OXYTOCIN 10 IU/ML SOLUTION FOR INFUSION

PL 15760/0036

UKPAR

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This is a summary of the public assessment report (PAR) for Oxytocin 10 IU/ml Solution for infusion (PL 15760/0036). It explains how Oxytocin 10 IU/ml Solution for was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Oxytocin 10 IU/ml Solution for infusion.

For practical information about using Oxytocin 10 IU/ml Solution for infusion, patients should read the package leaflet or contact their doctor or pharmacist.

**What is Oxytocin 10 IU/ml Solution for infusion and what is it used for?**
Oxytocin 10 IU/ml Solution for infusion is a ‘generic medicine’. This means that Oxytocin 10 IU/ml Solution for infusion is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Syntocinon 10 IU/ml Injection.

Oxytocin 10 IU/ml Solution for infusion is used: to start or help contractions during childbirth; to help in the management of miscarriage; during caesarean section; or to prevent and control bleeding after delivery of the baby.

**How is Oxytocin 10 IU/ml Solution for infusion used?**
Oxytocin 10 IU/ml Solution for infusion should only be given under medical supervision in a hospital. Patients and their babies are closely monitored during oxytocin treatment. The solution is usually diluted before being given as an intravenous infusion (drip) into the patient’s vein. The dose given depends on what Oxytocin 10 IU/ml Solution is being used for.

**How does Oxytocin 10 IU/ml Solution for infusion work?**
Oxytocin 10 IU/ml Solution for infusion contains a manufactured form of oxytocin (a natural hormone). It belongs to a group of medicines called oxytocics that make the muscles of the womb contract.

**How has Oxytocin 10 IU/ml Solution for infusion been studied?**
No clinical studies were conducted as Oxytocin 10 IU/ml Solution for infusion is a generic medicine that is given by infusion and contains the same active substance as the reference medicine, Syntocinon 10 IU/ml Injection.

**What are the benefits and risks of Oxytocin 10 IU/ml Solution?**
Because Oxytocin 10 IU/ml Solution for infusion is a generic medicine and is bioequivalent to the reference medicine, its benefits and risks are taken as being the same as those of the reference medicine.
Why is Oxytocin 10 IU/ml Solution for infusion approved?
It was concluded that Oxytocin 10 IU/ml Solution for infusion has been shown to have comparable quality and to be bioequivalent to Syntocinon 10 IU/ml Injection. Therefore, the view was that, as for Syntocinon 10 IU/ml Injection, the benefits outweigh the identified risks of taking this medicinal product.

What measures are being taken to ensure the safe and effective use of Oxytocin 10 IU/ml Solution for infusion?
A Risk Management Plan has been developed to ensure that Oxytocin 10 IU/ml Solution for infusion is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and package leaflet for Oxytocin 10 IU/ml Solution.

Other information about Oxytocin 10 IU/ml Solution for infusion
The Marketing Authorisation for Oxytocin 10 IU/ml Solution for infusion was granted in the UK on 23 April 2014.

This summary was last updated in 06-2014.

The full PAR for Oxytocin 10 IU/ml Solution for infusion follows this summary.
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SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Peckforton Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Oxytocin 10 IU/ml Solution for infusion (PL 15760/0036) on 23 April 2014.

This prescription-only medicine (POM) is indicated for the induction of labour for medical reasons, for the stimulation of labour in women with hypotonic uterine inertia or as adjunctive therapy for the management of incomplete, inevitable, or missed abortion during the early stages of pregnancy. This medicine is also used following delivery of a child by caesarean section and for the prevention and treatment of postpartum uterine atony and haemorrhage.

The application was submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal product of the reference product Syntocinon 10 IU/ml Injection (PL 16853/0020). Syntocinon 10 IU/ml Injection was first authorised to Novartis Pharmaceuticals UK Limited on 3 October 1977 (PL 00101/0070) and, following a change of ownership on 25 June 1998, is now authorised to Alliance Pharmaceuticals Ltd.

Oxytocin is a cyclic nonapeptide that is obtained by chemical synthesis. This synthetic form is identical to the natural hormone that is stored in the posterior pituitary and released into the systemic circulation in response to suckling and labour. Oxytocin stimulates the smooth muscle of the uterus, more powerfully towards the end of pregnancy, during labour, and immediately postpartum.

No non-clinical studies were conducted, which is acceptable given that the application was based on the product being a generic medicinal product of the reference product, which has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on the product being a parenterally-administered aqueous solution that is a generic medicinal product of the reference product, which has been licensed for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
INN: Oxytocin
Compendial name: Oxytocinum
Chemical name: L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide cyclic (1 → 6) disulphide
CAS: 50-56-6
Molecular formula: C_{43}H_{66}N_{12}O_{12}S_{2}
Molecular weight: 1007.20
Structure:

Physical form: White or almost white fluffy powder, hygroscopic
Solubility: Very soluble in water and in dilute solutions of acetic acid and ethanol

Synthesis of the active 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 specifications are provided for the active substance oxytocin, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specifications.

