Public Assessment Report

Decentralised Procedure

Pinexel PR 400 micrograms Prolonged-Release Hard Capsules
(tamsulosin hydrochloride)

UK/H/1462/01/DC

UK licence numbers: PL 29831/0366

Wockhardt UK Ltd
LAY SUMMARY

On 4th May 2010, the MHRA granted Wockhardt UK Limited a Marketing Authorisation (licence) for the medicinal product Pinexel PR 400 micrograms Prolonged-Release Hard Capsules (PL 29831/0366, UK/H/1462/01/DC). This is a prescription-only medicine (POM).

The active ingredient in Pinexel PR Capsules is tamsulosin, which belongs to a group of medicines called alpha-blockers (alpha-adrenoreceptor antagonists). Tamsulosin is used for the treatment of urination symptoms caused by benign prostatic hyperplasia (BPH).

BPH means that the prostate gland enlarges (hypertrophy) but the growth is not cancerous (it is benign). The prostate gland is just underneath the bladder. The urethra (the tube through which urine passes from the bladder to the outside of the body) runs through the prostate gland. If the prostate enlarges, it presses on the urethra, causing it to narrow. This makes it difficult to pass urine. Pinexel PR Capsules relax the muscle of the prostate gland widening the urethra and so ease the passing of urine.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of Pinexel PR 400 micrograms Prolonged-Release Hard Capsules outweigh the risks; hence a Marketing Authorisation was granted.
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### Module 1

#### Information about Initial Procedure

<table>
<thead>
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<th>Product Name</th>
<th>Pinexel PR 400 micrograms Prolonged-Release Hard Capsules</th>
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<td>Type of Application</td>
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<td>Form</td>
<td>Prolonged-release hard capsules</td>
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<td>Strength</td>
<td>400 micrograms</td>
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<td>MA Holder</td>
<td>Wockhardt UK Ltd</td>
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<td></td>
<td>Ash Road North</td>
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<td>Wrexham</td>
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<td></td>
<td>LL13 9UF</td>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Pinexel PR 400 micrograms Prolonged-Release Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains tamsulosin hydrochloride 400 microgram, equivalent to 367 microgram tamsulosin.

Also contains the excipient sunset yellow (E110) (see section 4.4).
For full list of the excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Prolonged-release capsule, hard

Pinexel PR Capsules consist of a light green opaque cap and tan opaque body containing white to off white pellets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration
For oral use.

One capsule a day after breakfast or the first meal of the day. The capsule is swallowed whole with a glass of water while standing or sitting (not lying down). The capsule should not be broken or pulled apart as this may have an effect on the release of the long-acting active ingredient.

There is no relevant indication for the use of Pinexel PR in children.

4.3 Contraindications
Hypersensitivity to tamsulosin hydrochloride, including drug-induced angio-oedema, or to any other component of the product; a history of orthostatic hypotension; severe hepatic insufficiency.

4.4 Special warnings and precautions for use
As with other alpha1 blockers, a reduction in blood pressure can occur in individual cases during treatment with Pinexel PR, as a result of which, rarely, syncope can occur. At the first signs of orthostatic hypotension (dizziness, weakness) the patient should sit or lie down until the symptoms have disappeared.

Before therapy with Pinexel PR is initiated the patient should be examined in order to exclude the presence of other conditions which can cause the same symptoms as benign prostatic hyperplasia. Digital rectal examination and when necessary determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards.

The treatment of severely renally impaired patients (creatinine clearance of less than 10 ml/min) should be approached with caution as these patients have not been studied.

Angio-oedema has been reported rarely after the use of tamsulosin. Treatment should be discontinued immediately, the patient should be monitored until the disappearance of the oedema, and tamsulosin should not be readministered.

The ‘Intraoperative Floppy Iris Syndrome’ (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamsulosin. IFIS may lead to
increased procedural complications during the operation. The initiation of therapy with tamsulosin in patients for whom cataract surgery is scheduled is not recommended.

Discontinuing tamsulosin 1 – 2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of stopping of theapy prior to cataract surgery has not yet been established.

