Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

Pabal 100 micrograms/ml solution for injection

UK/H/838/001/E001

UK licence no: PL 03194/0058

Ferring Pharmaceuticals Ltd

Medicines and Healthcare products Regulatory Agency

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Module 1

Product Name	Pabal 100 micrograms/ml solution for injection
Type of Application	Full dossier, Article 8.3(i), known active substance
Active Substance	Carbetocin
Form	Solution for injection
Strength	100 micrograms/ml
MA Holder	Ferring Pharmaceuticals Ltd
RMS	UK
CMS	Pabal 100 micrograms/ml solution for injection**:** AT, BE, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LU, LT, LV, NL, NO, PL, PT, SE, SK
Procedure Number	1st wave: UK/H/838/001 2nd wave: UK/H/838/001/E001
Timetable	1st wave Day 90 – 8th March 2006 2nd wave Day 90 – 17th January 2007

Module 2

Summary of Product Characteristics

European Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

PABAL 100 micrograms/ml solution for injection

2. QUALITATIVE AND QUANTITAVE COMPOSITION

Carbetocin 100 micrograms/ml.
Oxytocic activity: approximately 50 IU of oxytocin/ampoule
For a 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

PABAL is indicated for the prevention of uterine atony following delivery of the infant by Caesarean section under epidural or spinal anaesthesia.

4.2. Posology and method of administration

Withdraw 1 ml of PABAL containing 100 micrograms carbetocin and administer only by intravenous injection, under adequate medical supervision in a hospital.

PABAL must be administered only after delivery of the infant by Caesarean section. It should be given as soon as possible after delivery, preferably before removal of the placenta. PABAL is intended for single use only. No further doses of carbetocin should be administered.

4.3. Contraindications

- During pregnancy and labour before delivery of the infant.
- Carbetocin must not be used for the induction of labour.
- Hypersensitivity to carbetocin, oxytocin or to any of the excipients.
- Hepatic or renal disease.
- Cases of pre-eclampsia and eclampsia.
- Serious cardiovascular disorders.
- Epilepsy.

4.4. Special warnings and precautions for use

Carbetocin is intended for use only at well equipped specialist obstetrics units with experienced and qualified staff available at all times.

The use of carbetocin at any stage before delivery of the infant is not appropriate because its uterotonic activity persists for several hours after a single bolus injection. This is in marked contrast to the rapid reduction of effect observed after discontinuation of an oxytocin infusion.

In case of persistent uterine bleeding after administration of carbetocin the cause must be determined. Consideration should be given to causes such as retained placental fragments, inadequate emptying or repair of the uterus, or disorders of blood coagulation.

Carbetocin is intended for single administration only. In case of persisting uterine hypotonia or atonia and the consequent excessive bleeding, additional therapy with oxytocin and/or ergometrine should be considered. There are no data on additional doses of carbetocin or on the use of carbetocin following persisting uterine atony after oxytocin.

Animal studies have shown carbetocin to possess some antidiuretic activity (vasopressor activity: <0,025 IU/ampoule) and therefore the possibility of hyponatraemia cannot be excluded, particularly in patients also receiving large volumes of intravenous fluids. The early signs of drowsiness, listlessness and headache should be recognised to prevent convulsions and coma.

In general, carbetocin should be used cautiously in the presence of migraine, asthma and cardiovascular disease or any state in which a rapid addition to extracellular water may produce hazard for an already overburdened system. The decision of administering carbetocin can be made by the physician after carefully weighing the potential benefit carbetocin may provide in these particular cases.

Specific studies have not been undertaken in gestational diabetes mellitus.

The efficacy of carbetocin has not been assessed following vaginal delivery.

4.5. Interactions with other medicinal products and other forms of interaction

During clinical trials, carbetocin has been administered in association with a number of analgesics, spasmolytics and agents used for epidural or spinal anaesthesia, and no drug interactions have been identified. Specific interaction studies have not been undertaken.

Since carbetocin is closely related in structure to oxytocin, the occurrence of interactions known to be associated with oxytocin cannot be excluded:

Severe hypertension has been reported when oxytocin was given 3 to 4 hours following prophylactic administration of a vasoconstrictor in conjunction with caudalblock anaesthesia.

During combination with ergot-alkaloids, such as methylergometrine, oxytocin and carbetocin may enhance the blood pressure enhancing effect of these agents. If oxytocin or methylergometrine are administered after carbetocin there may be a risk of cumulative exposure.

Since it has been found that prostaglandins potentiate the effect of oxytocin, it is expected that this can also occur with carbetocin. Therefore, it is not recommended that prostaglandins and carbetocin be used together. If they are concomitantly administered, the patient should be carefully monitored.

Some inhalation-anesthetics, such as halothane and cyclopropane may enhance the hypotensive effect and weaken the effect of carbetocin on the uterus. Arrhythmias have been reported for oxytocin during concomitant use.

4.6. Pregnancy and lactation

Carbetocin is contraindicated during pregnancy and must not be used for the induction of labour (see section 4.3).

No significant effects on milk let-down have been reported during clinical trials. Small amounts of carbetocin have been shown to pass from plasma into breast milk of nursing women (see section 5.2). The small amounts transferred into colostrum or breast milk after a single injection of carbetocin, and subsequently ingested by the infant are assumed to be degraded by enzymes in the gut.

4.7. Effects on ability to drive and use machines

Not relevant.

4.8. Undesirable effects

The adverse events observed with carbetocin during the clinical trials were of the same type and frequency as the adverse events observed with oxytocin when administered after Caesarean section under spinal or epidural anaesthesia.

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 and < 1/10
Blood and lymphatic system disorders		Anaemia
Nervous system disorders	Headache, tremor	Dizziness
Vascular disorders	Hypotension, flushing	
Respiratory, thoracic and mediastinal disorders		Chest pain, dyspnoea
Gastrointestinal disorders	Nausea, abdominal pain	Metallic taste, vomiting
Skin and subcutaneous tissue disorders	Pruritus	
Musculoskeletal and connective tissue disorders		Back pain
General disorders and administration site conditions	Feeling of warmth	Chills, pain

In the clinical trials sweating and tachycardia were reported as sporadic cases.

4.9. Overdose

Overdosage of carbetocin may produce uterine hyperactivity whether or not due to hypersensitivity to this agent.

Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions resulting from oxytocin overdose can lead to uterine rupture or postpartum haemorrhage.

Overdosage of oxytocin may lead to hyponatraemia and water intoxication in severe cases, especially when associated with excessive concomitant fluid intake. As carbetocin is an analogue of oxytocin, the possibility of a similar event cannot be excluded.

Treatment of overdosage of carbetocin consists of symptomatic and supportive therapy. When signs or symptoms of overdosage occur 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Oxytocin and analogues
ATC code: H01BB03

The pharmacological and clinical properties of carbetocin are those of a long acting oxytocin agonist.

Like oxytocin, carbetocin selectively binds to oxytocin receptors in the smooth muscle of the uterus, stimulates rhythmic contractions of the uterus, increases the frequency of existing contractions, and raises the tone of the uterus musculature.

On the postpartum uterus, carbetocin is capable of increasing the rate and force of spontaneous uterine contractions. The onset of uterine contraction following carbetocin is rapid, with a firm contraction being obtained within 2 minutes.

A single 100 micrograms intravenous dose of carbetocin administered after the delivery of the infant is sufficient to maintain adequate uterine contraction that prevents uterine atony and excessive bleeding comparable with an oxytocin infusion lasting for several hours.

5.2. Pharmacokinetic properties

Carbetocin shows a biphasic elimination after intravenous administration with linear pharmacokinetics in the dose range of 400 to 800 micrograms. The terminal elimination half-life is approximately 40 minutes. Renal clearance of the unchanged form is low, with <1% of the injected dose excreted unchanged by the kidney.

In 5 healthy nursing mothers, plasma carbetocin concentrations were detectable by 15 min and peaked at a maximum of 1035 ± 218 pg/ml within 60 min. Peak concentrations in milk were approximately 56 times lower than in plasma at 120 min.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicicology and genotoxicity. A reproductive toxicity study in rats, with daily drug administration from parturition to day 21 of lactation, showed a reduction in offspring body weight gain. No other toxic effects were observed. The indication did not warrant studies on fertility or embryotoxicity.

Carcinogenicity studies have not been performed with carbetocin due to the single dose nature of the indication

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride
Glacial acetic acid for pH adjustment
Water for injections.

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf life

2 years.
Shelf life after first opening the container:
After first opening the ampoule: the solution should be used immediately.

6.4. Special precautions for storage

Keep ampoules in the outer carton, in order to protect from light. Store in a refrigerator (2°C to 8°C). Do not freeze.

6.5. Nature and contents of container

Type I glass ampoule with a white identification ring and a blue dot indicating the pre-cut area containing 1 ml of solution for injection.

Packs of 5 ampoules.

6.6. Special precautions for disposal

PABAL is for intravenous use only.
Only clear solutions practically free from particles should be used.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Module 3
Product Information Leaflet

Package leaflet: Information for patients

PABAL 100 micrograms/ml solution for injection
carbetocin

Read all of this leaflet carefully before you are given an injection of PABAL.

Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor, midwife or nurse.

If you have serious side effects, or if you notice any side effects not listed in this leaflet, tell your doctor, midwife or nurse.

In this leaflet:

1 What PABAL is and what it is used for

PABAL is used to treat women who have just had a baby by caesarean section.
In some women, after a caesarean, the womb (uterus) doesn't contract (shrink) quickly enough. This makes it more likely that they'll bleed more than normal. PABAL makes the womb contract and so reduces the risk of bleeding.

The active ingredient in PABAL is carbetocin. It is similar to a substance called oxytocin, which is naturally produced by the body to make the womb contract during childbirth.

2 Before you are treated with PABAL

PABAL must not be given until after the baby has been delivered.

Before giving you PABAL, your doctor needs to know about any medical conditions you may have. You should also tell your doctor about any new symptoms that develop while you are being treated with PABAL.

PABAL must not be used

• if you are allergic to carbetocin or any of the ingredients of PABAL (see section 6).
• if you have any disease of the liver or kidneys.
• if you have pre-eclampsia (high blood pressure in pregnancy) or eclampsia (toxaemia of pregnancy).
• if you have any serious heart disease.
• if you have epilepsy.
• if you ever have had an allergic reaction to oxytocin (sometimes given as a drip or injection during or after labour).

If any of these apply to you, tell your doctor.

Doctors need to take special care when using PABAL

• if you get migraines.
• if you have asthma.
• if you have problems with your heart or your circulation (such as high blood pressure).
• if you have any other medical condition.

If any of these apply to you, tell your doctor.

Taking other medicines
Tell your doctor if you are taking, or have recently taken, any other medicines – including medicines obtained without a prescription.

Pregnancy and breast-feeding

PABAL must not be used during pregnancy, but may be given after delivery by Caesarean section
Small amounts of carbetocin have been shown to pass from the nursings mother's blood into the breast milk, but it is assumed to be degraded in the infant's bowels.

3 How PABAL is given to you

PABAL is given as an injection into one of your veins, immediately after your baby has been delivered by caesarean section under an epidural or spinal anaesthetic. The dose is one ampoule (100 micrograms).

If someone is given too much PABAL

If you are accidentally given too much PABAL, your womb may contract strongly enough to become damaged or to bleed heavily. You may also suffer drowsiness, listlessness and headache, caused by water building up in your body. You will be treated with other medication, and possibly surgery.

4 Possible side effects

Like all medicines, PABAL can have side effects, but not everybody gets them.

The most common side effects may affect at least 10 of every 100 women treated with PABAL. They include:
• nausea
• pain in the stomach
• itching
• flushing (red skin)
• feeling of warm
• low blood pressure
• headaches
• shakiness

Other side effects, which may affect between 1 and 10 of every 100 women, include:
• vomiting
• dizziness
• pain in the back or chest
• a metallic taste in the mouth
• anaemia
• breathlessness
• chills

Infrequently some women might experience rapid heartbeat or sweating.

PABAL may cause a build up of water in the body which can lead to drowsiness, listlessness and headache.

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

5 How PABAL is stored

PABAL ampoules are stored in the outer carton in order to protect from light. Store in a refrigerator (2 °C - 8 °C). Do not freeze.
PABAL must not be used after the expiry date printed on the carton and ampoule.

6 Further information

What PABAL contains:
The active substance is carbetocin. Each millilitre contains 100 micrograms of carbetocin.
The other ingredients are sodium chloride, glacial acetic acid, water for injections.
Pabal contains less than 1 mmol sodium chloride (23 mg) per dose, so it is essentially ‘sodium-free’.

What PABAL looks like and contents of the pack

Pabal is clear colourless solution for injection, ready for intravenous injection, supplied in packs of five 1 ml ampoules.

PABAL should be used only in well equipped specialist obstetrics units.

Marketing authorisation holder

To be completed nationally

Manufacturer
Ferring GmbH, Wittland 11, D-24109 Kiel, Germany.

This medicinal product is authorised in other Member States of the EEA under the following names:

PABAL / DURATOCIN / DURATOBAL (to be completed nationally)

This leaflet was last approved in {MM/YYYY}

Module 4
Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

PABAL 100 micrograms/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains:
Carbetocin 100 micrograms
(Oxytocin activity approx. 50 IU/ampoule. Vasopressor activity <0.025 IU/ampoule).

3. LIST OF EXCIPIENTS

1 ml contains:
Sodium chloride 9.0 mg
Glacial acetic acid to pH 3.8
Water for injections to 1.0 ml

4. PHARMACEUTICAL FORM AND CONTENTS

5 x 1 ml ampoules. Solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous injection

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Keep ampoules in the outer carton in order to protect from light.
Store in a refrigerator at 2 to 8ºC. Do not freeze

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

POM (Medicinal product subject to medical prescription only)

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PABAL 100 micrograms/ml injection

2. METHOD OF ADMINISTRATION

For IV use only

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Carbetocin 100 micrograms in 1ml

Store at 2 to 8°C

Module 5

Scientific discussion during initial procedure

1. INTRODUCTION

Background

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Pabal 100 micrograms/ml solution for injection in the prevention of uterine atony following delivery of the infant by Caesarean section under epidural or spinal anaesthesia, could be approved. A national marketing authorisation was granted on 6th October 1997.

The mutual recognition applications concerned Pabal 100 micrograms/ml solution for injection which were granted marketing authorisations in the UK on 6th October 1997.

The Marketing Authorisation Holder Ferring Pharmaceuticals Ltd applied for marketing authorisations in several CMS's via two mutual recognition procedures as outlined below.

A first use mutual recognition procedure determined on 8th March 2006 led to the grant of marketing authorisation in: Austria, Belgium, Czech Republic, Germany, Greece, Spain, France, Hungary, Ireland, Italy, Luxembourg, Netherlands, Poland, Portugal, Slovakia.

A repeat use (2nd wave) mutual recognition procedure determined on 17th January 2007 led to the grant of marketing authorisation in: Denmark, Estonia, Finland, Iceland, Lithuania, Latvia, Norway and Sweden.

Overall Benefit/Risk Assessment

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites outside the community, the RMS has accepted a satisfactory inspection summary report issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

Pivotal non-clinical studies were carried out in accordance with Good Laboratory Practice (GLP), and in accordance with recognised guidelines. No unexpected toxicity was demonstrated, and no new toxicological problems for the product were observed.

Clinical studies on Pabal 100 micrograms/ml solution for injection were carried out in accordance with the legislation for proper clinical trial conduct in force in Canada and USA at the time.

2. PHARMACEUTICAL ASSESSMENT

INTRODUCTION

An application for a marketing authorisation has been made for Pabal 100 micrograms/ml solution for injection (PL 03194/0058). Ferring Pharmaceuticals Limited, The Courtyard, Waterside Drive, Langley, Berks, SL3 6EZ, UK is to be the marketing authorisation holder for this application.

BACKGROUND

The active ingredient in Pabal 100 micrograms/ml solution for injection is carbetocin (INN). It is a synthetic analogue of oxytocin with desamination of the N-terminal, replacement of the 1-6 disulphide bridge with a methylene ether group and the addition of a methyl group to the phenolic OH of the tyrosine residue; Deamino-2-O-methyltyrosine-1-carbaoxytocin. The Company note that these changes protect the molecule from aminopeptidase and disulphidase cleavage and prolong its pharmacological effects.

Pabal 100 micrograms/ml solution for injection is presented as a sterile solution containing carbetocin l00µg/ml in ampoules. The excipients are sodium chloride and acetic acid.

The proposed therapeutic indication is for the prevention of uterine atony and excessive bleeding following delivery of the infant by caesarean section under epidural or spinal anaesthesia. Pabal is for intravenous injection. The dose is l00µg.

MANUFACTURE

The synthesis of carbetocin is described in section 3.2.S.2.2 of the dossier and a flow chart of the manufacturing process is provided. Manufacture comprises solid-phase synthesis followed by chromatographic purification and lyophilisation.

ELUCIDATION OF STRUCTURE AND OTHER CHARACTERISTICS

The characterisation and proof of structure of carbetocin is discussed in section 3.2.S.3.1 of the dossier. Carbetocin is a synthetic nonapeptide. It is an oxytocin analogue with the following structural amendments:

- Lack of N-terminal amino group in position 1
- Replacement of S of cysteine in position 1 by CH_2 (carba analogue)
- Substitution of Tyr^2 by Tyr(O-Me)

The absence of the amino group and the carba substitution stabilises the molecule towards enzymes (aminopeptidase, disulphidase and oxidoreductase) and gives the molecule a longer half life.