Appropriate proof-of-structure data have been supplied for the drug substance. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Satisfactory specifications have been provided for all packaging used for storing the oxytocin. The primary packaging has been shown to comply with current legislation concerning materials in contact with foodstuff.
Appropriate stability data have been generated showing the drug substance to be physically and chemically stable. A suitable retest period has been set based on stability data submitted for the drug substance stored in the proposed packaging.

**DRUG PRODUCT**

**Other Ingredients**
As well as the drug substance the solution contain the excipients acetic acid (glacial), sodium acetate trihydrate, sodium chloride, sodium hydroxide and water for injections. The excipients are controlled in line with Ph.Eur monographs.

None of the excipients are of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**
The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the reference product Syntocinon 10 IU/ml Injection. A satisfactory account of the pharmaceutical development has been provided.

**Manufacture**
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Process validation has been carried out on commercial-scale batches of the finished product. The results are satisfactory.

**Finished Product Specification**
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The finished product is packaged in transparent 1 ml Ph.Eur type 1 glass ampoules. Pack sizes of 5 and 10 ampoules have been authorised, although not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

**Stability of the Product**
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 3
years when the storage precautions ‘store in a refrigerator (2 °C – 8 °C)’ and ‘keep the
ampoules in the outer carton in order to protect from light’ are applied.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and
Labels
The SmPC, PIL and labels are acceptable from a pharmaceutical perspective.

The results of consultations with target patient groups (‘user testing’), in accordance with
Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet for
Oxytocin 10 IU/ml Solution for infusion were provided. The results indicate that the package
leaflet is well structured and organised, easy to understand and written in a comprehensive
manner. The test shows that the patients/users are able to act upon the information that it
contains.

Marketing Authorisation Application (MAA) form
The MAA form is satisfactory from a pharmaceutical perspective.

Quality Overall Summary (Expert report)
The quality overall summary has been written by an appropriately qualified person and is a
suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of Oxytocin 10
IU/ml Solution for infusion are well-known, no non-clinical studies are required and none
have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified
person and is satisfactory, providing an appropriate review of the product’s pharmacology
and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk
assessment. As this product is intended for generic substitution with products that are
currently marketed, no increase in environmental burden is expected. Thus, the justification
for non-submission of an Environmental Risk Assessment is accepted.

There are no objections to the approval of this product from a non-clinical viewpoint.
CLINICAL ASSESSMENT

PHARMACOKINETICS
Oxytocin 10IU/ml solution for injection or infusion is indicated for parenteral use only. No bioequivalence studies are required for this type of product according to the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) and the applicant has submitted none.

EFFICACY
No new data on efficacy have been submitted and none are required for this type of application.

SAFETY
No new data on safety have been submitted and none are required for this type of application.

PHARMACOVIGILANCE SYSTEM
The pharmacovigilance system, as described by the applicant, fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A risk management plan has been submitted in accordance with the EU RMP template and is acceptable.

EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
This is consistent with the SmPC for the reference product and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
This is satisfactory

MARKETING AUTHORISATION APPLICATION (MAA) FORMS
The MAA form is satisfactory from a clinical perspective.

CONCLUSION
The grant of a marketing authorisation is recommended for this application.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Oxytocin 10 IU/ml Solution for 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 this type of application.

CLINICAL
No new clinical data were submitted and none are required for this type of application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with oxytocin products is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
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STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation application on 27 February 2013.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 5 March 2013.
3. Following assessment of the application the MHRA requested further information relating to the dossier on 13 June 2013 and 10 February 2014.
4. The applicant responded to the MHRA’s requests, providing further information on 31 December 2013 and 7 March 2014.
5. The applications were granted on 28 March 2014.
STEPS TAKEN AFTER INITIAL AUTHORISATION – SUMMARY

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
LABELLING

Label:
Oxytocin 10 IU/ml Solution for infusion

Each 1ml ampoule contains 10 IU (16.7 micrograms) oxytocin. Other ingredients: Acetic acid, glacial; sodium acetate trihydrate; sodium chloride; sodium hydroxyde; water for injections.

For intravenous use only.

Read the package label before use. Store in a refrigerator (2°C - 8°C). Keep the ampoules in the outer carton in order to protect from light.

Keep out of the sight and reach of children.

Marketing Authorisation Holder:
Peckforton Pharmaceuticals Limited, Crewe Hall, Crewe, Cheshire, CW1 6UL, United Kingdom

FOR INTRAVENOUS USE ONLY

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Cartons: