

**OXYTOCIN 5IU SOLUTION FOR INJECTION
PL 19364/0019**

**OXYTOCIN 10IU SOLUTION FOR INJECTION
PL 19364/0020**

UKPAR

TABLE OF CONTENTS

Lay Summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 12
Steps taken after authorisation – summary	Page 13
Summary of Product Characteristics	Page 14
Patient Information Leaflet	Page 24
Labelling	Page 27

**OXYTOCIN 5IU SOLUTION FOR INJECTION
PL 19364/0019**

**OXYTOCIN 10IU SOLUTION FOR INJECTION
PL 19364/0020**

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.

**OXYTOCIN 5IU SOLUTION FOR INJECTION
PL 19364/0019**

**OXYTOCIN 10IU SOLUTION FOR INJECTION
PL 19364/0020**

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 8
Clinical assessment	Page 9
Overall conclusions and risk benefit assessment	Page 11

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.

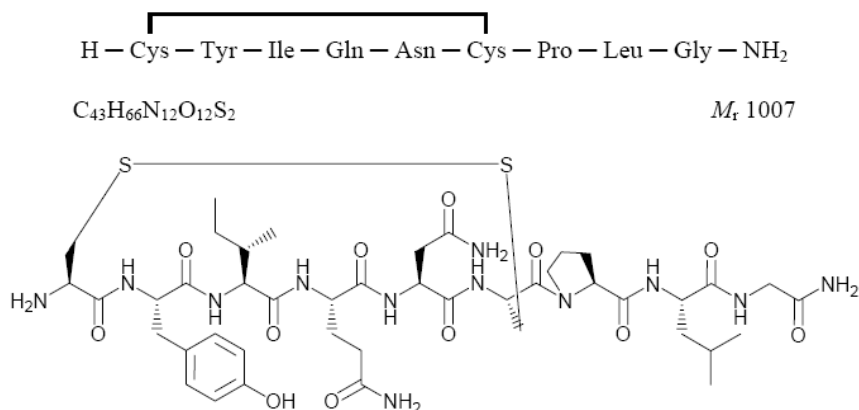
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Oxytocin

INN: Oxytocin

Structure



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.

Deleted: .

Bioequivalence/Bioavailability

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, where as 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 of 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.

**OXYTOCIN 5IU SOLUTION FOR INJECTION
PL 19364/0019**

**OXYTOCIN 10IU SOLUTION FOR INJECTION
PL 19364/0020**

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 8 th December 2006.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 28 th February 2007.
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 10 th August 2007, 20 th August 2007 and 10 th December 2009.
4	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 20 th August 2007, 28 th May 2009 and 12 th January 2010.
5	The applications were determined on 23 rd February 2010.

**OXYTOCIN 5IU SOLUTION FOR INJECTION
PL 19364/0019**

**OXYTOCIN 10IU SOLUTION FOR INJECTION
PL 19364/0020**

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

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 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; 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 partum 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.

Immune system disorders	
Rare:	Anaphylactoid reaction associated with dyspnoea, hypotension or shock.
Nervous system disorders	
Common:	Headache
Cardiac disorders	
Common:	Tachycardia, bradycardia
Uncommon:	Arrhythmia
Gastrointestinal disorders	
Common:	Nausea, vomiting
Skin and subcutaneous tissue disorders	
Rare:	Rash

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 "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-eclampsic 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. 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, tetanic contractions 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 partum 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.

Immune system disorders	
Rare:	Anaphylactoid reaction associated with

	dyspnoea, hypotension or shock.
Nervous system disorders	
Common:	Headache
Cardiac disorders	
Common:	Tachycardia, bradycardia
Uncommon:	Arrhythmia
Gastrointestinal disorders	
Common:	Nausea, vomiting
Skin and subcutaneous tissue disorders	
Rare:	Rash

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 19364/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/02/2010

10 DATE OF REVISION OF THE TEXT

23/02/2010

PATIENT INFORMATION LEAFLET

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

PL 19364/0019-20

OXYTOCIN 5 IU OXYTOCIN 10 IU solution for injection

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet please tell your doctor or pharmacist.

In this leaflet:

1. What Oxytocin 5 and Oxytocin 10 IU solutions for injection are and what they are used for
2. Before you take Oxytocin 5 IU solution for injection or Oxytocin 10 IU solution for injection
3. How to take Oxytocin 5 IU solution for injection or Oxytocin 10 IU solution for injection
4. Possible side effects
5. Storing your Oxytocin 5 IU solution for injection or Oxytocin 10 IU solution for injection
6. Further information

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

Each Oxytocin ampoule contains oxytocin EP, 5 IU (International Units) or 10 IU in 1ml solution, equivalent to 8.5 micrograms or 17 micrograms respectively.

Oxytocin is a drug that belongs to the group of medicines called oxytocins and it is identical with 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, 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 or treat uterine bleeding. It may also be used during Caesarean section or as 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 (hypersensitive) to oxytocin or any of the other ingredients of the solution,
- if you have any of the following conditions:
 - where there is mechanical obstruction to delivery foetal distress (your baby may be short of oxygen),
 - where your healthcare professional considers spontaneous delivery is inadvisable for foetal or maternal reasons, (such as foetal malpresentation, placenta praevia (the placenta is over the cervix), cord presentation, previous classical caesarean section, and other conditions which your healthcare professional will advise you about).

Oxytocin will not be used for a prolonged period if:

- your contractions do not respond,
- you have severe problems with your heart or circulation,
- you have a condition known as severe pre-eclamptic toxemia (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 mild or moderately raised blood pressure or heart problems,
- if normal delivery may be difficult for you due to the small size of your pelvis or the large head of the baby,
- if you are likely to need high doses over a long period of time,
- if you have had an epidural (caudal) anaesthetic block, oxytocin may increase the effects of some drugs used to constrict the blood vessels,
- if you are taking or have taken other medicines:
 - prostaglandins in the last 6 hours (the effect may be increased),
 - some anaesthetics given by inhalation such as halothane or cyclopropane (they may reduce the effect of oxytocin or may cause heart problems).

Please tell your doctor or midwife if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Important information about some of the ingredients of Oxytocin:

Each ampoule contains 2.9 mg (0.13 mmol) 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 infusion or intravenous injection

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.

Instructions on preparation and dilution:

Snap ampoules: no file required.

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%, Ringier's solution.

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. To ensure even mixing, the bottle or bag must be turned upside down several times before use.

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 not 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.

3. Treatment with Oxytocin

Oxytocin should only be given under medical supervision and in a hospital.

The dose used will vary depending on the reason for its use.

When being used for induction of labour or to stimulate existing labour, oxytocin will usually be diluted in 500 ml Saline or 5% Dextrose before use and will be given directly into a vein (intravenously) by drip infusion (slowly) or using an infusion pump. The initial infusion rate will be 2 to 8 drops/min; this may be gradually increased to a maximum rate of 40 drops/min. Once your contractions reach an adequate level of about 3-4 contractions per 10 minutes, the infusion rate will often be reduced.

- For Caesarean section, 5 IU will slowly be injected into the vein immediately after delivery of your baby.
- For prevention of bleeding after delivery, 5 IU will slowly be injected into your vein after delivery of the placenta.
- For treatment of bleeding after delivery, 5 IU will be slowly injected into your vein, followed, in some cases, by a drip containing 5 to 20 IU oxytocin.
- For miscarriage, 5 IU will be slowly injected into your vein, followed, if necessary by a drip at a high rate (40 to 80 drops/min).

If you receive more Oxytocin than you should or if you miss a dose:

As this medicine will be given to you by a healthcare professional in hospital, it is very unlikely that an overdose or missed dose will happen.

If you have any further questions on the use of this product, ask your doctor or midwife.

4. Possible side effects

Like all medicines, Oxytocin can cause side effects, although not everybody gets them.

Common side effects (more than 1 in 100 patients) of Oxytocin include:

- feeling or being sick,
- headache,
- fast or slow heartbeat,
- haemorrhage (bleeding).

Uncommon side effects (more than 1 in 1,000 patients) of Oxytocin include:

- an irregular heartbeat.

Rare side effects (more than 1 in 10,000 patients) of Oxytocin include:

- skin rashes,
- a severe allergic reaction causing dizziness, lightheadedness, feeling faint or difficulty in breathing,
- a blood clot following the birth of your baby.

If high doses of Oxytocin are given with large volumes of fluids through a drip the condition of water intoxication may occur.

Symptoms may include:

- headache,
- anorexia (loss of appetite),
- feeling or being sick,
- stomach pain,
- sluggishness,
- drowsiness,
- unconsciousness,
- low levels of certain chemicals in the blood (e.g. sodium or potassium),
- fits.

Rapid injection into a vein may cause a sudden but short-lasting drop in blood pressure (feeling faint or lightheaded) accompanied by reddening of the skin and a fast heartbeat.

Some patients may experience spasm of the muscles of the womb at what would normally be considered low doses. An overdose may cause very strong contractions of the womb, tearing of the womb, tissue damage. This could result in distress, suffocation or death of the baby.

If any of the side effects gets worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or midwife.

5. How to store Oxytocin

The hospital pharmacy will store this medicine in a refrigerator at 2°C to 8°C. It may be stored at 25°C for 6 months, but then discarded.

Keep Oxytocin out of the reach and sight of children.

The pharmacy will not use OXYTOCIN after the expiry date that is stated on the label.

6. Further information

What Oxytocin contains:

- The active substance is oxytocin.
- The other ingredients are sodium chloride, sodium acetate trihydrate, acetic acid, glacial and water for injection.

What Oxytocin looks like and contents of the pack

Your medicinal product comes in a clear glass 1ml ampoule. Boxes of 5, 10, 50 or 100 ampoules.

Marketing Authorisation Holder:

UKR Regulatory Affairs Limited
The Bull Pen, Home Farm, Banbury Road
Caversfield, Nr. Bicester, OX27 8TG

Manufacturer:

Laboratoire Aguettant
1 rue Alexander Fleming
69007 LYON - France

This leaflet was last approved in January 2010.

000000 00/00

The initial infusion rate should be set at 1 to 4 mL/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 10 mL/min (20 drops/min), and the recommended maximum rate is 20 mL/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 4 mL/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.

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.

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

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.

Children: Not applicable.

Elderly: Not applicable.

Storage and Shelf Life:

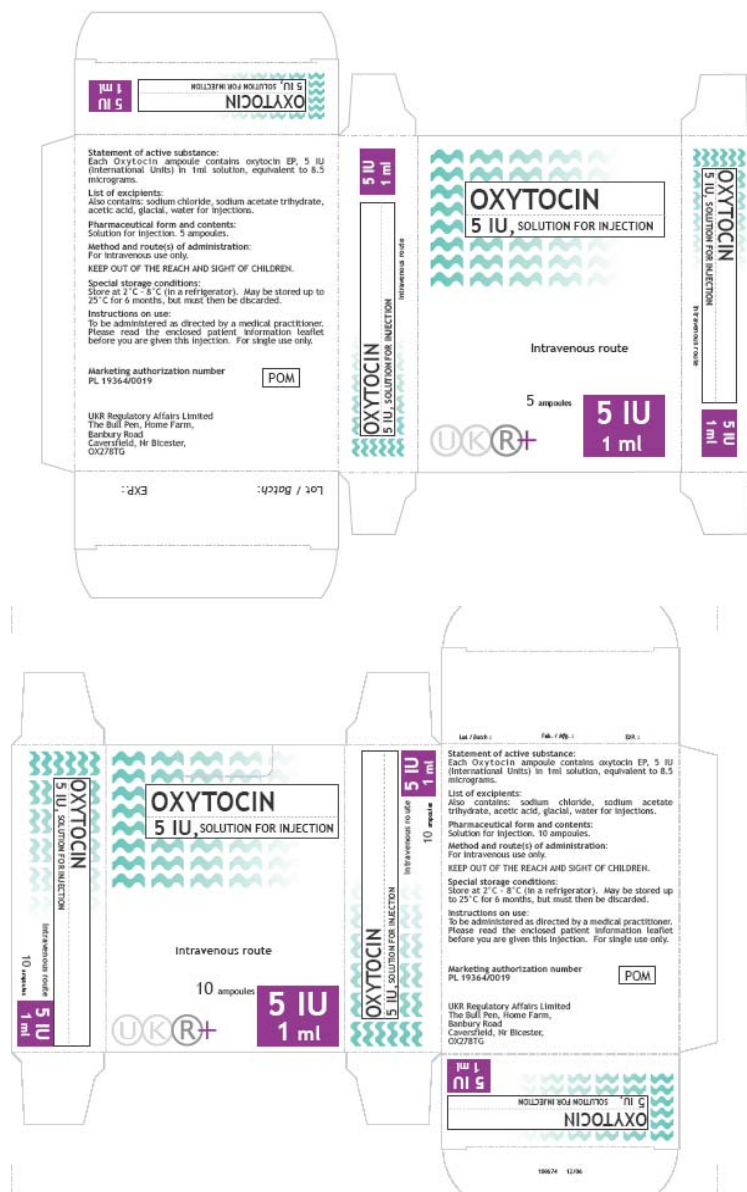
Store between 2°C and 8°C. May be stored up to 25°C for 6 months, but must then be discarded.

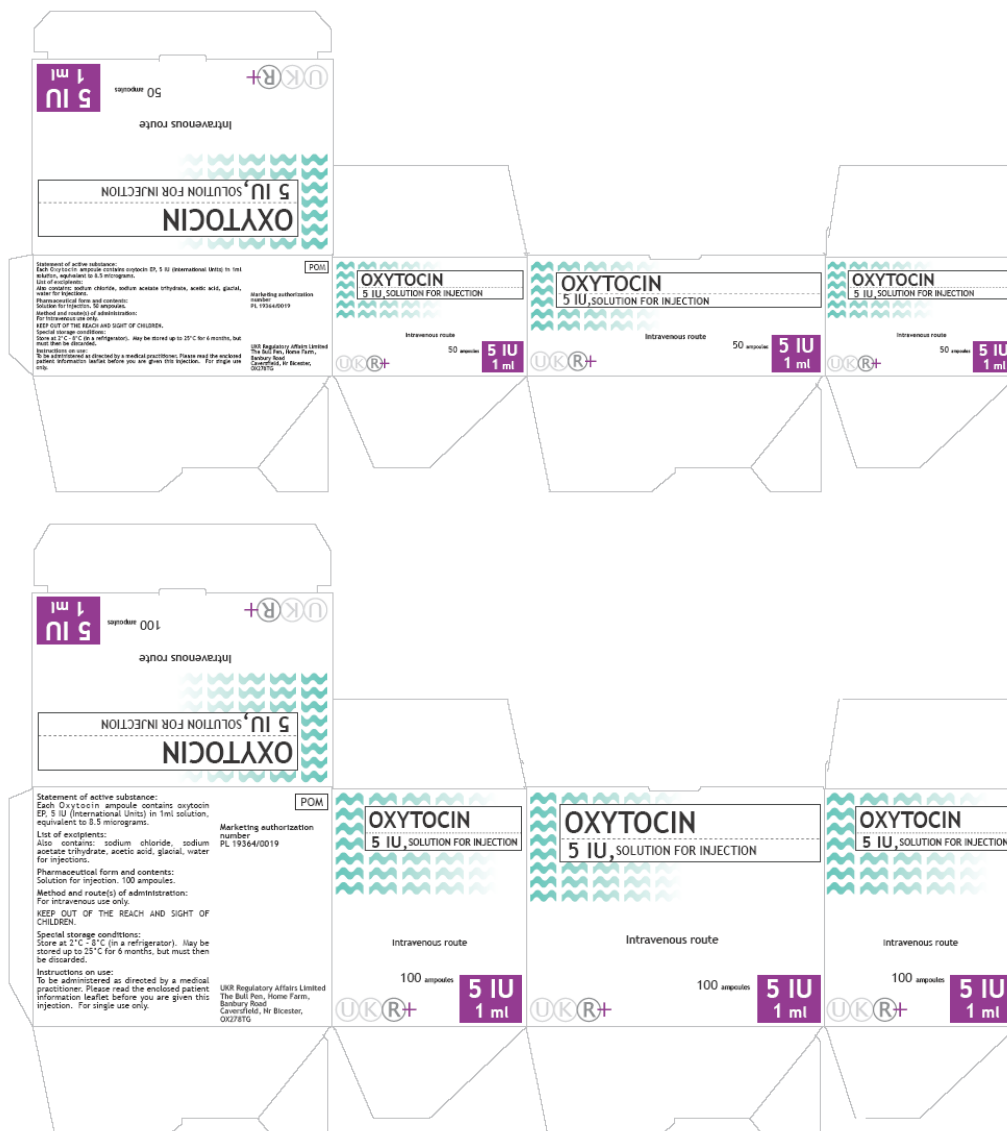
Shelf life: Three years.

