OXYTOCIN 5IU SOLUTION FOR INJECTION
PL 19364/0019

OXYTOCIN 10IU SOLUTION FOR INJECTION
PL 19364/0020

UKPAR

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LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted UKR Regulatory Affairs Limited Marketing Authorisations (licences) for the medicinal products Oxytocin 5IU Solution for Injection (PL 19364/0019) and Oxytocin 10IU Solution for Injection (PL 19364/0020) on 23rd February 2010. These are prescription-only medicines (POM).

Oxytocin Solution for Injection contains the active ingredient oxytocin and belongs to a group of medicines called oxytocins and is identical to the hormone oxytocin.

Oxytocin is a hormone released by the pituitary gland, which has an effect on the muscles of the uterus (womb). Oxytocin is used to help the muscles of the womb contract.

Oxytocin may be used to induce labour, or to stimulate labour where the contractions are not adequate, or after delivery of the baby where there may be weak or absent contraction of the uterus or to prevent uterine bleeding. It may also be used during Caesarean section or as additional therapy for the management of miscarriage.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Oxytocin 5IU Solution for Injection and Oxytocin 10IU Solution for Injection outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal products Oxytocin 5IU Solution for Injection (PL 19364/0019) and Oxytocin 10IU Solution for Injection (PL 19364/0020) to UKR Regulatory Affairs Limited on 23rd February 2010. These products are prescription-only medicines.

These applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC. The products are claimed to be generic medicinal products of the original, Syntocinon Ampoules 5 IU/ml and 10 IU/ml (PL 16853/0019 & PL 16853/0020), currently authorised to Alliance Pharmaceuticals Ltd UK following a change of ownership on the 25th May 1998. These products were originally authorised on 3rd October 1977 to Novartis Pharmaceuticals UK Limited. The reference products have therefore been authorised in the EU for more than 10 years.

The product contains the active ingredient oxytocin. Oxytocin is a hormone released by the pituitary gland and is used to help the muscles of the womb contract. When given by low-dose intra-venous infusion, oxytocin elicits rhythmic uterine contractions that are indistinguishable in frequency, force, and duration from those observed during spontaneous labour. At higher infusion dosages, or when given by single injection, the drug is capable of causing sustained uterine contractions.

These applications were submitted at the same time and all sections of this Scientific Discussion refer to both products.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Oxytocin

INN: Oxytocin

Structure

\[
\text{H} - \text{Cys} - \text{Tyr} - \text{Ile} - \text{Gln} - \text{Asn} - \text{Cys} - \text{Pro} - \text{Leu} - \text{Gly} - \text{NH}_2
\]

\[\text{C}_{49}\text{H}_{68}\text{N}_{12}\text{O}_{12}\text{S}_2\quad M_r 1007\]

General Properties

Oxytocin is a white or almost white powder, hygroscopic, very soluble in water and in dilute solutions of acetic acid and of ethanol.

Manufacture

All aspects of the manufacture of the active substance oxytocin from its starting materials are controlled by a Certificate of Suitability.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guideline. Batch analysis data are provided and comply with the proposed specification.

Oxytocin meets the requirements of the current monograph of the European Pharmacopoeia and complies with the additional tests for residual solvents and the microbial limit is in line with Ph Eur requirements.

All potential known impurities have been identified and characterised. Suitable Certificates of Analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be physically and chemically stable drug and supporting an appropriate retest period.
DRUG PRODUCT

Other ingredients
Other ingredients consist of pharmaceutical excipients, namely sodium chloride, sodium acetate tri-hydrate, glacial acetic acid and water for injections. All ingredients comply with their European Pharmacopoeia monographs. Appropriate justification for the inclusion of each excipient has been provided. Satisfactory Certificates of Analysis have been provided for all the excipients.

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

Product development
The objective of the development programme was to produce products that could be considered generic medicinal products of Syntocinon Ampoules 5 IU/ml and 10 IU/ml (PL 16853/0019 & PL 16853/0020) granted to Alliance Pharmaceuticals Ltd UK, on 25th May 1998. Comparative analytical data has been provided to demonstrate that the proposed products are similar to the reference products. The formulated products meet the Pharmacopoeial requirements for sterility, bacterial endotoxins and particulate contamination for parenteral products.

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

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on three production scale batches for each strength has been provided and demonstrate compliance with the release specification. Certificates of Analysis have been provided for any working standards used.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate.

Container Closure System
The immediate packaging of the finished product consists of 1-ml Type 1 colourless glass ampoules. The ampoules are packed in box sizes of 5, 10, 50 and 100 ampoules. Not all pack sizes may be marketed. Specifications and Certificates of Analysis for all packaging types used have been provided. All primary product packaging complies with European Pharmacopoeia monograph 3.2.1 (glass containers for pharmaceutical use).

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 year has been set with the following special storage precautions, “Store in a refrigerator (2°C - 8°C)” and “May be stored below 25°C for 6 months, but then discarded”. A commitment should be provided to test at least one production batch per year.