Impurities

Impurities are discussed in section 3.2.S.3.2 of the dossier. Fifteen impurities have been detected. Four impurities arising from the synthetic route are controlled in the drug substance specification.
Palladium is used as a catalyst in the manufacturing process but is removed during manufacturing.
Methanol content of production batches was found to be below 0.3%.
Both acetic acid and water are present in the final product.

CONTROL OF DRUG SUBSTANCE

Five impurities arising from the synthetic route are controlled in the drug substance specification. Total unidentified impurities are controlled at 1.0 %. The total sum of impurities is set to 3.5 %. Methanol is controlled at the 0.3 % level and acetic acid at 5 %.

A validation report and full method descriptions have been provided.

CONTAINER CLOSURE SYSTEM

Carbocetin is stored in a glass container with rubber closure and sealing O-ring. When shipped, the glass container is stored protected from light in aluminium bags.

DRUG SUBSTANCE: STABILITY

The applicant has requested a re-test period of 12 months at -18 °C for the drug substance. This is satisfactory.

COMPOSITION OF THE DRUG PRODUCT

The composition of Pabal 100 micrograms/ml solution for injection is shown in the table below. Sodium chloride is present as an isotoniser

Name of Ingredients	Unit Formula	Function	Reference to Standards
Active Ingredient			
Carbetocin (anhydrous acetic acid free definition)	**100 µg**	active ingredient	FERRING
Other Ingredients			
Sodium chloride	**9 mg**	isotoniser	Ph. Eur.
Glacial acetic acid	to **pH 3,8** (approx. 50 nl)	pH-adjustment	Ph. Eur.
Water for injection	to **1 ml**	diluent	Ph. Eur.

Table 1: Composition of the Proprietary Medicinal Product

MANUFACTURE OF THE DOSAGE FORM

A flow chart and description of the manufacturing process is provided in section 3.2.P.3.3 of the dossier.

Process validation

Validation of the manufacturing process has been presented for 3 production-scale batches. The results were satisfactory.

Control of Excipients

Excipients (glacial acetic acid, sodium chloride, and water for injections) are of PhEur grade. Certificates of analysis are provided for all excipients.

CONTROL OF DRUG PRODUCT

In the finished product specification the limits of carbetocin are 95-105% at release and 90-105% at expiry. The total sum of impurities is set to 4.0 %.
Analytical methods are provided for non-PhEur tests in section 3.2.P.5.2 of the dossier. The HPLC method was validated for specificity, precision, accuracy, linearity, ruggedness and analyte stability. The method was also validated for robustness and forced degradation of carbocetin and LOD and LOQ of impurities.

CONTAINER CLOSURE SYSTEM

The product is filled into a 1 ml clear glass type I OPC (one-point cut) ampoule with a white identification ring and a blue dot indicating the one-point cut. The ampoules are packed in cardboard boxes that protect from light.

DRUG PRODUCT: STABILITY

The applicant has proposed a shelf life of 24 months at 2 – 8 °C. Do not freeze. Protect from light. This is satisfactory. The product contains one dose and should be used immediately after opening.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

A Summary of Product Characteristics has been presented with the marketing authorisation application by the Company. The pharmaceutical aspects of the SmPC are satisfactory.

LABELS

The proposed labels are satisfactory.

RECOMMENDATION OF PHARMACEUTICAL ASSESSOR

The pharmaceutical aspects of this application are satisfactory.

3. NON CLINICAL ASSESSMENT

INTRODUCTION

Pabal 100 micrograms/ml solution for injection contains 100 µg of carbetocin in 1 ml normal saline solution. Carbetocin (desamino-l-monocarba-(2-O-methyltyrosine)-oxytocin) is a synthetic octapeptide, a structural analogue of the human oxytocin, resulting from the desamination of the N terminal and the replacement of the 1-6 disulphide bridge by a methyl ether group. These structural modifications are stated to protect the molecule from aminopeptidase and disulphidase cleavage, and prolong its pharmacological effects.

The therapeutic indications are (from SPC):

Pabal is indicated for the prevention of uterine atony and excessive bleeding following delivery of the infant by Caesarean section under epidural or spinal anaesthesia.

The posology and method of administration are (from SPC)

Withdraw 1ml of Pabal containing 100 micrograms carbetocin and administer only by intravenous injection, under adequate medical supervision in a hospital.

A single dose of Pabal must be administered only after delivery of the infant by Caesarean section. It should be given as soon as possible after delivery, preferably before removal of the placenta. Pabal is intended for single use only. No further doses of carbetocin should be administered.

Carbetocin is available in several countries for veterinary use only, particularly for treatment of agalactia in sows.

The Appendices are comprised of the Expert Report which generally provided an adequate summary of the data. However, the summary of the pharmacodynamic data was deficient in parts in important experimental details, e.g. species investigated, route of administration, therefore where necessary the Expert Report has been supplemented with the Company's summary of the study.

PHARMACODYNAMICS (APPENDIX 1)

Carbetocin was originally developed as a veterinary product. There are some studies conducted in the laboratory rat. However, much of the information available on pharmacodynamics was gained from veterinary studies, and no further studies were performed to document the effect relating to the proposed indication. The majority of the data were extracted from either published data or studies conducted between 1970 and 1980. These studies were conducted and reported to standards prevailing at that time and were not conducted to GLP.

The pharmacodynamic data demonstrated two effects of carbetocin, the uterotonic and the milk ejecting effects in rats, sows and cows. In several studies the uterotonic and milk ejecting activity of oxytocin and several structural analogues were investigated *in vitro* in isolated rat tissue and *in vivo* in lactating rats. The data appeared to indicate that it was not possible to separate the two activities by the structural modifications conducted to the oxytocin molecule. In a separate *in vitro* study using rat uterine strips, carbetocin was shown to have uterotonic effects but was less potent than oxytocin.

In an *in vitro* and *in vivo* comparison of the uterine contractile effects of both oxytocin and carbetocin in sexually mature sows in oestus, both compounds increased the contraction rate. The Expert claimed that a prolonged effect of carbetocin was demonstrated but in both cases the dose levels of carbetocin were much greater than those of oxytocin.

In complication-free cows in early puerperium, carbetocin administered i.m. shortened uterine involution.

In a study comprising a total 684 sows, when carbetocin was administered i.m. at 0.3 or 0.6 mg to sows of 150 to 260 kg bw (therefore the exact dose on a mg/kg basis is uncertain), there appeared to be evidence of a uterogenic effect at 0.3 mg. There was an increased frequency and intensity of contraction of the uterus by up to 100% at 0.6 mg. The maximum effect occurred at 30 to 45 minutes post-dose. Repeat administration 24 hours post partum of the same dose produced a much weaker response.

Carbetocin (0.6 or 1 mg i.v.) administered to 3 gilts and 2 sows (bodyweight not stated) induced a release of $PGF_{2\alpha}$ lasting 40 to 410 minutes. The level did not reach the luteolytic levels of the spontaneous surge of $PGF_{2\alpha}$ and did not alter the progress of normal oestrus cycle.

In vitro, using isolated rat uterine strips the myometrial activity and the binding affinity to oxytocin receptors of carbetocin and oxytocin were compared. Both compounds increased myometrial tone and induced rhythmic contractions. The uterotonic activity of carbetocin was approximately 30 times less than that of oxytocin. The dissociation constant was 2.3×10^{-9} in mmole/litre for oxytocin and 3.3×10^{-9} in mmole/litre for carbetocin. The lypophilicity constants were 0.799 for oxytocin and 1.072 for carbetocin. Oxytocin induced contractions were immediately terminated upon washing the preparations whilst after carbetocin washing only reduced the amplitude of contractions. The study authors speculate that the apparent prolonged uterotonic activity of carbetocin previously reported in vivo may not only be due to an increased plasma half life but also to a longer half life at the receptor compartment itself.

The milk ejecting activity of carbetocin was investigated in rats and sows. Since this activity is not directly relevant to that intended for therapeutic use it will only be briefly considered in this assessment. In the rat the relationship between the chemical structure of oxytocin analogues including carbetocin and milk ejecting activity was studied: the

effect of carbetocin was stated to be characterised by a biphasic response, which was explained by the demethylation which results in the formation of more active compound. This putative pharmacologically active metabolite was not chemically characterised. The site of the demethylation reaction was considered to be located directly in the target tissue, the mammary gland. In lactating sows the mean duration of milk let down (6.2 hours) was much longer following a single injection of carbetocin (0.2, 0.4 or 0.6 mg, (animal bodyweight not stated) than for oxytocin (5 or 10 iu) of 14 minutes. For carbetocin there was no statistical difference between the i.v. and s.c. routes of administration or the three dose levels used. Oxytocin (10 iu) i.v. produced a strong initial increase in intramammary pressure with an amplitude of 75 mmHg and approximately 7 minutes duration without secondary oscillations whilst carbetocin at 0.6 mg i.v. caused a similar initial response with an average amplitude of 80 mmHg followed by secondary oscillations with amplitudes of about 20 mmHg lasting at least 4 hours.