During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with tamsulosin in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and tamsulosin may lead to symptomatic hypotension in some patients. In order to minimise the risk for developing postural hypotension the patient should be stable on the alpha-blocker therapy before initiating use of phosphodiesterase-5-inhibitors.

Pinexel PR contains sunset yellow (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions have been seen when Pinexel PR was given concomitantly with either atenolol, enalapril, nifedipine or theophylline. Concomitant cimetidine brings about a rise in plasma levels of tamsulosin, and furosemide a fall, but as levels remain within the normal range posology need not be changed.

In vitro neither diazepam nor propranolol, trichlormethiazide, chlormadinon, amitryptylne, diclofenac, glibenclamide, simvastatin, and warfarin change the free fraction of tamsulosin in human plasma. Neither does tamsulosin change the free fractions of diazepam, propranolol, trichlormethiazide, and chlormadinon.

No interactions at the level of hepatic metabolism have been seen during in vitro studies with liver microsomal fractions (representative of the cytochrome P450-linked drug metabolising enzyme system), involving amitryptylne, salbutamol, glibenclamide and finasteride. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin.

There is a theoretical risk of enhanced hypotensive effect when given concurrently with drugs which may reduce blood pressure, including anaesthetic agents and other α1-adrenoceptor antagonists. Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and tamsulosin may lead to symptomatic hypotension in some patients (see section 4.4).

4.6 Pregnancy and lactation

Not applicable as Pinexel PR is intended for male patients only.

4.7 Effects on ability to drive and use machines

No data is available on whether Pinexel PR adversely affects the ability to drive or operate machines. However, in this respect patients should be aware of the fact that drowsiness, blurred vision, dizziness and syncope can occur.

4.8 Undesirable effects

The assessment of side effects is based on the following frequencies:

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
</tr>
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<tr>
<td>Very common</td>
<td>(≥ 1/10)</td>
</tr>
<tr>
<td>Common</td>
<td>(≥ 1/100, &lt; 1/10)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>(≥ 1/1,000, &lt; 1/100)</td>
</tr>
<tr>
<td>Rare</td>
<td>(≥ 1/10,000, &lt; 1/1000)</td>
</tr>
<tr>
<td>Very rare</td>
<td>(&lt; 1/10, 000)</td>
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</tbody>
</table>

Not well known (frequency on the basis of the available data, not assessable).
<table>
<thead>
<tr>
<th>Common (≥1/100, &lt;1/10)</th>
<th>Uncommon (≥1/10 000, &lt;1/100)</th>
<th>Rare (≥1/10 000, &lt;1/10 000)</th>
<th>Very rare (&lt;1/10 000)</th>
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</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>Headache</td>
<td>Syncope</td>
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<tr>
<td>Cardiac disorders</td>
<td></td>
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<tr>
<td>Vascular disorders</td>
<td>Postural hypotension</td>
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<tr>
<td>Respiratory, thoracic and mediastinum-related disorders</td>
<td>Rhinitis</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation, diarrhoea, nausea, vomiting</td>
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<td>Skin and subcutaneous tissue disorders</td>
<td>Rash, pruritus, urticaria</td>
<td>Angio-oedema</td>
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<tr>
<td>Reproductive systems and breast disorders</td>
<td>Abnormal ejaculation</td>
<td>Priapism</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia</td>
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During cataract surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been associated with therapy of tamsulosin during post-marketing surveillance (see also section 4.4)

### 4.9 Overdose

Acute overdose with 5 mg tamsulosin hydrochloride has been reported. Acute hypotension (systolic blood pressure 70 mm Hg), vomiting and diarrhoea were observed, which were treated with fluid replacement and the patient could be discharged the same day. In case of acute hypotension occurring after overdosage cardiovascular support should be given. Blood pressure can be restored and heart rate brought back to normal by lying the patient down. If this does not help then volume expanders, and when necessary, vasopressors could be employed. Renal function should be monitored and general supportive measures applied. Dialysis is unlikely to be of help as tamsulosin is very highly bound to plasma proteins.

Measures, such as emesis, can be taken to impede absorption. When large quantities are involved, gastric lavage can be applied and activated charcoal and an osmotic laxative, such as sodium sulphate, can be administered

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

*Pharmacotherapeutic group:*

ATC Code G04C A02

Alpha1-adrenoceptor antagonist.

Preparations for the exclusive treatment of prostatic disease.

*Mechanism of action:*

Tamsulosin binds selectively and competitively to postsynaptic alpha1-receptors, in particular to the subtype alpha1A, which bring about relaxation of the smooth muscle of the prostate, whereby tension is reduced.

*Pharmacodynamic effects:*

Pinexel PR increases maximum urinary flow rate by reducing smooth muscle tension in prostate and urethra and thereby relieving obstruction.

It also improves the complex of irritative and obstructive symptoms in which bladder instability and tension of the smooth muscles of the lower urinary tract play an important role.
Alpha1-blockers can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with Pinexel PR.

5.2 Pharmacokinetic properties

Absorption:
Tamsulosin is absorbed from the intestine and is almost completely bioavailable.

Absorption of tamsulosin is reduced by a recent meal. Uniformity of absorption can be promoted by the patient always taking Pinexel PR after the same meal each day.

Tamsulosin shows linear kinetics. After a single dose of Pinexel PR in the fed state, plasma levels of tamsulosin peak at around 6 hours and, in the steady state, which is reached by day 5 of multiple dosing, $C_{\text{max}}$ in patients is about two thirds higher than that reached after a single dose. Although this was seen in elderly patients, the same finding would also be expected in young ones. There is a considerable inter-patient variation in plasma levels both after single and multiple dosing.

Distribution:
In man, tamsulosin is about 99% bound to plasma proteins and volume of distribution is small (about 0.2 l/kg).

Biotransformation:
Tamsulosin has a low first pass effect, being metabolised slowly. Most tamsulosin is present in plasma in the form of unchanged drug. It is metabolised in the liver.

In rats, hardly any induction of microsomal liver enzymes was seen to be caused by tamsulosin.

No dose adjustment is warranted in hepatic insufficiency.

None of the metabolites are more active than the original compound.

Elimination:
Tamsulosin and its metabolites are mainly excreted in the urine with about 9% of a dose being present in the form of unchanged drug.

After a single dose of Pinexel PR in the fed state, and in the steady state in patients, elimination half-lives of about 10 and 13 hours respectively have been measured.

The presence of renal impairment does not warrant lowering the dose.

5.3 Preclinical safety data

Single and repeat dose toxicity studies were performed in mice, rats and dogs. In addition reproduction toxicity studies were performed in rats, carcinogenicity in mice and rats and in vivo and in vitro genotoxicity were examined. The general toxicity profile as seen with high doses of tamsulosin is consistent with the known pharmacological actions of the alpha-adrenergic blocking agents. At very high dose levels the ECG was altered in dogs. This response is considered to be not clinically relevant. Tamsulosin showed no relevant genotoxic properties.

Increased incidences of proliferative changes of mammary glands of female rats and mice have been reported. These findings which are probably mediated by hyperprolactinaemia and only occurred at high dose levels are regarded as irrelevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
- Microcrystalline cellulose
- Methacrylic acid–ethyl acrylate copolymer (1:1) dispersion 30 per cent
- Talc
- Purified water
- Magnesium stearate
- Triethyl citrate

PAR Pinexel PR 400 micrograms prolonged-release hard capsules  PL 29831/0366; UK/H/1462/01/DC
Capsule shell contents:
Hard gelatin
Sodium laurilsulfate
Quinoline yellow E104
Titanium dioxide E171
Sunset yellow E110
Brilliant blue E133

6.2 Incompatibilities
None known.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Blisters strips (PVC/PE/PVDC base, aluminium lid) containing 10 capsules contained in a cardboard box. Pack sizes of 30 capsules.