Bioequivalence/Bioavailability

Deleted:
The applicant has provided satisfactory justification for the bio waiver, based on 5.1.6 Parenteral solution CPMP/EWP/QWP/1401/98, page 13. The applicant’s product is an IV injection that contains the same active substance in the same concentration as the currently authorised reference product ‘Syntocinon’.

The applicant’s product differs from the reference product with respect to excipients. This change in the excipients of the applicant formulation is unlikely to affect its in vivo performance.

**Essential Similarity**
The drug substance complies with Ph Eur monograph for Oxytocin. A biowaiver is claimed. Comparative analytical data for the proposed and reference products confirmed identical pH 3.95, assay and related substances and gave identical impurity profile by chromatograms. The applicant product is isotonic, whereas the reference product is not. Essential similarity is considered to be demonstrated.

**ADMINISTRATIVE**
**Expert Report**
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are pharmaceutically acceptable.

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. 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.

**MAA form**
The MAA form is pharmaceutically satisfactory.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

These applications for Oxytocin 5IU and 10IU Solution for Injection were submitted as a national abridged application, according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of Syntocinon Ampoules 5 IU/ml and 10 IU/ml (PL 16853/0019 & PL 16853/0020) granted to Alliance Pharmaceuticals Ltd UK, on 25th May 1998.

No new preclinical data have been supplied with these applications and none are required for applications of this type.

A preclinical expert report has been written by a suitably qualified person and is satisfactory.

The Marketing Authorisation Holder has been provided adequate justification for not submitting an Environmental Risk Assessment.
CLINICAL ASSESSMENT

BACKGROUND
Active ingredient oxytocin is a synthesized hormone and a polypeptide constituted by nine amino acids. Synthetic oxytocin is identical with a hormone released by the posterior lobe of the pituitary gland. Oxytocin is indicated for the induction of labour, stimulation of labour in hypotonic uterine inertia, and for the prevention and treatment of postpartum uterine atony and haemorrhage.

Concentration of oxytocin in the test product is identical to the reference product. The test and reference product, however, differ by composition of excipients. The reference product contains in addition two preservatives in its formulation, chlorbutanol and ethanol. Test product is simpler.

Assessor’s comment:
Differences in pharmaceutical composition are not clinically relevant.

CLINICAL ASSESSMENT
Indications

Introduction
The clinical expert report has been written by an appropriately qualified person and is a suitable summary if the clinical aspects of the dossier.

Clinical study reports
No bioequivalence studies have been conducted. The applicant claims for biowaiver and refers to the NfG on the Investigation of BA & BE (CPMP/EWP/QWP/1401/98). Oxytocin UKR 5 (and 10) IU/ml solution for injection is for intravenous administration only. For parenteral aqueous solutions no bioequivalence study is needed.

Assessor's comment:
Oxytocin is a synthetic peptide which contains nine amino acids in its chain. Oxytocin is synthesised by chemical synthesis, therefore there are no extra immunogenicity issues compared to other chemical medicines. Biowaiver is acceptable. No other new clinical studies have been submitted.

Efficacy
No new data has been provided

Safety
No new data has been provided

Expert Reports
The clinical expert report has been written by a suitably qualified person and is satisfactory.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are medically acceptable.

Application form (MAA)
These are satisfactory.

Benefit-Risk assessment
No post-marketing data is available for the Oxytocin UKR 5 (and 10) IU/ml. The medicinal product has not been marketed in any country.

Synthetic oxytocin is an established active ingredient which has been used clinically throughout the world for fifty years. The applicant has not conducted any clinical trials with their formulations.

Pharmacovigilance System
The Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant 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.

Risk Management System
Oxytocin 5IU and 10IU Solution for Injections are generic products. No specific risks are related to oxytocin as an active ingredient. A risk management plan is therefore not required.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Oxytocin 5IU Solution for Injection (PL 19364/0019) and Oxytocin 10IU Solution for Injection (PL 19364/0020) 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.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Oxytocin is a well-known drug and has been used for many years. No bioequivalence studies have been performed and none are required for these applications, as the product is administered as a parental aqueous solution rapidly in vivo.

No formal data on clinical efficacy or safety have been presented for these applications and none are required.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with oxytocin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

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<td>1</td>
<td>The MHRA received the marketing authorisation application on 8th December 2006.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 28th February 2007.</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 10th August 2007, 20th August 2007 and 10th December 2009.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 20th August 2007, 28th May 2009 and 12th January 2010.</td>
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<tr>
<td>5</td>
<td>The applications were determined on 23rd February 2010.</td>
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OXYTOCIN 5IU SOLUTION FOR INJECTION
PL 19364/0019

OXYTOCIN 10IU SOLUTION FOR INJECTION
PL 19364/0020

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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OXYTOCIN 5IU SOLUTION FOR INJECTION
PL 19364/0019

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Oxytocin 5IU Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution contains 5IU oxytocin, equivalent to 8.5 micrograms of oxytocin EP in solution.
Each 1ml ampoule also contains 2.9 mg (0.13 mmol) of sodium.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection.
A clear, colourless solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Induction of labour for medical reasons; stimulation of labour in hypotonic uterine inertia; during caesarean section, following delivery of the child; prevention and treatment of postpartum uterine atony and haemorrhage.
Early stages of pregnancy as an adjunctive therapy for the management of incomplete, inevitable, or missed abortion.