LABELLING

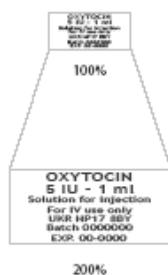
OXYTOCIN 5IU SOLUTION FOR INJECTION OXYTOCIN 10IU SOLUTION FOR INJECTION

Carton

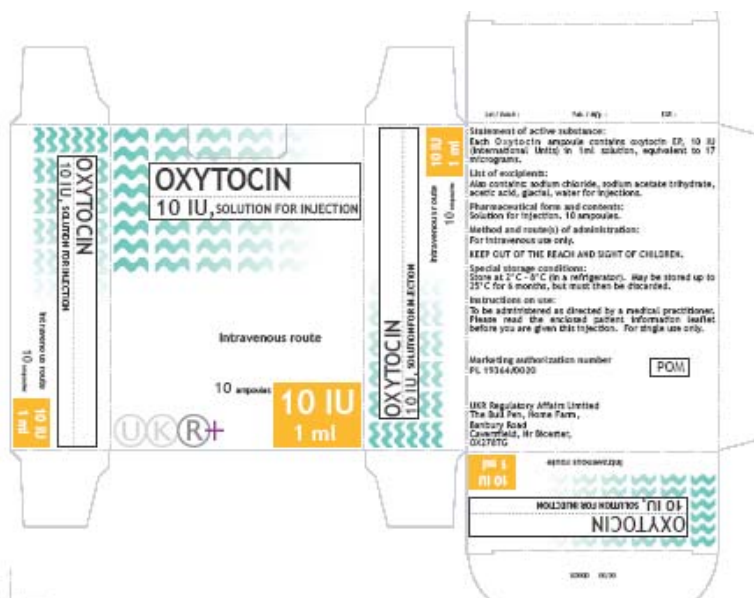


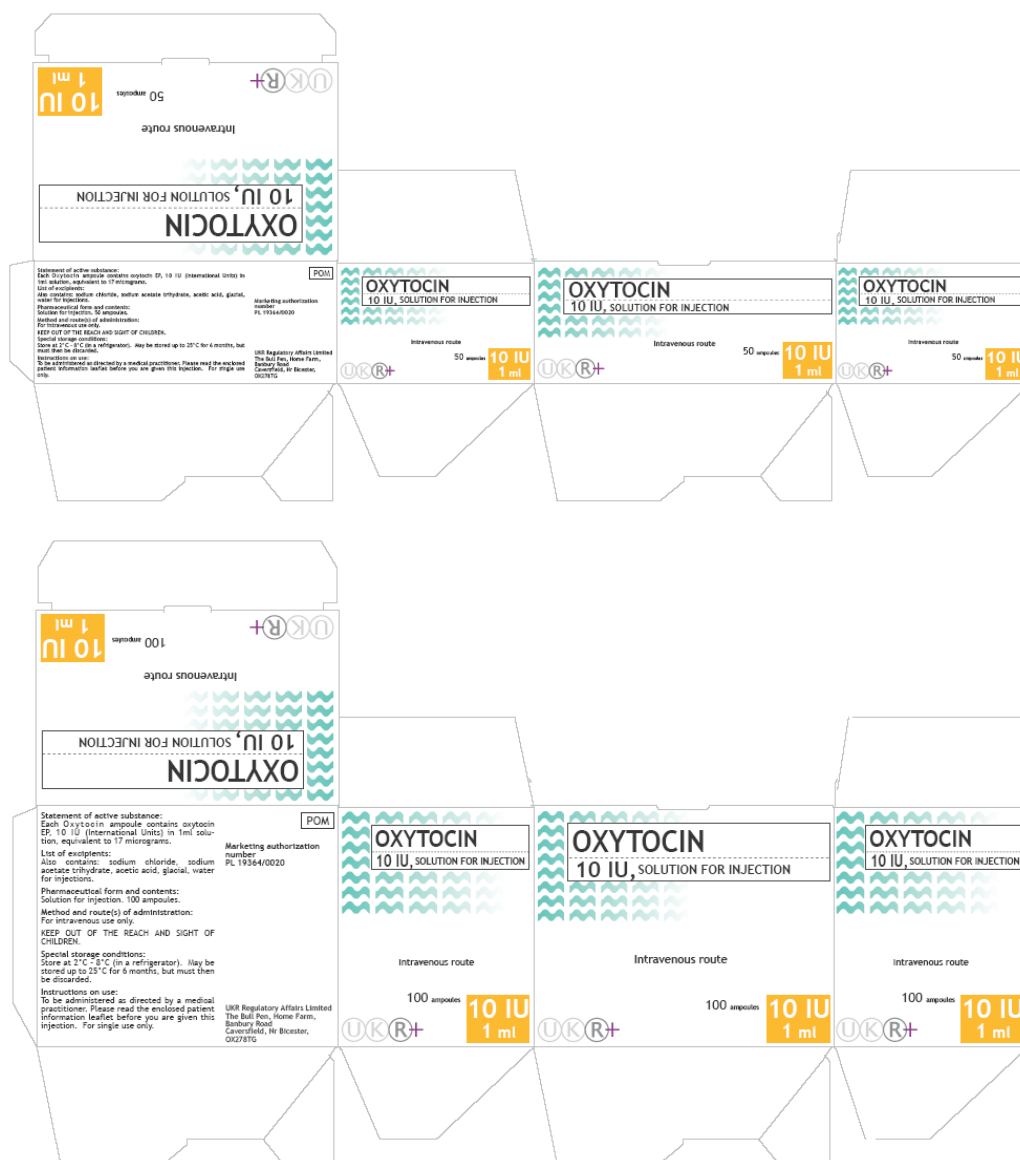


Label

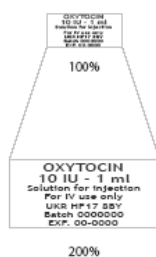


Carton





Label



200%

+