Secondary pharmacology

In the rat carbetocin had a much lower antidiuretic activity compared to arginine vasopressin and about 3 times less than the value for oxytocin.

In a 1987 study conducted according to GLP, in anaesthetised beagle dogs bolus injections of carbetocin at dose levels up to 1000 µg/kg (not mg/kg as stated in Expert Report) had little effect on the blood pressure. The heart rate was increased but this was attributed to the anaesthetics. There was no effect on the ECG. Carbetocin had little effect on respiratory system. Carbetocin had no consistent effect on intestinal motility, producing increased motility in 3/4 dogs at various dose levels.

The Expert Report states that a review of the published literature did not bring reliable data on drug interactions.

PHARMACOKINETICS (APPENDIX 2)

Very limited pharmacokinetic data was reported in the pig, rat and dog. In lactating sows, after i.v. or i.m. injection of 0.6 mg carbetocin (animal weight not given) the disappearance rate of carbetocin (expressed as oxytocin equivalent measured by radioimmunoassay) was biphasic, with an initial rapid clearance (t½ 7.5 to 10 minutes) followed by a more gradual decrease (t½ to 85 to 100 minutes). There were no apparent differences in the plasma kinetics between the i.m. and i.v. routes.

In the rat, following a single dose of 1.5 µg carbetocin (equivalent to 5 µg/kg in a 300g rat) the plasma peak 5 minutes post-dose was between 4360 and 8070 pg/ml and it progressively decreased to totally disappear after 90 minutes.

In female dogs the plasma levels of "carbetocin-like immuno reactivity" after 22 days i.v. dosing at dose levels up to 1 µg/kg/day were similar throughout the dosing period.

TOXICITY

Single dose toxicity (Appendix 3)

In a GLP study, in female rats dosed i.v. at up to 10 mg/kg there were no deaths. Overt signs of toxicity included transient lethargy, piloerection, hunched posture, unco-ordinated movements and rapid breathing. Gross pathological examination revealed no treatment related effects. In a non-GLP study, the s.c. LD_{50} of female rats was >10 mg/kg.

Repeat dose toxicity (Appendix 4)

In a study in which groups of 3 rats/sex were dosed at 0 or 1 mg/kg carbetocin i.v. for 7 days there were no deaths and no overt signs of toxicity. Gross pathological examination revealed sores on the tails of all animals. Two treated males had slight thickening of the fundic region of the stomach and 1 female had slightly enlarged mesenteric lymph nodes.

In a study in which groups of 12 female rats were dosed at 0, 0.01, 0.05 or 0.5 mg/kg carbetocin i.v. for 14 or 15 days there were no deaths, no overt signs of toxicity and no other treatment related effects.

In a study in which groups of 10 rats/sex were dosed at 0, 0.01, 0.1 or 1.0 mg/kg carbetocin i.v. for 28 days there were no treatment related effects except for a slight increase in blood glucose levels. The cause of this finding was not addressed, but the study authors stated that the magnitude was not large enough to cause concern.

Based on the results of a dose range finding study, groups of 4 female beagle dogs were dosed at 0, 0.01, 0.1 or 1.0 mg/kg carbetocin i.v. for 28 days. There were no deaths and no overt signs of toxicity. Food consumption and bodyweight gain were reduced at 0.1 and 1 mg/kg. There was a dose related decrease in white blood cell count at week 4 which was stated to be within normal range. The cause of these findings was not addressed by the Company. These findings were not reported in the repeat dose rat study. However the dose response is indicative of a treatment related effect, which occurred at even the lowest dose level of 0.01 mg/kg (x5 human dose). Therefore the clinical significance of this finding must be considered since a decrease in white blood cell count has been reported in the clinical studies following carbetocin administration.

Reproductive toxicity (Appendix 5)

The therapeutic indication is for the use of the product after delivery of the infant, therefore Segment I and Segment II studies are not required.

In a post-natal study conducted according to GLP groups of 5 rats were dosed at 0, 0.01, 0.1 or 1.0 mg/kg carbetocin i.v. from the day of parturition to day 21 of lactation. There were no maternal deaths, signs of toxicity or effects on maternal bodyweights. At the top dose mean pup weight was slightly reduced on day 1 postpartum. Mean pup bodyweight

gain was also reduced in a dose related manner at weaning (weight 36.4, 28.1, 25.3, 15.6 g in dams treated at 0, 0.01, 0.1, 1.0 mg/kg respectively). The Company did not address the significance of these findings. The rationale for the selection of the dose levels was not stated. However, the dose response is indicative of a treatment related effect which occurred at even the lowest dose level of 0.01 mg/kg. This finding should be included in section 4.6 of the SPC.

Acute Toxicity Study

The toxicity of carbetocin produced by PPL-Prague was assessed by an intravenous acute toxicity study in female Sprague-Dawley rats. The highest dose level was 10.0 mg carbetocin/kg b. wt., containing a total of 15.9% impurities, corresponding to 1.422 mg impurities/kg b. wt.

No signs of systemic toxicity were seen at any of the dose levels including the highest dose. No signs of toxicity were seen at the gross necropsy.

It was concluded that the acute intravenous LD_{50} value of carbetocin spiked with a total of 15.8% impurities was in excess of 9.0 mg carbetocin/kg b. wt. for female Sprague-Dawley rats.

Mutagenicity (Appendix 6)

Carbetocin was investigated for mutagenicity in a full battery of conventional tests which were satisfactorily conducted including Ames tests using *S. typhimurium* and *E. Coli*, mouse lymphoma TK assays, and *in vitro* and *in vivo* clastogenicity assays. Carbetocin was not genotoxic.

Carcinogenicity

These studies are not required.

Local tolerance

Local tolerance was not considered in the Expert Report.

In a very poorly described study, rabbits of the Chinchilla breed had carbetocin applied into the serai musculature in a volume of 1 ml (dose 0.2 mg/kg). The study report states that histological examination of the injection sites at various times up to 14 days post injection revealed similar tissue reactions between saline controls and treated sites but the changes were greater after administration of carbetocin.

Local tolerance studies were stated to have been conducted in cows and sows but since the administration route and treatment of controls was not stated they cannot be considered to be of value and will not be considered in this assessment.

OTHER INFORMATION

Environmental Risk Assessment

The MAH submitted an ERA with the first wave MRP application in which the predicted environmental concentration of carbetocin in surface water was calculated and found to be six orders of magnitude below the action limit of 0.01 µg/l proposed in the Draft Paper "Guidance on the Environmental Risk Assessment of Medicinal Products for Human Use" (CPMP/SWP/4447/00 draft. London, 20 January 2005)
On this basis it can be concluded that Pabal is unlikely to present a risk for the environment following its prescribed usage in patients.

CONCLUSION

In vitro carbetocin was shown to have uterotonic effects and appeared to be less potent than oxytocin. *In vivo*, carbetocin was shown to have uterotonic effects in rats, sows and cows. The Company claim a prolonged effect for carbetocin compared to oxytocin but in comparative studies the dose levels of carbetocin were much higher than those of oxytocin and the data available to not allow a firm conclusion. In most studies it was not possible to make a direct comparison of the potency of oxytocin and carbetocin since the applied doses were stated in different units (IU units for oxytocin, mg dose per animal for carbetocin). In the case of carbetocin often the weight of the animal was not stated, therefore the applied dose could not be calculated on a mg/kg bodyweight basis. In some cases carbetocin was administered i.m. or s.c. but no data was available on the disposition of the compound following these routes of administration.

The data on secondary pharmacology was deficient. The very limited data available indicated that carbetocin possessed anti-diuretic activity which was lower than that of oxytocin. Carbetocin appeared to have no adverse effect on the heart rate, blood pressure and respiratory system in dogs at doses up to 1000 µg/kg (x 500 human dose).

The pharmacokinetic data was deficient. There was no information on distribution, metabolism or comparative pharmacokinetics. The very limited data available indicated that following a single i.v. dose there was a biphasic rate of clearance in sows and a rapid rate of clearance from plasma in rats.

The single dose toxicity study in the rat revealed very low acute toxicity for carbetocin with no deaths and no treatment related gross pathological changes at a dose of 10 mg/kg (x 5000 human dose).