4.2 Posology and method of administration
Induction or enhancement of labour: Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins. Oxytocin should be administered as an iv drip infusion or, preferably, by means of a variable-speed infusion pump. For drip infusion it is recommended that 5 IU of oxytocin be added to 500ml of a physiological electrolyte solution. For patients in whom infusion of sodium chloride must be avoided, 5% dextrose solution may be used as the diluent (see Section 4.4 “Special warnings and precautions for use”). To ensure even mixing, the bottle or bag must be turned upside down several times before use.
The initial infusion rate should be set at 1 to 4mU/min (2 to 8 drops/min). It may be gradually increased at intervals not shorter than 20 min, until a contraction pattern similar to that of normal labour is established. In pregnancy near term this can often be achieved with an infusion of less than 10mU/min (20 drops/min), and the recommended maximum rate is 20mU/min (40 drops/min). In the unusual event that higher rates are required, as may occur in the management of foetal death in utero or for induction of labour at an earlier stage of pregnancy, when the uterus is less sensitive to oxytocin, it is advisable to use a more concentrated oxytocin solution, e.g., 10 IU in 500ml.
When using a motor-driven infusion pump which delivers smaller volumes than those given by drip infusion, the concentration suitable for infusion within the recommended dosage range must be calculated according to the specifications of the pump. The frequency, strength, and duration of contractions as well as the foetal heart rate must be carefully monitored throughout the infusion. Once an adequate level of uterine activity is attained, aiming for 3 to 4 contractions every 10 minutes, the infusion rate can often be reduced. In the event of uterine hyperactivity and/or foetal distress, the infusion must be discontinued immediately.
If, in women who are at term or near term, regular contractions are not established after the infusion of a total amount of 5 IU, it is recommended that the attempt to induce labour be ceased; it may be
repeated on the following day, starting again from a rate of 1 to 4mU/min (see Section 4.3 “Contra-
indications”).

**Caesarean section**: 5 IU by slow iv injection immediately after delivery.

**Prevention of postpartum uterine haemorrhage**: The usual dose is 5 IU slowly iv after delivery of
the placenta. In women given oxytocin for induction or enhancement of labour, the infusion should
be continued at an increased rate during the third stage of labour and for the next few hours
thereafter.

**Treatment of postpartum uterine haemorrhage**: 5 IU slowly iv, followed in severe cases by iv
infusion of a solution containing 5 to 20 IU of oxytocin in 500ml of a non-hydrating diluent, run at
the rate necessary to control uterine atony.

**Incomplete, inevitable, or missed abortion**: 5 IU slowly iv, if necessary followed by iv infusion at a
rate of 20 to 40mU/min or higher.

**Children**: Not applicable.

**Elderly**: Not applicable.

**Route of administration**: Intravenous infusion or intravenous injection.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Hypertonic uterine contractions, mechanical obstruction to delivery, foetal distress. Any condition in
which, for foetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is
contra-indicated: e.g., significant cephalopelvic disproportion; foetal malpresentation; placenta
praevia and vasa praevia; placental abruption; cord presentation or prolapse; overdistension or
impaired resistance of the uterus to rupture as in multiple pregnancy; polyhydramnios; grand
multiparity and in the presence of a uterine scar resulting from major surgery including classical
caesarean section.

Oxytocin should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia,
severe pre-eclamptic toxemia or severe cardiovascular disorders.

### 4.4 Special warnings and precautions for use

The induction of labour by means of oxytocin should be attempted only when strictly indicated for
medical reasons. Administration should only be under hospital conditions and qualified medical
supervision. When given for induction and enhancement of labour, oxytocin must only be
administered as an iv infusion and never by iv bolus injection.

Administration of oxytocin at excessive doses results in uterine overstimulation which may cause
foetal distress, asphyxia and death, or may lead to hypertonicity, titanic contracts or rupture of the
uterus.

Careful monitoring of foetal heart rate and uterine motility (frequency, strength, and duration of
contractions) is essential, so that the dosage may be adjusted to individual response.

When oxytocin is given for induction or enhancement of labour, particular caution is required in the
presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate
degrees of pregnancy-induced hypertension or cardiac disease, and in patients above 35 years of age
or with a history of lower-uterine-segment caesarean section.