6.6 Special precautions for disposal
No special instructions.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0366

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/05/2010

10 DATE OF REVISION OF THE TEXT
04/05/2010
Module 3
Patient Information Leaflet

Paroxetine PR 400 micrograms prolonged-release hard capsules
Tamsulosin hydrochloride

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again while you are receiving your treatment.
- If you have any further questions, please ask your doctor or nurse.
- This medicine has been prescribed for you. Do not pass it to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

The name of your medicine is Paroxetine PR 400 micrograms Prolonged-Release Hard Capsules. In the rest of this leaflet it is called Paroxetine PR Capsules.

In this leaflet:
1. What Paroxetine PR Capsules are and what they are used for
2. Before you take Paroxetine PR Capsules
3. How to take Paroxetine PR Capsules
4. Possible side effects
5. How to store Paroxetine PR Capsules
6. Further information

1. WHAT PAROXETINE PR CAPSULES ARE AND WHAT THEY ARE USED FOR

The active substance in Paroxetine PR Capsules is tamsulosin (as hydrochloride), which belongs to a group of medicines called alpha-blockers (alpha-adrenoceptor antagonists).
Tamsulosin is used for the treatment of lower urinary tract symptoms caused by benign prostate hyperplasia (BPH).

BPH means that the prostate gland enlarges (hypertrophy) but the growth is not cancerous (it is benign).
The prostate gland is just underneath the bladder. The urethra (the tube through which urine passes from the bladder to the outside of the body) runs through the prostate gland. If the prostate enlarges, it presses on the urethra, causing it to narrow. This makes it difficult to pass urine.

Paroxetine PR Capsules relax the muscle of the prostate gland, widening the urethra and so easing the passing of urine.

2. BEFORE YOU TAKE PAROXETINE PR CAPSULES

Do not take Paroxetine PR Capsules if:
- you are allergic to tamsulosin hydrochloride, or any of the other ingredients of Paroxetine PR Capsules (see list under ‘What Paroxetine PR Capsules contain’ in section 6).
- you have experienced dizziness or have fainted due to an abnormal decrease in blood pressure when standing up (orthostatic hypotension)
- you suffer from severe liver problems.

Talk to your doctor before taking this product if any of the above applies to you.

Take special care with Paroxetine PR Capsules if:
- you suffer from severe kidney problems
- you are due to have surgery to remove a cataract.

If any of the above apply to you, it is important that you tell your doctor or pharmacist before taking Paroxetine PR Capsules and they will decide what to do.

Paroxetine PR Capsules contain sunset yellow RCF (E110), this may cause allergic reactions in some patients. Allergy is more common in these people who are allergic to aspirin.

STOP TAKING PAROXETINE PR CAPSULES AND CONTACT YOUR DOCTOR OR PHARMACIST IMMEDIATELY IF:
- you experience dizziness or fainting during the use of Paroxetine PR Capsules. Please sit or lie down straight away until the symptoms disappear
- you experience sudden swelling of the face, hands or feet, difficulties in breathing and/or itch and rash caused by an allergic reaction (angio-oedema) while taking Paroxetine PR Capsules.

Taking other medicines

Taking other medicines when taking Paroxetine PR Capsules can affect how it is or the other medicine works. Make sure that your doctor knows what other medicines you are taking.
Do not take any other medicines while you are taking Paroxetine PR Capsules unless you have told your doctor or pharmacist and asked their advice. This includes medicines you may have bought yourself without a prescription.

Please check with your doctor if you are taking any of the following (or any other medication):
- Any medicines which are used to reduce inflammation in the body (anti-inflammatory medicines e.g. ibuprofen)
- Any medicines used to prevent the clotting of blood (anticoagulants e.g. warfarin)
- Other medicines used to reduce blood pressure, including analgesics and other alpha-blocker (alpha-adrenoceptor antagonists, e.g. doxazosin, prazosin and indoramin).

Some patients who take alpha-blocker therapy for the treatment of high blood pressure or prostate enlargement may experience dizziness or lightheadedness, which may be caused by low blood pressure on standing or standing up quickly. Certain patients have experienced these symptoms when taking drugs for erectile dysfunction (impotence) with alpha-blockers. In order to reduce the likelihood of these symptoms occur, you should be on a regular daily dose of your alpha-blocker before you start drugs for erectile dysfunction.