Although carbetocin is intended as a single dose therapy, repeat dose studies of up to 28 days duration were conducted in the rat and dog using dose levels up to 1 mg/kg/day. The rationale for the selection of dose levels was not stated. In the dog there was a dose related statistically significant decrease in white blood cell count indicating a treatment related effect. The Company claimed the values were within normal range. These

findings were not reported in the rat. However, a decrease in white blood cell count has been reported in the clinical studies.
In a post-natal reproductive toxicity study mean pup bodyweights at weaning were reduced in a dose related manner and on day 1 post partum at the top dose of 1 mg/kg. The significance of this finding was not considered by the Company. Section 4.6 of the SPC needs to be amended. The first sentence of the last paragraph: "Post-natal studies in lactating rats have shown no toxic effects on pups" is not in accordance with the data and should be corrected. The Company claim in section 4.6 of the SPC that the small amounts of carbetocin transferred into colostrum or breast milk after a single injection of duration and subsequently ingested by the infant are degraded by enzymes in the gut. The Medical Assessor is of the opinion that the Company have not provided data to support this statement.

Carbetocin was not genotoxic.

The local tolerance of carbetocin by the intended clinical route was not investigated. In the rabbit, carbetocin appeared to exacerbate the adverse effects of an i.m. injection.

In conclusion, the pharmaco-toxicological data were generally deficient most notably in the secondary pharmacology and pharmacokinetics. However in view of the intended clinical use and the very low acute toxicity of carbetocin the data are probably adequate to support the use of carbetocin as a single dose therapy only.

4. CLINICAL ASSESSMENT

INTRODUCTION

This is a national application now about to enter the mutual recognition procedure with the UK as the reference member state.

Carbetocin is an old product used in veterinary practice in the Czech Republic, Germany and Sweden but there is little published data on the use in man and the studies which are published are presented in the documentation.

Carbetocin has the N-terminal amino acid group removed to protect from aminopeptidase cleavage. The disulfide bridge in position 1 has been replaced with a carba analogue giving protection from disulfidase cleavage. This prolongs the half life and extends the duration of action.

BACKGROUND

Oxytocic agents are routinely used in obstetric practice. They are used post Caesarean section to provide uterine contraction and thus reduce the risk of haemorrhage. Oxytocin has the advantage of a short half life for most obstetric uses, but following post placental delivery in Caesarean section patients a longer acting preparation would be advantageous, providing it had a similar safety profile. The company are seeking a marketing authorisation for a new synthetic analogue of oxytocin to be indicated "for the prevention of uterine atony and excessive bleeding following delivery of the infant by Caesarean section under epidural or spinal anaesthesia."
The company are requesting a single dose regime of one i.v. bolus of 100 micrograms of carbetocin.
Many of the contraindications and unwanted effects described for oxytocin are therefore not relevant in the requested indication and dosage.

INDICATIONS

100 micrograms in 1ml of solution for injection is indicated for the prevention of uterine atony and excessive bleeding following delivery of the infant by Caesarean section under epidural or spinal anaesthesia.

PHARMACOLOGY

Pharmacodynamics

Preclinical data are very limited and no evidence is presented to support the claim about the relative potency of carbetocin and oxytocin. No data are presented to adequately assess the cardiovascular and antidiuretic effects.

The metabolic pathways have not been determined.

One study CLN 6.3.1 which is a kinetic study shows that carbetocin causes volunteers to have a feeling of warmth (97%), facial flushing (67.6%) and headache (59.9%) after administration. The diastolic blood pressure was reduced and the pulse rate increased.

Study CLN 6.3.3 looked at dosing in women who were 24 to 48 hours post partum and showed sustained uterine contraction on tocographs with subsequent rhythmic contractions for up to one hour. The AUCs for the tocograph recordings suggest there is some uterine activity for up to one hour. A feeling of milk let down was noted in a third of the patients.

Comment
In view of the lack of preclinical data it is surprising that detailed dynamic investigation was not undertaken. Volunteers given carbetocin respond in terms of facial flushing and decreases in diastolic blood pressure occur with increases in pulse rate. Volunteers who were post partum experienced marked uterine contraction and some milk let down.

Pharmacokinetics

CLN 6.3.1 Healthy volunteer study

The study examined single rising dose tolerance and recruited 25 healthy non pregnant women who received 20 micrograms (n=3), 100 micrograms (n=3), 200 micrograms (n=6), 400 micrograms (n=6) and 800 micrograms (n=6) as a single i.v. bolus dose. One subject withdrew due to a positive pregnancy test. Twelve patients also received at a later study period intramuscular dosing of carbetocin. This submission does not request i.m. dosage. Only data for 400 and 800 micrograms are presented. The kinetics of carbetocin (see table 1 and figure 3 in appendix 1) followed a two compartment model with a distribution half life of between 3.3 and 8.2 minutes and an elimination half life of between 28.7 and 59.2 minutes. The Vd was 9.0L. AUCs appeared to increase in a dose proportional manner. Clearance was independent of dose over the dose range studied. Only 0.7% of administered drug was detected in the urine. After i.m. administration the absolute bioavailability was 76.0± 10.8% and 83.4±17.6% for the 400 and 800 doses respectively.

Comment
The data are based upon 400 to 800 microgram doses and no data are presented at the requested dose recommendation. Over the range 400 to 800 micrograms the kinetics are dose independent. There is rapid distribution and a short elimination half life. There are no data evaluating the metabolism and elimination of Carbetocin.

Dosing

CLN 6.3.3 Dose ranging study in Volunteers who were post partum.

Seventeen subjects post partum (second day) were studied using tocography recordings in a dose ascending study. It is claimed that the dose was initially estimated on the basis of animal data which showed that the potency of carbetocin was one tenth that of oxytocin. The initial dose planned was 50 micrograms increasing to a maximum of 800 micrograms.

Two patients (no. 1 and 5) received high doses (50 micrograms and 100 micrograms) and experienced severe abdominal pain as a result of marked uterine contraction. The treatment protocol was changed so that 10 micrograms were administered followed by 10 microgram increments. When ten patients had been studied five received 2 micrograms with 2 microgram increments to detect minimal effective dose.

Six of the 10 patients receiving 10 microgram increments got a tetanic contraction with the first dose. Two patients (cases 3 and 8) who failed probably did get tetany but the recording was affected by urinary obstruction and excessive body fat. The other two patients (cases 6 and 7) required 20 and 30 micrograms to go into tetany.

There were two tetanic contractions at 8 micrograms and one at 10 micrograms. Two patients failed to get a tetanic contraction in the low dose group.
Seventy three per cent of patients experienced a tetanic contraction in the range 8-30 micrograms.
Four subjects had tocograph traces which were analysed for duration of tetany, the mean duration was 6.9 mins (range 4.5 to 10.2 mins).

Three patients reported sustained contractions lasting 12, 13 and 15 minutes and the patient who received the 100 microgram dose experienced a contraction for 30 minutes. The total duration of action was estimated from the tocograph records excluding case 7 and the mean duration was 59.9 (SD 17.5) mins.

CLN 6.3.4 IM dose ranging study

This route of administration is not requested.

CLN 6.3.5 Dose ranging study in patients undergoing Caesarean section

There was some concern about the possibility of dose dependent changes in diastolic blood pressure and pulse rate, see the safety section.
Eighteen patients were enrolled in the study. Patients received 10 microgram increments to a maximum of five doses. The primary response was the appearance of the uterus as tetanic, firm or boggy (uncontracted).

There were no initial responses below 100 micrograms. Six patients receiving the 100 microgram dose responded, five experienced a tetanic contraction and the other had a firm uterus. The responses of the other twelve patients were also recorded. The duration of action is difficult to assess but no patient was reported to have a boggy uterus during all study phases which lasted nine hours.

Comment
The dose finding studies show the effect of Carbetocin increases in strength from healthy non pregnant volunteer to Caesarean section patient with greatest effect seen in volunteers who were post partum. Based upon the end point of uterine contraction it was reasonable to select 100 micrograms as the dose for phase III studies in Caesarean section patients.

Studies in special groups

CLN 6.3.7 Lactation

Five patients were studied to evaluate the ratio of milk to plasma AUCs of Carbetocin following the intramuscular administration of 70 micrograms Carbetocin in mothers who were between 6.6 to 13.8 weeks post partum.
The plasma Carbetocin concentrations reached a maximum of 1035 (sd218) pg/ml at between 15 and 30 minutes. The breast milk concentration reached a maximum concentration of 19.6 (sd 7.1) pg/ml for the left breast and 17.8 (sd 7.6) pg/ml for the right breast. Table 5 (appendix 1) shows AUCs for each patient and the milk to plasma ratio. The study shows that Carbetocin enters the breast milk in small quantities.

CLN 6.3.2 Study on the effect of Carbetocin on the plasma ACTH and Cortisol levels in patients with pituitary dependant Cushings disease.