In rare circumstances, the pharmacological induction of labour using uteronic agents increases the
risk of post patum disseminated intravascular coagulation (DIC). The pharmacological induction
itself and not a particular agent is linked to such a risk. This risk is increased in particular if the
woman has additional risk factors for DIC such as being 35 years of age or over, complications
during pregnancy and gestational age more than 40 weeks. In these women, oxytocin or any other
alternative drug should be used with care, and the practitioner should be alerted by signs of DIC.
In the case of foetal death in utero, and/or in the presence of meconium-stained amniotic fluid, tumultuous labour must be avoided, as it may cause amniotic fluid embolism. Because oxytocin possesses slight antiuretic activity, its prolonged iv administration at high doses in conjunction with large volumes of fluid, as may be the case in the treatment of inevitable or missed abortion or in the management of postpartum haemorrhage, may cause water intoxication associated with hyponatraemia. To avoid this rare complication, the following precautions must be observed whenever high doses of oxytocin are administered over a long time: an electrolyte-containing diluent must be used (not dextrose); the volume of infused fluid should be kept low (by infusing oxytocin at a higher concentration than recommended for the induction or enhancement of labour at term); fluid intake by mouth must be restricted; a fluid balance chart should be kept, and serum electrolytes should be measured when electrolyte imbalance is suspected.

When oxytocin is used for prevention or treatment of uterine haemorrhage, rapid iv injection should be avoided, as it may cause an acute short-lasting drop in blood pressure.

4.5 Interaction with other medicinal products and other forms of interaction
Since it has been found that prostaglandins potentiate the effect of oxytocin, it is not recommended that these drugs are used together. If used in sequence, the patient's uterine activity should be carefully monitored.

Some inhalation anesthetics, e.g., cyclopropane or halothane, may enhance the hypotensive effect of oxytocin and reduce its oxytocic action. Their concurrent use with oxytocin has also been reported to cause cardiac rhythm disturbances.

When given during or after caudal block anaesthesia, oxytocin may potentiate the pressor effect of sympathomimetic vasoconstrictor agents.

4.6 Pregnancy and lactation
Animal reproduction studies have not been conducted with oxytocin. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it is not expected to present a risk of foetal abnormalities when used as indicated. Oxytocin may be found in small quantities in mothers’ breast milk. However, oxytocin is not expected to cause harmful effects in the newborn because it passes into the alimentary tract where it undergoes rapid inactivation.

4.7 Effects on ability to drive and use machines
Oxytocin can induce labour, therefore caution should be exercised when driving or operating machines. Women with uterine contractions should not drive or use machines.

4.8 Undesirable effects
As there is a wide variation in uterine sensitivity, uterine spasm may be caused in some instances by what are normally considered to be low doses. When oxytocin is used by iv infusion for the induction or enhancement of labour, administration at too high doses results in uterine overstimulation which may cause foetal distress, asphyxia, and death, or may lead to hypertonicity, tetrican contractions, soft tissue damage or rupture of the uterus.

Water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high doses of oxytocin together with large amounts of electrolyte-free fluid have been administered over a prolonged period of time (see Section 4.4 “Special warnings and precautions for use”). Symptoms of water intoxication include:

1. Headache, anorexia, nausea, vomiting and abdominal pain.
2. Lethargy, drowsiness, unconsciousness and grand-mal type seizures.
3. Low blood electrolyte concentration.

Rapid iv bolus injection of oxytocin at doses amounting to several IU may result in acute short-lasting hypotension accompanied with flushing and reflex tachycardia.

In rare circumstances the pharmacological induction of labour using uterotonic agents increases the risk of postpartum disseminated intravascular coagulation (see section 4.4 Special warnings and special precautions for use).
Oxytocin may occasionally cause nausea, vomiting, haemorrhage or cardiac arrhythmias. In a few cases, skin rashes and anaphylactoid reactions associated with dyspnoea, hypotension, or shock have been reported.

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<td>Anaphalactoid reaction associated with dyspnoea, hypotension or shock.</td>
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<td>Arrhythmia</td>
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<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Rare:</td>
<td>Rash</td>
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4.9 Overdose

The fatal dose of oxytocin has not been established. Oxytocin is subject to inactivation by proteolytic enzymes of the alimentary tract. Hence it is not absorbed from the intestine and is not likely to have toxic effects when ingested.

The symptoms and consequences of overdosage are those mentioned under Section 4.8 “Undesirable effects”. In addition, as a result of uterine overstimulation, placental abruption and/or amniotic fluid embolism have been reported.

_Treatment:_ When signs or symptoms of overdosage occur during continuous iv administration of oxytocin, the infusion must be discontinued at once and oxygen should be given to the mother. In cases of water intoxication it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance, and control convulsions that may eventually occur, by judicious use of diazepam. In the case of coma, a free airway should be maintained with routine measures normally employed in the nursing of the unconscious patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic hormonal preparations excl sex hormones and insulins

ATC code: H01B B02

The active principle of oxytocin is a synthetic nonapeptide identical with oxytocin, a hormone released by the posterior lobe of the pituitary. It exerts a stimulatory effect on the smooth musculature of the uterus, particularly towards the end of pregnancy, during labour, after delivery, and in the puerperium, i.e., at times when the number of specific oxytocin receptors in the myometrium is increased.