If you have any doubts about whether you should be given this medicine, then talk to your doctor.

Pregnancy and breast-feeding
Not applicable as Paroxetine PR Capsules are intended for male patients only.

Driving and using machines
Paroxetine PR Capsules may cause drowsiness, blurred vision and dizziness. If you are affected you should not drive or operate machinery.

3. HOW TO TAKE PAROXETINE PR CAPSULES

Always take Paroxetine PR Capsules exactly as your doctor has instructed you to. You should check with your doctor or pharmacist if you are not sure.

10/17/22
How to take your medicine
The usual dose is one capsule a day after the first meal of the
day. The capsule should be taken while standing or sitting
upright (not lying down) and should be swallowed whole with a
glass of water.

Taking Pineoxel PR Capsules with food and drink
Pineoxel PR Capsules should be taken after the same meal each
day. Taking Pineoxel PR Capsules on an empty stomach may
increase the risk of side effects.

Pineoxel PR is a specially designed capsule from which the
active ingredient is gradually released. Do not crush or chew
the capsule as this will interfere with how the medicine works.

If you take more Pineoxel PR Capsules than you should
Your doctor will decide the dose that is best for you. If you
think you have taken too many capsules, contact your doctor,
nurse, pharmacist or nearest hospital immediately.

Signs that you or someone else has taken too many Pineoxel PR
Capsules include fainting, dizziness, light-headedness,
palpitations, blurred vision and confusion, vomiting and diarrhoea.

If you forget to take Pineoxel PR Capsules
If you forget to take a dose of Pineoxel PR Capsules, wait until
your next dose is due and take this as normal. Do not take a
double dose to make up for a forgotten capsule.

4. POSSIBLE SIDE EFFECTS

Like many medicines, Pineoxel PR Capsules may cause side effects
in some patients, although not everybody gets them. You should
inform your doctor or nurse immediately if you feel unwell.

Common (less than 1 in 10 but more than 1 in 100 patients)
• dizziness

Uncommon (less than 1 in 100 but more than 1 in 1,000
patients)
• headache, a lack of strength or energy
• a fall in blood pressure (often when you stand up resulting in
  light-headedness), palpitations
• rhinitis (sneezing, blocked or stuffy nose, runny nose, itchy
  nose, throat and eyes)
• nausea, vomiting, diarrhoea and constipation
• rash; itchy skin; raised, itchy skin (known as hives)
• abnormal evacuation (i.e. less, or no, noticeable, semen
  ejaculated).

Rare (less than 1 in 1,000 patients)
• angio-oedema (severe swelling of the skin, particularly of the
  face, hands, feet or voice box, difficulties in breathing and/or
  itch and rash)
• temporary loss of consciousness.

Very rare (less than 1 in 10,000 patients)
• priapism (a painful prolonged erection).

In some occasions possible complications in connection to
cataract operations have been observed.

If you notice any side effects not mentioned in this leaflet, or
feel that the medicine is affecting you badly, please tell your
doctor or pharmacist.

5. HOW TO STORE PINEIXEL PR CAPSULES

Keep this medicine out of the reach and sight of children.
• The medicine should not be used after the expiry date

shown on the carton and blister label. The expiry date refers
to the last day of that month.
• This medicinal product does not require any special storage
  conditions.

Medicines should not be disposed of via wastewater or
household waste. Ask your pharmacist how to dispose of
medicines no longer required. These measures will help to protect
the environment.

6. FURTHER INFORMATION

What Pineoxel PR Capsules contain
Pineoxel PR Capsules contain the active ingredient tamsulosin hydrochloride.
Each capsule contains 400 micrograms of tamsulosin hydrochloride (equivalent to 367 micrograms
tamsulosin).

The other ingredients are microcrystalline cellulose, methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30 per cent, talc,
purified water, magnesium stearate and methyl cellulose. The
outer shell of the capsule contains hard gelatin, sodium
laurylsulfate, quinoline yellow (E104), titanium dioxide (E171),
sunset yellow (E110) and brilliant blue (E133).

