisted of 12 questions specific to the key safety issues of Remifentanyl and 3 general questions regarding the format of the leaflet. The questions sufficiently address the key safety messages. No revisions were made to the PIL after the preliminary testing round with three participants.

In the first round at least 90% of the participants were able to find the information requested and at least 90% showed that they understood and were able to act upon it. There were 3 questions presenting some difficulty. The three questions not traced were also not comprehended, but by not more than one subject per question. The three questions posing difficulty were related to the contraindication hypersensitivity, the 'before you receive Remifentanyl'-section (impaired lung and/or liver function) and the interaction section (interactions with benzodiazepines). No corrective actions were taken to the PIL for round 2.

In the second round, at least 90% of the participants were able to find the information requested and at least 90% showed that they understood and were able to act upon it. The correct answer was traced in 10 out of 12 questions. Two questions were not traced and thus not comprehended by two different participants. Although traced, one question was not comprehended by one participant and another question by another participant. All remaining subjects were able to show comprehension of the information, and the PIL passed the test criteria.

The test results and the current information present in the leaflet support the conclusion of the readability report not to amend the PIL. The content and lay-out of the PIL are acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Remifentanil hameln rds 1 mg, 2 mg and 5 mg, powder for concentrate for solution for injection or infusion have a proven chemical-pharmaceutical quality and are generic forms of Ultiva Powder for concentrate for solution for injection or infusion. Ultiva 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 has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is in line with that of the reference product; minor changes were implemented during the procedure (see above). The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Remifentanil hameln rds 1 mg, 2 mg and 5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 2 September 2009. Remifentanil hameln rds 1 mg, 2 mg and 5 mg were authorised in the Netherlands on 3 December 2009.

A European harmonised birth date has been allocated (17 May 1996) and subsequently the first data lock point for remifentanil is May 2011. The first PSUR will cover the period from September 2009 to May 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 2 September 2014.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to continue the ongoing stability studies on the drug product up to the proposed shelf life of 24 months.

List of abbreviations

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| 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 _{1/2} | Half-life |
| t _{max} | Time for maximum concentration |
| TSE | Transmissible Spongiform Encephalopathy |
| USP | Pharmacopoeia in the United States |