When given by low-dose iv infusion, oxytocin elicits rhythmic uterine contractions that are indistinguishable in frequency, force, and duration from those observed during spontaneous labour. At higher infusion dosages, or when given by single injection, the drug is capable of causing sustained uterine contractions.

Being synthetic, oxytocin does not contain vasopressin, but even in its pure form oxytocin possesses some weak intrinsic vasopressin-like antidiuretic activity.

Another pharmacological effect observed with high doses of oxytocin, particularly when administered by rapid iv bolus injection, consists of a transient direct relaxing effect on vascular smooth muscle, resulting in brief hypotension, flushing and reflex tachycardia.
5.2 Pharmacokinetic properties
The plasma half-life of oxytocin is of the order of five minutes, hence the need for continuous iv infusion. Elimination is via the liver, kidney, functional mammary gland and oxytocinase.

5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium chloride
Sodium acetate tri-hydrate,
Acetic acid, glacial
Water for injections.

6.2 Incompatibilities
Oxytocin should not be infused via the same apparatus as blood or plasma, because the peptide linkages are rapidly inactivated by oxytocin-inactivating enzymes. Oxytocin is incompatible with solutions containing sodium metabisulphite as a stabiliser.

6.3 Shelf life
Three years

6.4 Special precautions for storage
Store in a refrigerator (2°C - 8°C). May be stored below 25°C for 6 months, but then discarded.

6.5 Nature and contents of container
Colourless glass (Type I) 1ml ampoules. Boxes containing 5, 10, 50 and 100 ampoules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Oxytocin is compatible with the following infusion fluids, but due attention should be paid to the advisability of using electrolyte fluids in individual patients: sodium/potassium chloride (103mmol Na⁺ and 51mmol K⁺), sodium bicarbonate 1.39%, sodium chloride 0.9%, sodium lactate 1.72%, dextrose 5%, laevulose 20%, macrodex 6%, rheomacrodex 10%, Ringer's solution.

7 MARKETING AUTHORISATION HOLDER
UKR Regulatory Affairs Limited
The Bull Pen,
Home Farm,
Banbury Road
Caversfield, Nr Bicester
OX27 8TG

8 MARKETING AUTHORISATION NUMBER(S)
PL 19364/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/02/2010

10 DATE OF REVISION OF THE TEXT
OXYTOCIN 10IU SOLUTION FOR INJECTION
PL 19364/0020

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Oxytocin 10IU Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution contains 10IU oxytocin, equivalent to 17 micrograms of oxytocin EP in solution.
Each 1ml ampoule also contains 2.9 mg (0.13 mmol) of sodium.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection.
A clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Induction of labour for medical reasons; stimulation of labour in hypotonic uterine inertia; during caesarean section, following delivery of the child; prevention and treatment of postpartum uterine atony and haemorrhage.
Early stages of pregnancy as a adjunctive therapy for the management of incomplete, inevitable, or missed abortion.

4.2 Posology and method of administration

Induction or enhancement of labour:
Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins. Oxytocin should be administered as an iv drip infusion or, preferably, by means of a variable-speed infusion pump. For drip infusion it is recommended that 5 IU of oxytocin be added to 500ml of a physiological electrolyte solution. For patients in whom infusion of sodium chloride must be avoided, 5% dextrose solution may be used as the diluent (see Section 4.4 “Special warnings and precautions for use”). To ensure even mixing, the bottle or bag must be turned upside down several times before use.
The initial infusion rate should be set at 1 to 4mU/min (2 to 8 drops/min). It may be gradually increased at intervals not shorter than 20 min, until a contraction pattern similar to that of normal labour is established. In pregnancy near term this can often be achieved with an infusion of less than 10mU/min (20 drops/min), and the recommended maximum rate is 20mU/min (40 drops/min). In the unusual event that higher rates are required, as may occur in the management of foetal death in utero or for induction of labour at an earlier stage of pregnancy, when the uterus is less sensitive to oxytocin, it is advisable to use a more concentrated oxytocin solution, e.g., 10 IU in 500ml.

When using a motor-driven infusion pump which delivers smaller volumes than those given by drip infusion, the concentration suitable for infusion within the recommended dosage range must be calculated according to the specifications of the pump. The frequency, strength, and duration of contractions as well as the foetal heart rate must be carefully monitored throughout the infusion. Once an adequate level of uterine activity is attained, aiming for 3 to 4 contractions every 10 minutes, the infusion rate can often be reduced. In the event of uterine hyperactivity and/or foetal distress, the infusion must be discontinued immediately.