What Pineoxel PR Capsules look like and contents of the pack
Pineoxel PR Capsules consist of a light green opaque cap and
tan opaque body containing white to off white pellets. The
capsules are contained in a blister pack in a cardboard box.
They are available in packs of 30 capsules.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Wockhardt UK Ltd,
Ash Road North, Wrexham, LL13 9UF, UK.
Manufacturer: CP Pharmaceuticals Ltd,
Ash Road North, Wrexham, LL13 9UF, UK.

This medicinal product is authorised in the Member States of
the EEA under the following names:
UK: Pineoxel PR 400 micrograms Prolonged-Release Hard
Capsules
Ireland: Pineoxel PR 400 micrograms Prolonged-Release Hard
Capsules
Cyprus: Pineoxel PR 400 micrograms Prolonged-Release Hard
Capsules
Malta: Pineoxel PR 400 micrograms Prolonged-Release Hard
Capsules
Germany: Pineoxel PR 400 microgramm Hartkapseln, retardiert
Poland: Pineoxel PR

Other formats:
To listen to or request a copy of this leaflet in Braille, large print
or audio please call, free of charge: 0800 198 5000 (UK Only).
Please be ready to give the following information:

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<th>Reference number</th>
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<tr>
<td>Pineoxel PR 400 micrograms Prolonged-Release Hard Capsules</td>
<td>29831/0366</td>
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</table>

This is a service provided by the Royal National Institute of
Blind People.

For the Republic of Ireland please call +353 52 36253

Leaflet prepared: February 2010.

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CP!
Module 4

Labelling

Carton for blisters
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Wockhardt UK Limited a Marketing Authorisation for the medicinal product Pinexel PR 400 micrograms Prolonged-Release Hard Capsules (PL 29831/0366, UK/H/1462/01/DC) on 4th May 2010. The product is a prescription-only medicine.

This is an abridged application for Pinexel PR 400 micrograms Prolonged-Release Hard Capsules, submitted under Article 10.1 of 2001/83 EC, as amended. The application refers to the EU and UK reference product, Omnic® MR, 400 micrograms, modified release capsule, hard (PL 00166/0171), authorised to Astellas Pharma Ltd on 16th April 1996. The reference product has been authorised in the UK for more than 10 years, so the period of data exclusivity has expired. With the UK as the Reference Member State in this Decentralised Procedure, Wockhardt UK Limited applied for a Marketing Authorisation for Pinexel PR 400 micrograms Prolonged-Release Hard Capsules in Cyprus, Germany, Ireland, Malta and Poland.

Pinexel PR Capsules are indicated for lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). The active ingredient, tamsulosin, belongs to the pharmacotherapeutic group, alpha 1- adrenoceptor antagonists (ATC code – G04C A02).

Tamsulosin binds selectively and competitively to postsynaptic alpha1-receptors, in particular to the subtype alpha1A, to bring about relaxation of the smooth muscle of the prostate, whereby tension is reduced. Pinexel PR Capsules increase maximum urinary flow rate by reducing smooth muscle tension in the prostate and urethra, and thereby relieve obstruction. This medicine also improves the complex of irritative and obstructive symptoms in which bladder instability and tension of the smooth muscles of the lower urinary tract play an important role.

Tamsulosin is absorbed from the intestine and is almost completely bioavailable. Absorption of tamsulosin is reduced by a recent meal. Uniformity of absorption can be promoted by the patient always taking Pinexel PR Capsules after the same meal each day. Tamsulosin shows linear kinetics. After a single dose of Pinexel PR in the fed state, plasma levels of tamsulosin peak at around 6 hours. There is a considerable inter-patient variation in plasma levels both after single and multiple dosing. In man, tamsulosin is about 99% bound to plasma proteins and volume of distribution is small (about 0.2 l/kg). Tamsulosin has a low first pass effect, being metabolised slowly. Most tamsulosin is present in plasma in the form of unchanged drug. It is metabolised in the liver and no dose adjustment is warranted in hepatic insufficiency. None of the metabolites are more active than the original compound. Tamsulosin and its metabolites are mainly excreted in the urine with about 9% of a dose being present in the form of unchanged drug.

No new non-clinical or clinical efficacy studies were conducted, which is acceptable given that the application cross-refers to a product that has been licensed for over 10 years.
The application is supported by three bioequivalence studies presented by the applicant comparing the pharmacokinetic profile of the test product, Pinexel PR 400 micrograms Prolonged-Release Hard Capsules, to that of the reference product, Omnic® MR 0.4 mg capsules (sourced from the Netherlands). The applicant conducted two single dose bioequivalence studies (fasting and fed) and a steady state bioequivalence study with 400 microgram hard capsules. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ 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.

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

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Pinexel PR 400 micrograms Prolonged-Release Hard Capsules |
| Name(s) of the active substance(s) (INN) | tamsulosin hydrochloride |
| Pharmacotherapeutic classification (ATC code) | Alpha1-adrenoceptor antagonist (G04C A02) |
| Pharmaceutical form and strength(s) | Prolonged-release hard capsules 400 micrograms |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1462/01/DC |
| Reference Member State | United Kingdom |
| Member States concerned | CY, DE, IE, MT, PL |
| Marketing Authorisation Number(s) | PL 29831/0366 |
| Name and address of the authorisation holder | Wockhardt UK Ltd Ash Road North Wrexham LL13 9UF UK |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

ACTIVE SUBSTANCE

Tamsulosin Hydrochloride

Nomenclature:

INN: Tamsulosin Hydrochloride

Chemical name: 5-[(2R)-2-[2-(2-ethoxy-phenoxy) ethyl] amino] propyl]-2-methoxy-benzene sulfonamide hydrochloride

Structure:

![Structure of Tamsulosin Hydrochloride]

Molecular formula: C$_{20}$H$_{29}$ClN$_2$O$_5$S

Molecular weight: 445.6 g/mol

CAS No: 106463-17-6

Physical form: White or almost white powder

Solubility: Slightly soluble in water, freely soluble in formic acid, slightly soluble in anhydrous ethanol

The active substance, tamsulosin hydrochloride, is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided for three batches, in the form of Certificates of Analysis, and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. The primary packaging is low-density polyethylene (LDPE), food grade bags, which are sealed and placed in high molecular weight high-density polyethylene (HM-HDPE) bags. The HM-HDPE bags are then heat-sealed and placed into foil laminated sachets (outer bags), which are also heat-sealed. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary LDPE bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.
Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and an appropriate retest period of 24 months has been applied.

MEDICINAL PRODUCT

Description and Composition

The finished product is presented as hard, prolonged-release capsules, containing white to off-white pellets. Each capsule contains 400 micrograms of the active ingredient, tamsulosin hydrochloride, equivalent to 367 micrograms tamsulosin base.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, methacrylic acid–ethyl acrylate copolymer (1:1) dispersion 30 per cent, talc, purified water, magnesium stearate, and triethyl citrate making up the capsule contents; and hard gelatine, sodium laurilsulfate, quinoline yellow (E104), titanium dioxide (E171), sunset yellow (E110), and brilliant blue (E133) making up the capsule shell. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of the colourants, quinoline yellow (E104), titanium dioxide (E171), sunset yellow (E110), and brilliant blue (E133), which comply with satisfactory in-house specifications. Confirmation has been provided that these colourants comply with the requirements of EU directive 95/45/EEC, as required. Satisfactory Certificates of Analysis have been provided for all excipients.

Current legislation allows the use of sunset yellow (E110) in medicinal products. Guidance CHMP/QWP/396951/2006 explains that such colourants should not be used for aesthetic purposes in the paediatric population. The proposed product is only intended for use in adults. However, the MAH has agreed to remove the colourant within 6 months of licence approval via variation.

The magnesium stearate is of vegetable origin. A satisfactory Certificate of Suitability has been provided for ‘hard gelatin’ stating that it meets the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Comparative dissolution and impurity data were provided for the test and appropriate reference products. The dissolution and impurity profiles were found to be similar, with all impurities within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.
In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted on three production scale batches and the results were satisfactory.