This study was designed to evaluate the effect of carbetocin on the ACTH and Cortisol levels because studies have shown that oxytocin infusion can lower ACTH and cortisol levels with rebound on discontinuation of the infusion.
The patient group comprised six patients who were not well matched.
The dose used was 800 micrograms i.v. which is much higher than the recommended dose.

The study did not show clear-cut effects although all patients experienced a reduced plasma ACTH recording at 30 to 60 minutes following drug administration. It is difficult to make any meaningful comments about this study.

Comment
Carbetocin enters breast milk.
The data in Cushings syndrome are inconclusive.
No other special groups are studied.
There are no data relating to drug interactions.

EFFICACY

CLN 6.3.10 Study to compare the efficacy and safety of a single iv bolus of Carbetocin compared to placebo.

The primary efficacy variable was the degree of intervention with oxytocic therapy. One potential weakness of the efficacy studies is the failure to define specific criteria for the administration of Oxytocic intervention.
The trial had 80% power to detect a difference of intervention rates of 25% for placebo and 5% for carbetocin at the 0.05 level of probability. One hundred and twenty two patients completed the study, 64 in the carbetocin group and 58 in the placebo group. There were three protocol violations where the patients received oxytocin because it was routine practice. In all three cases the investigator considered the administration as clinically unnecessary. These were regarded as treatment failures in the intent to treat population.
There were 10 interventions in the carbetocin group and 42 in the placebo group (p =0.001). Although there was a centre effect it was not treatment specific. From the per protocol population eight patients in the carbetocin group required a mean dose of oxytocin of 49 IU (range 40 to 60) and the 41 patients in the placebo group required 35 IU (range 10 to 80). Two patients in the carbetocin group and four in the placebo group required further treatment intervention with agents other than oxytocin.
All interventions occurred in the first three hours (study duration 24 to 48 hours) and the majority were in the operating room. Uterine tone was greater in the carbetocin group and significantly so for the first 20 minutes after which the large proportion of placebo patients had received intervention.
The amount and type of lochia did not differ between the groups.

CLN 6.3.6 Study comparing blood loss in patients receiving carbetocin or oxytocin infusion

This was a parallel group randomised double blind double dummy technique trial comparing a single 100 microgram bolus i.v dose of carbetocin with a 16 hour infusion of 32.5 IU oxytocin.
The primary end points were blood loss and uterine tone. Twenty nine patients received carbetocin and 28 oxytocin.
The mean blood loss recorded was lower in the carbetocin group (159 SD 92 mls) compared to the oxytocin group (188 SD 115 mls) but not statistically significantly so. There were significantly more patients in the carbetocin group with a blood loss less than or equal to 200 mls.
The uterine tone was less in the carbetocin group at base line and following drug administration there were no differences between the groups and most patients had a firm uterus for the 24 hour study period.

CLN 6.3.9 A double blind randomised comparison of carbetocin versus an eight hour infusion of oxytocin

The study is of a sequential design after the work of Whitehead and tests three hypotheses by interim analyses until one is shown to be significant and then the study terminates. No difference implies that equivalence is shown.
Patients received in a double blind, double dummy fashion either 100 micrograms of carbetocin or 5 IU i.v. bolus of oxytocin followed by a 20 IU infusion over eight hours. The primary efficacy variable is the need for further oxytocic intervention, with the timing of such intervention as a secondary efficacy variable. The time delay to uterine contraction, the uterine tone, the fundal position and the appearance of lochia are secondary parameters.
The study assigned 694 patients to treatment but four patients withdrew before randomisation. Thirty one patients withdrew before receiving test drug. Six hundred and fifty nine patients received drug and 635 completed treatment. Three hundred and twenty nine patients received carbetocin and three hundred and thirty patients oxytocin. The patients were considered to complete the study when the 48 hour period was completed or when they needed an additional dose of oxytocic medication. Rescue medication was with the normal oxytocic regime for that centre.
The patients appear well matched for demographics. After 674 patients were enrolled and 616 analysed, a significant difference in favour of carbetocin was shown. This represented 14 of 306 patients receiving carbetocin and 31 of 310 receiving oxytocin. The estimated treatment difference was -0.7075 (Cl 1.334, -0.066) which was significant at $p< 0.05$ with a calculated p value of 0.0312. When all 659 randomised patients were analysed the results were similar.
All early terminations were regarded as treatment success which could effect the overall results, (see statistics report).
Six hundred and thirty five patients were studied for the entire 48 hour period; 15 (5%) in the carbetocin group and 32 (10%) in the oxytocin group required oxytocic intervention. The mean and median times to intervention were longer with carbetocin. Mean time carbetocin 13.3 hrs, oxytocin 4.2hrs: Median time carbetocin 2.03 hrs, oxytocin 0.18 hrs Three carbetocin patients and 25 oxytocin patients required intervention in the operating room, and seven carbetocin and two oxytocin in the recovery area. Five in each group needed oxytocin in the ward.
Uterine tone was increased rapidly in both groups there being no significant difference between them. There were no significant differences between treatment groups with respect to position of the fundus and the type and amount of lochia.

Comment
The three controlled trials show that a single 100 microgram iv dose of carbetocin is superior to both placebo and a 5 IU bolus dose followed by 20 IU infusion of oxytocin over eight hours.
The intervention rates in the three studies are summarised here.

	Carbetocin	*Oxytocin*	*Placebo*
CLN 6.3.6	*0/2 0%*	*3/28 11%*	
CLN 6.3.9	*15/317 5%*	*32/318 10%*	
CLN 6.3.10	*8/62 13%*		*41/57 72%*

Intervention was necessary sooner in the oxytocin treated patients and there was no difference in the dose of additional oxytocic treatment necessary.
There was preliminary evidence that patients who received carbetocin may have less blood loss.

STATISTICAL ASSESSMENT OF EFFICACY

Background

This is a statistical assessment of the efficacy of 100µg bolus of carbetocin for the prevention of uterine atony and excessive bleeding following caesarean section under epidural or spinal anaesthesia. The assessment is based upon review of the clinical expert report and reports of the phase III trials 6.3.9 and 6.3.10. Particular attention has been focused on the statistical methodology used in the sequential trial 6.3.9.

Trial 6.3.9

In trial 6.3.9 l00µg carbetocin was compared to an 8-hour infusion of oxytocin following caesarean section. Hospital pharmacists were unblinded to study medication, but it is presumed that they did not discuss treatment allocations with the investigators. Hence the study is considered as double-blind.

The primary variable was incidence rate of need for further oxytocic therapy. Secondary variables included time to alternative medication, postpartum complications, time to uterus contraction, change in haemoglobin and need for blood transfusion. Patients were assessed in the operating theatre, in the recovery room and in the ward.

The overall incidence of intervention was to be calculated and if this was <5% the study would have been terminated due to lack of power. This did not require unblinding of the data and is therefore unlikely to have introduced any bias.

Interim analyses of the primary variable were performed with a stopping rule (sequential design) in the form of a double triangular test (Whitehead, 1983). As the primary outcome of each patient was evaluated shortly after treatment, clear benefits were expected from the use of a sequential procedure and the design chosen was appropriate for the objectives of the trial.

It is highly commendable that the sequential procedure was clearly described in the protocol and that all analyses (including those of secondary variables) took account of the interim analyses performed on the primary variable. Unfortunately, the methods used for the design and analysis of the trial are somewhat outdated. Whitehead's work of 1983 has been updated to allow greater flexibility of designs and produce more accurate analyses, which are available in the computer package PEST3.

The package PEST3 has been used to check the design and analysis of this trial. According to the protocol, the double triangular was specified to detect a log odds-ratio of 1.0986 (odds-ratio of 3) arising from an overall response rate of 0.08 (e.g. a failure rate of 0.117 on oxytocin and 0.0423 on carbetocin) with an overall significance level of a=0.05 and power of 95%. However it is clear from the specification of the stopping boundaries that the power has been set as 97.5% in the double triangular test, not 95%. (The Whitehead methodology of 1983 only allowed design specifications of $\alpha/2=\beta$ and his notation was rather confusing concerning one and two-sided significance levels. Hence it is easy to see how the applicant made the mistaken specification.)

After each patient had been discharged from hospital, their key efficacy data were sent to a CRO and interim analyses were performed after each patient. (Analysis was probably performed after every patient to be in accordance with the main Whitehead methodology of 1983.) Bias may have been introduced if the applicant had access to the unblinded interim analyses of the accumulating data, but as these analyses were performed by a CRO it is presumed that this did not occur.

After 616 patients had been analysed, 31 of the 310 patient in the oxytocin group required additional oxytocin compared to 14 of the 306 patients in the carbetocin group, and the sequential procedure indicated that the trial should be terminated with significant evidence in favour of carbetocin. An additional 19 patients were treated after this, leading to an "overrunning" of the sequential analysis and the final incidence of oxytocin requirement was 32/316 in the oxytocin group and 15/313 in the carbetocin group.