If, in women who are at term or near term, regular contractions are not established after the infusion of a total amount of 5 IU, it is recommended that the attempt to induce labour be ceased; it may be repeated on the following day, starting again from a rate of 1 to 4mU/min (see Section 4.3 “Contraindications”).

Caesarean section: 5 IU by slow iv injection immediately after delivery.
Prevention of postpartum uterine haemorrhage: The usual dose is 5 IU slowly iv after delivery of the placenta. In women given oxytocin for induction or enhancement of labour, the infusion should be continued at an increased rate during the third stage of labour and for the next few hours thereafter.

Treatment of postpartum uterine haemorrhage: 5 IU slowly iv, followed in severe cases by iv infusion of a solution containing 5 to 20 IU of oxytocin in 500ml of a non-hydrating diluent, run at the rate necessary to control uterine atony.

Incomplete, inevitable, or missed abortion: 5 IU slowly iv, if necessary followed by iv infusion at a rate of 20 to 40mU/min or higher.

Children: Not applicable.

Elderly: Not applicable.

Route of administration: Intravenous infusion or intravenous injection.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Hypertonic uterine contractions, mechanical obstruction to delivery, foetal distress. Any condition in which, for foetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is contra-indicated: e.g., significant cephalopelvic disproportion; foetal malpresentation; placenta praevia and vasa praevia; placental abruption; cord presentation or prolapse; overdistension or impaired resistance of the uterus to rupture as in multiple pregnancy; polhydramnios; grand multiparity and in the presence of a uterine scar resulting from major surgery including classical caesarean section.

Oxytocin should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.

4.4 Special warnings and precautions for use
The induction of labour by means of oxytocin should be attempted only when strictly indicated for medical reasons. Administration should only be under hospital conditions and qualified medical supervision. When given for induction and enhancement of labour, oxytocin must only be administered as an iv infusion and never by iv bolus injection. Careful monitoring of foetal heart rate and uterine motility (frequency, strength, and duration of contractions) is essential, so that the dosage may be adjusted to individual response.

Administration of oxytocin at excessive doses results in uterine overstimulation which may cause foetal distress, asphyxia and death, or may lead to hypertonicity, titanic contracts or rupture of the uterus.

When oxytocin is given for induction or enhancement of labour, particular caution is required in the presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate degrees of pregnancy-induced hypertension or cardiac disease, and in patients above 35 years of age or with a history of lower-uterine-segment caesarean section.

In rare circumstances, the pharmacological induction of labour using uteronic agents increases the risk of post patum disseminated intravascular coagulation (DIC). The pharmacological induction itself and not a particular agent is linked to such a risk. This risk is increased in particular if the woman has additional risk factors for DIC such as being 35 years of age or over, complications during pregnancy and gestational age more than 40 weeks. In these women, oxytocin or any other alternative drug should be used with care, and the practitioner should be alerted by signs of DIC.

In the case of foetal death in utero, and/or in the presence of meconium-stained amniotic fluid, tumultuous labour must be avoided, as it may cause amniotic fluid embolism.

Because oxytocin possesses slight antidiuretic activity, its prolonged iv administration at high doses in conjunction with large volumes of fluid, as may be the case in the treatment of inevitable or missed abortion or in the management of postpartum haemorrhage, may cause water intoxication associated with hyponatraemia. To avoid this rare complication, the following precautions must be observed whenever high doses of oxytocin are administered over a long time: an electrolyte-
containing diluent must be used (not dextrose); the volume of infused fluid should be kept low (by infusing oxytocin at a higher concentration than recommended for the induction or enhancement of labour at term); fluid intake by mouth must be restricted; a fluid balance chart should be kept, and serum electrolytes should be measured when electrolyte imbalance is suspected.

When oxytocin is used for prevention or treatment of uterine haemorrhage, rapid iv injection should be avoided, as it may cause an acute short-lasting drop in blood pressure.

4.5 Interaction with other medicinal products and other forms of interaction

Since it has been found that prostaglandins potentiate the effect of oxytocin, it is not recommended that these drugs are used together. If used in sequence, the patient's uterine activity should be carefully monitored.

Some inhalation anaesthetics, e.g., cyclopropane or halothane, may enhance the hypotensive effect of oxytocin and reduce its oxytocic action. Their concurrent use with oxytocin has also been reported to cause cardiac rhythm disturbances.

When given during or after caudal block anaesthesia, oxytocin may potentiate the pressor effect of sympathomimetic vasoconstrictor agents.

4.6 Pregnancy and lactation

Animal reproduction studies have not been conducted with oxytocin. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it is not expected to present a risk of foetal abnormalities when used as indicated. Oxytocin may be found in small quantities in mothers’ breast milk. However, oxytocin is not expected to cause harmful effects in the newborn because it passes into the alimentary tract where it undergoes rapid inactivation.

4.7 Effects on ability to drive and use machines

Oxytocin can induce labour, therefore caution should be exercised when driving or operating machines. Women with uterine contractions should not drive or use machines.

