Public Assessment Report

Scientific discussion

Oxytocine Devrimed 5 IE/ml, solution for injection/infusion

(oxytocin)

NL License RVG: 117498

Date: 8 November 2017

This module reflects the scientific discussion for the approval of Oxytocine Devrimed 5 IE/ml, solution for injection/infusion. The marketing authorisation was granted on 5 January 2016. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
</tr>
<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
</tr>
<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
</tr>
<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
</tr>
<tr>
<td>ERA</td>
<td>Environmental Risk Assessment</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
</tr>
<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>PL</td>
<td>Package Leaflet</td>
</tr>
<tr>
<td>RH</td>
<td>Relative Humidity</td>
</tr>
<tr>
<td>RMP</td>
<td>Risk Management Plan</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
</tr>
</tbody>
</table>
I. **INTRODUCTION**

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Oxytocine Devrimed 5 IE/ml, solution for injection/infusion from DeVriMed B.V.

It is indicated for use antepartum:
- Induction of labour for medical reasons; e.g. in cases of post-term gestation, premature rupture of the membranes, pregnancy-induced hypertension (preeclampsia)
- Stimulation of labour in hypotonic uterine inertia

and postpartum:
- For adequate uterine contraction after caesarean section
- Prevention and treatment of postpartum uterine atony and haemorrhage

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

This national procedure concerns a generic application claiming essential similarity with the innovator product Syntocinon 5 IE/ml concentrate for solution for infusion/solution for injection (NL License RVG 03714) which has been registered in the Netherlands since 20 May 1990 by Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. **QUALITY ASPECTS**

II.1 **Introduction**

Oxytocine Devrimed 5 IE/ml is a clear, colourless, hypotonic solution with pH 3.5 – 4.5. The solution is packed in clear glass ampoules. Each 1 ml ampoule contains 5 IE oxytocin (= 5 IE/ml).

The excipients are sodium acetate trihydrate, acetic acid glacial, sodium hydroxide (pH adjustment) and water for injections.

II.2 **Drug Substance**

The active substance is oxytocin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, fluffy, hygroscopic powder. The active substance is a synthetic cyclic nonapeptide. It is very soluble in water and dissolves in dilute solutions of acetic acid and of ethanol (96%). Particle size and polymorphic form of the active substance are not deemed critical since it will be used for a solution for injection.

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 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.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is fully in line with the CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 4 full scaled batches.
Stability of drug substance
The active substance is stable for 36 months when stored between 2 – 8°C. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described. The choice of different excipients compared to the reference product is justified and their functions are explained. As the product is a monodose formulation, it does not contain a preservative, which is in line with current guidelines. Influence of heat, oxidation and light on the stability of the drug product have been investigated. The compatibility with different infusion solutions has been shown. Osmolarity and pH in relation to the reference product are similar. The choice of sterilizing method (sterile filtration) is sufficiently justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacture of the drug product is straightforward: preparation of the bulk solution, sterile filtration, filling into ampoules and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 full scaled batches.

Control of excipients
The excipients comply with Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, pH, extractable volume, particulate matter, assay, related substances, sterility and endotoxins. The release and shelf-life specifications are identical. The analytical methods have been adequately described and validated. Batch analytical data have been provided on 3 full scaled, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided 6 full scaled batches stored at 2 – 8°C (9 – 36 months) and stored at 25°C/60% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in clear glass (Ph.Eur. type I) ampoules. The sensitivity to light has been studied in line with the recommendations in ICH guideline Q1B Stability testing: photostability testing of new drug substances and products. Based on the results provided, the proposed shelf-life of 36 months and storage condition ‘store in the refrigerator, protected from light’ is acceptable.

Specific measures for 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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Oxytocine Devrimed 5 IE/ml, solution for injection/infusion has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.
III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Oxytocine Devrimed 5 IE/ml is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Syntocinon 5 IE/ml, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Oxytocin is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

Oxytocine Devrimed 5 IE/ml concentrate for solution for infusion/solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous 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 Oxytocine Devrimed 5 IE/ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Oxytocine Devrimed.

- Summary table of safety concerns as approved in RMP

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Uterine overstimulation due to excessive dose or hypersensitive patient (leading to hypertonicity, tetanic contractions or rupture of the uterus, or to foetal distress, asphyxia and death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important potential risks</td>
<td>None</td>
</tr>
<tr>
<td>Missing information</td>
<td>None</td>
</tr>
</tbody>
</table>
The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Syntocinon 5 IE/ml. No new clinical studies were conducted. The MAH demonstrated similarity to the reference product based on chemical-pharmaceutical properties. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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

Oxytocine Devrimed 5 IE/ml, solution for injection/infusion has a proven chemical-pharmaceutical quality and is a generic form of Syntocinon 5 IE/ml. Syntocinon 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 Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Oxytocine Devrimed 5 IE/ml, solution for injection/infusion was authorised in the Netherlands on 5 January 2016.
<table>
<thead>
<tr>
<th>Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tightening of the release limit for the oxytocin assay; Change in</td>
</tr>
<tr>
<td>storage conditions of the finished product or the diluted/reconsti</td>
</tr>
<tr>
<td>tributed product.</td>
</tr>
<tr>
<td>Type of modification</td>
</tr>
<tr>
<td>IB</td>
</tr>
</tbody>
</table>