The analysis performed by the applicant is presented in Table SI. This can be compared with the more accurate analysis performed using PEST3 which is presented in Table S3.

Table S1: Applicant's analysis of proportion of patients requiring oxytocin therapy
p=0.031

	Median unbiased estimate	95% confidence interval
Log odds-ratio	-0.7075	(-1.334, -0.0660)
Odds-ratio	2.0	(1.1, *2.8**).

*As the odds-ratio is the exp(log odds-ratio) it is clear that this is a typographical error and the upper 95% confidence limit of the odds-ratio should be 3.8.

Table S2: PEST3 analysis of proportion of patients requiring oxytocin therapy
p=0.031

	Median unbiased estimate	95% confidence interval
Log odds-ratio	-0.7144	(-1.3419, -0.0693)
Odds-ratio	2.0	(1.1, 3.8)
Failure rate on oxytocin	0.10	
Failure rate on carbetocin	0.05	

The old analysis techniques of Whitehead (1983) are most appropriate for interim analyses after every patient and it is therefore not surprising that re-analysis of the data with the current more accurate analytical techniques produces extremely similar results to those presented by the applicant.

An adjustment for the overrunning was made by the applicant to incorporate data from patients who completed treatment after the stopping boundary was crossed. It would have been preferable to consider the analysis with overrunning as definitive, but the applicant places little emphasis on it and only gives sparse details of the results. However, this is not an important point, because as shown in Table S3, there is very little difference between the analyses at termination and after overrunning.

Table S3 : PEST3 analysis of proportion of patients requiring oxytocin therapy - With overrunning
p=0.031

	Median unbiased estimate	95% confidence interval
Log odds-ratio	-0.7011	(-1.3174, -0.0648)
Odds-ratio	2.0	(1.1, 3.7).
Failure rate on oxytocin	0.10	
Failure rate on carbetocin	0.05.	

The only concern which remains over the sequential procedure is the exclusion of some patients from the analysis: those who were randomised but did not receive treatment and those who were considered as "early terminations". It may be deemed acceptable to exclude the patients who did not receive treatment. The exclusion of early terminations is more problematic because one category of early termination is protocol violation, one form of which was defined as administration of oxytocic treatment for no indication. The report states that "in most of these cases additional oxytocin was ordered as per routine hospital procedures with no consideration for the study. In these cases, careful review of the hospital charts confirmed no demonstrable need for additional oxytocic intervention either for uterine atony or increased bleeding. Since these protocol violations confounded

with the primary efficacy variable, a specific data clarification procedure was carried out to confirm that there was indeed no 'need for further oxytocic treatment' in these patients." As these violations cannot be attributed to one particular hospital the reasoning behind the violation may be questioned.
Furthermore there was a treatment imbalance in the violation: occurring in seven of the 12 early withdrawals on carbetocin and only three of twelve on oxytocin. Although the applicant redid the sequential analysis including all the early terminations, it was performed under the assumption that all early withdrawals were "successes", but it would seem more appropriate to re-do this analysis categorising those who received oxytocic treatment for no indication as failures. This analysis for the dataset with overrunning has been performed and is presented in Table S4.

Table S4 : PEST3 analysis of proportion of patients administered any oxytocin therapy (With overrunning : All patients who received treatment)
p=0.075

	Median unbiased estimate	95% confidence interval
Log odds-ratio	-0.5142	(-1.0901, 0.0519)
Odds-ratio	1.7	(0.95, 3.0)
Failure rate on oxytocin	0.11	
Failure rate on carbetocin	0.07.	

In this exploratory analysis which includes more additional failures on carbetocin, it is not surprising that the estimate of treatment effect is reduced compared to the previous analysis and is of borderline significance. However, it is reassuring that using this conservative intent to treat approach the changes in the results are fairly small and still indicate some benefit of carbetocin compared to the active comparator, oxytocin.
The randomisation in one of the seven centres was stopped because it had recruited 200 patients, but this centre was later permitted to recruit more patients. Various analyses are presented which provide reassurance that the treatment effect was not merely apparent due to the dominance of this one large centre and that although there was a centre effect there was no treatment by centre interaction.

The only secondary analysis which identified a significant difference between treatments was the time to oxytocic intervention, which was longer in the carbetocin treatment group (2.03 hours vs 0.13 hours). The reduction in haemoglobin from baseline was comparable between the groups. No information was presented about blood transfusions.

There was a baseline imbalance in the number of twins and patients with diabetes. As none of these patients received additional oxytocin therapy, this imbalance did not cause any bias in the results. The effect of other baseline characteristics on outcome was assessed, but none were found to be significant.

Trial 6.3.10

Trial 6.3.10 was similar in design to 6.3.9 but used a placebo comparator and therefore needed fewer patients to detect a difference. The treatment effect in terms of incidence of further oxytocic intervention appears convincing, with 72% on placebo and 13% on carbetocin (p=0.001).

The study was originally designed to enrol 30 evaluable patients per treatment in order to achieve an 80% power to detect a reduction in intervention rate from 40% to 5%. However this was increased after the study began to 60 patients per treatment, in order to detect a reduction in intervention rates from 25% to 5%. It is unclear what the rationale for this change in sample size was. It may be suspected that the data were analysed at the planned time, found to be non-significant and the trial expanded to enhance the power of the study to detect a smaller difference between treatments. However, this scenario is unlikely given the size of difference observed at the end of the trial which is much larger than that anticipated in the first design. Hence the results presented from this trial are probably adequate.

Discussion

The pivotal trials have made primary assessments based on the requirement for additional oxytocin therapy. The use of this variable is presumably acceptable given the difficulty in assessing the more clinically relevant outcomes of uterine tone and blood loss.

Although the rationale for expansion of the placebo controlled trial 6.3.10 was not clear, its results were probably sufficiently convincing to overcome the concerns. Trial 6.3.9 was a large phase III trial using an appropriate sequential design which allowed interim analyses after every patient. The analysis of this trial found significant evidence of the superiority of carbetocin over oxytocin, and although the analysis was somewhat outdated, it has been replicated using more modern techniques of analysis. Some unusual patient exclusions were made in the primary analysis, but a conservative re analysis of the data indicated that the estimate of treatment effect was only slightly reduced and the treatment effect was of borderline significance. As these comparisons were made to an active control, this evidence of efficacy seems sufficient.

Overall there appears to be sufficient evidence of the efficacy of the carbetocin bolus following caesarean section, but as uterine atony and excessive bleeding have not been directly assessed in the phase III trials it is unclear whether what specific indications are appropriate.

SAFETY

Adverse Events

The most frequently reported events in the clinical pharmacology data were a feeling of warmth (65%), flushing (54%), abdominal pain (54%), headache (35%), metallic taste (27%), back pain (26%) and injection site pain (21%).They were considered to be probably related to test drug. No serious events were reported. The adverse events reported in the therapeutic trials also affected the cardiovascular system, body, special senses, nervous system, urogenital system, skin and appendages, digestive system and respiratory system. The most commonly reported events were nausea (38%), vomiting (20%), abdominal pain (35%), headache (13%), pruritus (30%), flushing (25%), feeling of warmth (18%), hypotension (16%) and tremor (11%).
Serious or unexpected events were reported and the events (flushing, feeling of warmth, metallic taste, headache) which occurred in a high proportion of patients who received carbetocin in the pharmacology studies appeared with similar frequency in patients who received oxytocin in the therapeutic studies.
There were an equal percent of patients suffering hypotension between the carbetocin group (16%) and the oxytocin group (16%). A greater percentage of patients receiving placebo experienced hypotension.
There were also no differences seen for CVS.
There were no excess adverse events in the carbetocin group suggestive of water intoxication.
There were 12 cases (3%) of anaemia in the carbetocin group, three cases (0.8%) in the oxytocin group and 12 (21%) in the placebo group.
There were two cases of low WBC but these were not clinically significant and one case of thrombocytopenia in the carbetocin group.
There was one allergic reaction in the carbetocin group which was severe but related to cefotetan administration.
One case of chest pain and shortness of breath was considered to be severe and possibly related to carbetocin. The patient recovered and ECG and enzymes were normal.

Vital Signs

Concern was expressed in the study report for CLN 6.3.5, the Caesarean section dosing study, about the possibility of a dose dependant change in diastolic blood pressure and pulse rate. There was a mean drop in systolic blood pressure with a slow return to baseline measures in the recovery area and ward; a significant drop in diastolic blood pressure from 59 to 47 mm hg ($p<0.05$) which was dose dependant, with rebound in the recovery area to 66 mm hg (p,0.05). Pulse rate decreased in the operating room and recovery area and started to rebound in the ward. The changes in the first two phases were dependant on the initial and total dose of carbetocin. The expert does not regard the changes as clinically significant.

Phase III trials.

