IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Oxytocin 10 IU/ml Concentrate for Solution for Infusion
Oxytocin
PA0281/239/001

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/5476/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 13/12/2018 under procedure number IE/H/0886/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/239/001
Marketing Authorisation Holder: Pinewood Laboratories 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.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK and Ireland considered that the application for Oxytocin 10 IU/ml Concentrate for Solution for Infusion (PL 29942/0001; UK/H/5476/001/DC) could be approved. The product is a prescription-only medicine (POM) and is indicated for the following:

Antepartum:

- Induction of labour for medical reasons; e.g. in cases of post-term gestation, premature rupture of the membranes, pregnancy-induced hypertension (pre-eclampsia).
- Stimulation of labour in hypotonic uterine inertia.
- Early stages of pregnancy as an adjunctive therapy for the management of incomplete, inevitable, or missed abortion.

Postpartum:

- During caesarean section, but following delivery of the child.
- Prevention and treatment of postpartum uterine atony and haemorrhage.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Ireland as Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Syntocinon 10IU/ml Concentrate for solution for infusion (PL 16853/0020; Alliance Pharmaceuticals Limited), which was first granted in the UK on 03 October 1977 to Sandoz Pharmaceuticals (UK) Limited.

The active ingredient, 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. At these times, the oxytocin receptors in the myometrium are increased.

The oxytocin receptors are G-proteins coupled receptors. Activation of receptor by oxytocin triggers release of calcium from intracellular stores and thus leads to myometrial contraction.

Oxytocin elicits rhythmic contractions in upper segment of uterus, similar in frequency, force and duration to those observed during labour.

Being synthetic, oxytocin in Oxytocin 10 IU/ml Concentrate for Solution for Infusion does not contain vasopressin, but even in its pure form oxytocin possesses some weak intrinsic vasopressin-like antidiuretic activity.

Based on in vitro studies, prolonged exposure of oxytocin had been reported to cause desensitisation of oxytocin receptors probably due to down-regulation of oxytocin-binding sites, destabilisation of oxytocin receptors mRNA and internalisation of oxytocin receptors.

No new non-clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that have been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for a parenteral product, containing the same active substance as the reference product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. 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.

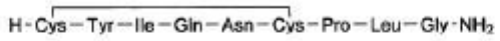
The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 21 April 2014. After a subsequent national phase, a licence was granted in the UK on 20 May 2014.

II. QUALITY ASPECTS

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN:	Oxytocin
Chemical name	L-Cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asapraginyl-1-cysteinyl-L-prolyl-L-leucylglycinamide cyclic (1-6) disulphide.
Molecular formula:	$C_{43}H_{66}N_{12}O_{12}S_2$
Structure:	
Mr:	1007.20 g/mol
Appearance:	White, fluffy, hygroscopic powder.
Solubility:	Very soluble in water, dilute solutions of ethanol and acetic acid.

Oxytocin is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance oxytocin, except for stability data to support a suitable retest period when stored in the proposed packaging, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated to support a suitable retest period for the active substance when stored in the proposed packaging.

MEDICINAL PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients sodium acetate tri-hydrate, glacial acetic acid, sodium hydroxide and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Certificates of Analysis have been provided for all excipients, showing compliance with their respective specifications.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development

The objective of the development programme was to a produce a safe, efficacious, stable concentrate for solution for infusion that was equivalent to the reference product Syntocinon 10IU/ml Concentrate for solution for infusion (Alliance Pharmaceuticals Limited).

Suitable pharmaceutical development data have been provided for this application.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches that have shown satisfactory results.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The finished product is supplied in Type I neutral glass 1ml ampoules. The product is packaged with the Patient Information Leaflet in cardboard outer cartons, in pack size of 5 and 10 ampoules. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with parenteral products.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years has been approved for the unopened product, with the special storage conditions "Store between 2°C and 8°C. May be stored up to 30°C for 3 months, but must then be discarded. Store in the original package in order to protect from light." After opening or dilution, the product should be used immediately.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this type of application for a parenteral product.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are satisfactory from a pharmaceutical perspective. Final text versions of the labelling and PIL have been provided. The Marketing Authorisation Holder has committed to submitting mock-ups to the relevant competent authorities for approval before marketing any pack size.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. 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 the leaflet contains.

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

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

Conclusion
The grant of a Marketing Authorisation is recommended.

III. NON-CLINICAL ASPECTS

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of oxytocin are well-known, no new non-clinical data have been submitted and none are required.

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

The grant of a Marketing Authorisation is recommended.

IV. CLINICAL ASPECTS

III.3 CLINICAL ASPECTS

Clinical Pharmacololgy

The clinical pharmacology of oxytocin is well-known .No new clinical pharmacology data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for a parenteral product. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the Investigation of Bioequivalence).

Efficacy

No new efficacy data have been submitted and none are required for this type of application. The clinical efficacy of oxytocin is well-established.

Safety

No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application. The safety profile of oxytocin is well-known.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPC, PIL and labels are acceptable from a clinical perspective. The PIL is consistent with the details in the SmPC and in line with current guidance. The labelling is in line with current guidance.

Clinical Expert Report (Clinical Overview)

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

Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the Marketing Authorisation Holder (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 Risk Management Plan (RMP) is considered adequate. Routine risk minimisation is provided through the Summary of Product Characteristics and the Patient Information Leaflet and this is sufficient.

Conclusion

The grant of a Marketing Authorisation is recommended.

V. OVERALL CONCLUSIONS

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics of Oxytocin 10 IU/ml Concentrate for 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.

EFFICACY

No new clinical data were submitted and none were required for this type of application. No bioequivalence studies were submitted or required for this application for a parenteral product.

SAFETY

The safety profile of oxytocin is well-known. No new or unexpected safety issues or concerns arose from this application.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate and in line with current guidance.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Oxytocin is a well-known active substance. Extensive clinical experience with oxytocin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

VI. REVISION DATE

02/03/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/5476/1/DC to IE/H/0886/1/DC			
MAH transfer				04/01/2021