4.8 Undesirable effects

As there is a wide variation in uterine sensitivity, uterine spasm may be caused in some instances by what are normally considered to be low doses. When oxytocin is used by iv infusion for the induction or enhancement of labour, administration at too high doses results in uterine overstimulation which may cause foetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft tissue damage or rupture of the uterus.

Water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high doses of oxytocin together with large amounts of electrolyte-free fluid have been administered over a prolonged period of time (see Section 4.4 “Special warnings and precautions for use”). Symptoms of water intoxication include:
1. Headache, anorexia, nausea, vomiting and abdominal pain.
2. Lethargy, drowsiness, unconsciousness and grand-mal type seizures.
3. Low blood electrolyte concentration.

Rapid iv bolus injection of oxytocin at doses amounting to several IU may result in acute short-lasting hypotension accompanied with flushing and reflex tachycardia. In rare circumstances the pharmacological induction of labour using uterotonic agents increases the risk of postpartum disseminated intravascular coagulation (see section 4.4 Special warnings and special precautions for use).

Oxytocin may occasionally cause nausea, vomiting, haemorrhage or cardiac arrhythmias. In a few cases, skin rashes and anaphylactoid reactions associated with dyspnoea, hypotension, or shock have been reported.

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<thead>
<tr>
<th>Immune system disorders</th>
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<td>Anaphalactoid reaction associated with</td>
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4.9 Overdose

The fatal dose of oxytocin has not been established. Oxytocin is subject to inactivation by proteolytic enzymes of the alimentary tract. Hence it is not absorbed from the intestine and is not likely to have toxic effects when ingested.

The symptoms and consequences of overdosage are those mentioned under Section 4.8 “Undesirable effects”. In addition, as a result of uterine overstimulation, placental abruption and/or amniotic fluid embolism have been reported.

Treatment: When signs or symptoms of overdosage occur during continuous iv administration of oxytocin, the infusion must be discontinued at once and oxygen should be given to the mother. In cases of water intoxication it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance, and control convulsions that may eventually occur, by judicious use of diazepam. In the case of coma, a free airway should be maintained with routine measures normally employed in the nursing of the unconscious patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic hormonal preparations excl sex hormones and insulins

ATC code: H01B B02

The active principle of oxytocin is a synthetic nonapeptide identical with oxytocin, a hormone released by the posterior lobe of the pituitary. It exerts a stimulatory effect on the smooth musculature of the uterus, particularly towards the end of pregnancy, during labour, after delivery, and in the puerperium, i.e., at times when the number of specific oxytocin receptors in the myometrium is increased.

When given by low-dose iv infusion, oxytocin elicits rhythmic uterine contractions that are indistinguishable in frequency, force, and duration from those observed during spontaneous labour. At higher infusion dosages, or when given by single injection, the drug is capable of causing sustained uterine contractions.

Being synthetic, oxytocin does not contain vasopressin, but even in its pure form oxytocin possesses some weak intrinsic vasopressin-like antidiuretic activity.

Another pharmacological effect observed with high doses of oxytocin, particularly when administered by rapid iv bolus injection, consists of a transient direct relaxing effect on vascular smooth muscle, resulting in brief hypotension, flushing and reflex tachycardia.

5.2 Pharmacokinetic properties

The plasma half-life of oxytocin is of the order of five minutes, hence the need for continuous iv infusion. Elimination is via the liver, kidney, functional mammary gland and oxytocinase.
5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium chloride
Sodium acetate tri-hydrate,
Acetic acid, glacial
Water for injections.

6.2 Incompatibilities
Oxytocin should not be infused via the same apparatus as blood or plasma, because the peptide linkages are rapidly inactivated by oxytocin-inactivating enzymes. Oxytocin is incompatible with solutions containing sodium metabisulphite as a stabiliser.

6.3 Shelf life
Three years

6.4 Special precautions for storage
Store in a refrigerator (2°C - 8°C). May be stored below 25°C for 6 months, but then discarded.

6.5 Nature and contents of container
Colourless glass (Type I) 1ml ampoules. Boxes containing 5, 10, 50 and 100 ampoules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Oxytocin is compatible with the following infusion fluids, but due attention should be paid to the advisability of using electrolyte fluids in individual patients: sodium/potassium chloride (103mmol Na⁺ and 51mmol K⁺), sodium bicarbonate 1.39%, sodium chloride 0.9%, sodium lactate 1.72%, dextrose 5%, laevulose 20%, macrodex 6%, rheomacrodex 10%, Ringer's solution.

7 MARKETING AUTHORISATION HOLDER
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Banbury Road
Caversfield, Nr Bicester,
OX27 8TG

8 MARKETING AUTHORISATION NUMBER(S)
PL 19364/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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10 DATE OF REVISION OF THE TEXT
23/02/2010
OXYTOCIN 5 IU SOLUTION FOR INJECTION
OXYTOCIN 10 IU SOLUTION FOR INJECTION

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PATIENT INFORMATION LEAFLET

OXYTOCIN 5 IU SOLUTION FOR INJECTION
OXYTOCIN 10 IU SOLUTION FOR INJECTION

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1. What Oxytocin 5 IU and Oxytocin 10 IU solutions for injection are and what they are used for

Each Oxytocin ampoule contains oxytocin (International Unit) in 1 ml solution, equivalent to 5 micrograms or 10 micrograms respectively.

Oxytocin is a drug that belongs to the group of medicines called oxytocics and its chemical name is oxytocin, a hormone released by the pituitary gland, which has an effect on the muscles of the uterus (womb). Oxytocin is used to help the muscles of the womb contract.

Oxytocin may be used to induce labour, to stimulate labour after a woman has been in labour for some time, or after delivery of the baby or to prevent or treat leaking of milk from the breasts. It may also be used during Caesarean section or as an additional therapy for the management of miscarriage.

2. Before you take Oxytocin 5 IU solution for injection or Oxytocin 10 IU solution for injection

Do not take Oxytocin:

- if you are allergic or hypersensitive to any of the ingredients of this medicine,
- if you have any of the following conditions, where there is a mechanical obstruction in the birth canal (such as a baby not ready to deliver, or a placenta that is not separated from the uterus),
- if you have a history of placental separation, placenta praevia (the placenta is near the cervix), vein presentation, previous classical caesarean section, and other conditions which your healthcare professional will advise you about.

Oxytocin will not be used if:

- you have a condition known as severe pre-eclampsia: swelling (high blood pressure, swelling, and protein in the urine).

Special care with Oxytocin will be taken:

- if you are over 35 years old,
- if you have had a previous caesarean section,
- if you have had a recent surgery (such as a cesarean section),
- if you have been told you have high blood pressure (called pre-eclampsia) or heart problems,
- if you have been told you have diabetes or heart disease,
- if you have been told you have high blood pressure (called pre-eclampsia) or heart problems,
- if you are taking a medicine that is an anticoagulant (such as aspirin or warfarin)
- if you are taking any other medicines (such as aspirin or warfarin) that may increase the risk of bleeding

Please tell your doctor or pharmacist if you are taking any other medicines, including medicines obtained without a prescription.

Important information about some of the ingredients of Oxytocin

Each ampoule contains 0.5 mg of sodium.
The following information is intended for medical or healthcare professionals only.

OXYTOCIN 5 IU
OXYTOCIN 10 IU
solution for injection

Safety Information:
For intravenous or intramuscular injection.

Incompatibilities:
Oxytocin should not be infused in the same apparatus as blood or plasma because the peptide bonds are rapidly inactivated by oxytocin-inactivating enzymes.

Oxytocin is incompatible with solutions containing sodium bisulfite as a stabilizer.

Introduction on preparation and injection:
For administration by injection:
Oxytocin is compatible with the following infusion fluids, but due attention should be paid to the advisability of using these fluids in individual patients:
- Normal saline (0.9%)
- Ringer's solution
- Lactated Ringer's solution
- Sodium bicarbonate 1.2%
- Sodium bicarbonate 8.4%
- Sodium lactate 3.8%

For depot injections, it is recommended that 1 IU of Oxytocin be added to 1 ml of a physiological saline solution. For patients in whom infusion of sodium chloride must be avoided, 0.9% dextrose solution may be used as the diluent.

To ensure even mixing, the bottle or vial must be turned upside down several times beforehand.

Administration:
Deposition or administration of labour: Oxytocin should be infused in large for 6 hours following administration of vaginal prostaglandins.
Oxytocin should be administered only drop at a time infused directly by means of a suitable infusion pump. For administration by drip administered IUI, Oxytocin is administered at a rate of 2 IU/hour of a physiological saline solution. For patients in whom infusion of sodium chloride must be avoided, 0.9% dextrose solution may be used as the diluent.

Special warnings and precautions to be taken in the use of:

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3. Treatment with Oxytocin
Oxytocin should only be given under medical supervision and in a hospital.
For routine use, oxytocin must be given intravenously.

- When using oxytocin for induction of labour or for termination of pregnancy, the dosage should be increased at intervals of 5 minutes or more to a maximum of 50 IU per hour or 150 IU per 24 hours.
- In the management of postpartum haemorrhage, oxytocin should be given intravenously at a dose of 50 IU per 24 hours or 150 IU per 24 hours.

- If oxytocin is given in injectable form, it should be mixed with saline or with an appropriate diluent at the rate of 1:1000 to 1:5000.

- Oxytocin is not recommended for use in the treatment of postpartum haemorrhage.

4. Possible side effects

- Nausea, vomiting, diarrhoea, or abdominal pain.
- Dizziness, dizziness, or feeling light-headed.
- Headache, dizziness, or feeling faint.
- Feels hot, feels cold.