Patients in study CLN 6.3.6 showed slow decreases in mean systolic and diastolic blood pressures in both carbetocin and oxytocin groups with reversion toward baseline at 20 minutes. Heart rate was high at baseline and increased slightly at two minutes but returned to baseline levels in the recovery area.

Patients receiving carbetocin in study CLN 6.3.9 experienced a significantly lower systolic blood pressure at three and four minutes post drug administration compared to oxytocin patients, similar changes were seen in diastolic blood pressure with a significantly lower value during the first five minutes. Pulse rate rose in both groups in the initial few minutes.

Patients in the placebo controlled study CLN 6.3.10 dropped the mean systolic and diastolic pressures with the placebo group recording significantly lower levels for most time points after 30 minutes in the operating room. Pulse rate was higher at baseline in the carbetocin group and remained so for the first two minutes after administration.

The company have further examined blood pressure as shown in table 10 and there do not appear to be differences between carbetocin and oxytocin.
The respiratory rate data were not of concern.

Laboratory data

The company define normal reference ranges for haematology and chemistry parameters for non pregnant, pregnant and post partum women.
The data presented are not regarded by the expert as showing any clinically significant abnormalities.

There was only one volunteer study showing the effect of carbetocin on laboratory parameters without the associated effects of pregnancy and parturition. Study CLN 6.3.1, which used dosages between 20 and 800 micrograms found statistically significant changes in the following parameters all were considered clinically insignificant by the investigator. Compared with baseline there was an increase in haemoglobin, haematocrit, and GOT levels following 800 micrograms i.m. The WBC showed increases after six hours in the 400 and 800 microgram groups at six hours but these changes were not significantly different at 24 hours.

The WBC increased above baseline in the 200 microgram dose but not with the higher dose groups. Neutrophil count was increased at six hours after the 400 microgram i.m. administration.

Twenty of the 37 subjects studied had a rise in WBC of > 1.

Study 6.3.3 which examined dosage in women post partum did not measure laboratory parameters.

Study 6.3.5 which was the dose ranging study in Caesarean section patients showed significant changes in haematological parameters which were consistent with the operative procedure and there was no significant difference between carbetocin and oxytocin.

A number of patients in the phase III studies were found to have abnormal post drug haematology results. There were no substantial differences in between the active groups. Study CLN 6.3.9 recorded an increased platelet count in the Carbetocin group and a decrease in the oxytocin group but the differences are not clinically significant.

Few patients had abnormal chemistry variables other than GGT. There were similar proportions of patients in both active groups showing these changes. An increased Urea was found in the carbetocin group in the placebo controlled Study CLN 6.3.10. There was no clear rationale for this difference and it was regarded as being clinically insignificant.

The expert report states that the safety profile in patients with high post drug creatinine, AST and ALT were similar to normals but it should be noted that only 7 patients had high values for AST and ALT.

There were no obvious differences in safety profile in patients who were over 35 years of age, > 100 kg in weight, twin gestation, gestational diabetes, history of pre eclampsia or high blood pressure. However these conditions have not been specifically studied.

The studies have not looked for antibodies which could theoretically cross react with oxytocin.

Drug interactions

Although specific studies were not undertaken to look at the interaction profile, the database for study CLN 6.3.9 was interrogated to look for differences in adverse event reporting.
Two hundred and sixty five patients had spinal and 393 had epidural anaesthesia. It is difficult to assess the data due to the potential for multiple confounding factors but there was little evidence of major unexpected differences.

Comment
The safety profile of carbetocin does not appear to differ substantially from oxytocin. The adverse events reported did not give cause for concern. Carbetocin appears to cause a drop in blood pressure and an increase in pulse rate which would be similar to the effect of a bolus dose of oxytocin. These haemodynamic changes do not cause a clinical concern with the dosage regime requested.

The data do not point to a problem in terms of water retention.
However, specific studies have not been submitted and there are no animal data presented to support the statements that the antidiuretic effect is one third that of vasopressin. It is unlikely to be a clinical concern with the dosage regime requested.
There is preliminary evidence that higher doses of carbetocin may cause an increase in white cell count in volunteers although the effect did not appear dose dependant. This was not evident in the therapeutic trials.
There are no data to support recurrent use of carbetocin.

POST-MARKETING SAFETY

The safety of carbetocin has been monitored since 24 June 1997 and cumulative exposure until 31 June 2004 is estimated to 66, 600 patients. During the period of the Periodic Safety Update Report (PSUR), covering the period 24 June 1997 to 23 June 2004, no adverse events were reported. Additionally, no adverse events concerning carbetocin were identified in the literature during this period.

It is considered that the benefit/risk profile for carbetocin remains favourable.

EXPERT REPORT

This is written by Professor Andrew Calder, Department of Obstetrics and Gynaecology, Edinburgh. It is a clear description of the data but does not address the lack of pharmacological and kinetic data.

SPC

Generally satisfactory

PIL

Generally satisfactory.

OVERALL CONCLUSIONS

The data support the clinical position that a single 100 microgram i.v. injection of carbetocin is at least as effective as an infusion of oxytocin in causing uterine contraction. There are preliminary data supporting a trend to less blood loss in patients receiving carbetocin.
Carbetocin has a similar profile and incidence of adverse events as oxytocin.

5. OVERALL CONCLUSIONS

QUALITY

The important quality characteristics of Pabal 100 micrograms/ml solution for injection are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

The non-clinical data submitted with the original application indicate that carbetocin has very low actute toxicity. In view of the intended clinical use the data support the use of carbetocin as a single dose therapy only.

EFFICACY

The data support the clinical position that a single 100 microgram i.v. injection of carbetocin is at least as effective as an infusion of oxytocin in causing uterine contratction. Carbetocin has a similar profile and incidence of adverse events as oxytocin and no new or unexpected safety concerns arose from this application.

The SPC, PIL and labelling are satisfactory.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns were identified. The clinical data indicate that carbetocin is at least as effective as an infusion of oxytocin with a similar profile and incidence of adverse events. The risk-benefit assessment is therefore considered to be favourable.

RECOMMENDATIONS

Based on the review of the data on quality, safety and efficacy, it was considered that the application for Pabal 100 micrograms/ml solution for injection in the prevention of uterine atony following delivery of the infant by Caesarean section under epidural or spinal anaesthesia could be approved for use as described in the Summary of Product Characteristics.

Module 6

In Module 1.2 (application form) of the application the company propose the MR renewal date for Pabal 100 micrograms/ml solution for injection to be 24 August 2007 to comply with the international birth date. The company also propose that all Module 3 commitments are commented and outstanding committed reports submitted in connection with the renewal application in 2007.

The company have submitted the following commitments:-

Scope	Reference in dossier	Type of modification	Submission date	Approval/ non approval	Assessment report attached (Y/N)
To monitor Pd content and if needed submit a variation to control it in the active substance specification in Feb 2007.	3.2.S.4.1	Commitment	Feb 2007	N/A	N
To validate the Ph. Eur method for determination of methanol and submit the report in Feb 2007.	3.2.S.4.3	Commitment	Feb 2007	N/A	N
To perform a verification of the structure of the reference standard and submit results in Feb 2007.	3.2.S.5	Commitment	Feb 2007	N/A	N
To update long-term stability data and submit results in Feb 2007.	3.2.S.7.3	Commitment	Feb 2007	N/A	N
To perform a bacterial retention validation of the filter and to submit the report in February 2007.	3.2.P.3.5	Commitment	Feb 2007	N/A	N

Steps taken after the initial procedure:-

Scope	Procedure Number	Type of modification	Approval/ non approval	Assessment report attached (Y/N)
Repeat use MRP	UK/H/838/001/E001	Repeat use MRP	Approved 23.05.07	N
To update section 4.8 of the SPC and PIL in order to comply with the updated QRD as agreed during the recent repeat use of MRP. To also correct some editorial errors in sections 1, 4.2, 4.3, 4.4, 4.6, 5.3 and 6.5 of the SPC.	UK/H/838/001/II/001	Variation Type II Mutual Recognition	Approved 1.10.07	N
To change the address of the marketing authorisation holder in Germany, Ferring Arzneimittel GmbH, from the current Wittland 11, D - 24109 Kiel, Germany to Fabrikstrasse 7, D - 24103 Kiel, Germany.	UK/H/0838/001/IA/002	Variation Type 1A Mutual Recognition	Approved 28.06.07	N
To register a change in the name of the marketing authorisation holder in Portugal, Ferring Portuguesa LDA, from the current Rua Professor Henrique de Barros, Edifico Sagres, * A, 2685-338 Prior Velho, Portugal to Avenida Alexandre Herculano, Edifico 1 - 6 piso, 2795 - 240 Linda-a-Velha, Portugal.	UK/H/0838/001/IA/003	Variation Type 1A Mutual Recognition	Approved 28.06.07	N