**Finished product specification**

The finished product specifications are provided for both release and shelf life and are satisfactory; providing an assurance of the quality and consistency of the finished product. 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. Satisfactory batch analysis data are provided for three production scale batches of the product; they demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

The bulk shipment packaging (for transportation and repackaging of tablets) consists of the primary, LDPE bags which are sealed and then packed into triple laminated sachets, with two silica gel bags on the top, which are thermosealed. The thermosealed triple laminated bags are kept in HDPE containers.

The finished product is licensed for marketing in PVC (polyvinylchloride) - PE (polyethylene) - PVdC (polyvinylidene chloride) / aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 30 capsules.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. This medicinal product does not require any special storage conditions.

**Bioequivalence Study**

Three bioequivalence studies (single dose fasted, single dose fed, and multiple dose steady state) were presented comparing the test product, Pinexel PR 400 micrograms Prolonged-Release Hard Capsules, to the reference product, Omnic® MR 0.4 mg capsules.

An evaluation of the bioequivalence studies is found in the Clinical Aspects section.

**Quality Overall Summary**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved SmPC, leaflet, and labelling are satisfactory. Mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.
Conclusion

The test product corresponds to the current EU definition of a generic medicinal product because it complies with the criteria of having the same qualitative and quantitative composition, in terms of the active substance and pharmaceutical form, as the reference product. On this basis, and considering the bioequivalence data provided, the applicant’s claim that Pinexel PR 400 micrograms Prolonged-Release Hard Capsules is a generic medicinal product of Omnic® MR, 400 micrograms, modified release capsule, hard (PL 00166/0171, Astellas Pharma Ltd) is justified.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation has therefore been granted.

III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for this application for a generic version of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of tamsulosin hydrochloride, which is a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the reference medicinal product, Omnic® MR, 400 micrograms, modified release capsule, hard.
III.3 CLINICAL ASPECTS

BACKGROUND

Tamsulosin is an alpha1-adrenoceptor blocker with actions similar to those of prazosin; it is reported to be more selective for the alpha1A-adrenoceptor subtype, which accounts for about 70% of the \( \alpha_1 \) adrenoceptors in the prostate. It is used in benign prostatic hyperplasia to relieve symptoms of urinary obstruction. In benign prostatic hyperplasia, tamsulosin hydrochloride is given by mouth in a modified-release formulation, in a dose of 400 micrograms once daily. Tamsulosin is absorbed from the gastrointestinal tract and is almost completely bioavailable. The extent and rate of absorption are reduced by food. After oral doses of an immediate-release preparation, peak plasma concentrations occur after about 1 hour. Tamsulosin is about 99% bound to plasma proteins. It is metabolised slowly in the liver primarily by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4; it is excreted mainly in the urine as metabolites and some unchanged drug. The plasma elimination half-life has been reported to be between 4 and 5.5 hours.

INDICATIONS

Pinexel PR Capsules are indicated for the relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

The indications are consistent with those of the reference product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The recommended posology is one 400 microgram prolonged-release capsule to be taken orally once daily, after breakfast or the first meal of the day. Full details concerning the posology are provided in the SmPC.

The posology is consistent with that for the reference product and is satisfactory.

TOXICOLOGY

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

CLINICAL PHARMACOLOGY

The clinical pharmacology of tamsulosin hydrochloride is well known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

Pharmacokinetics – bioequivalence study

Prolonged release formulations are assessed as bioequivalent on the basis of single and multiple dose studies which are designed to demonstrate that the test formulation exhibits the claimed prolonged release characteristics of the reference, the active substance is not released unexpectedly from the test formulation (dose dumping), performance of test and reference product is similar after a single dose and at steady state and that the effect of food on the in vivo performance is comparable.

The applicant has conducted two single dose BE studies (fasting and fed) and a steady state BE study with the dosage form and strength applied for (400mcg hard capsules). The bioequivalence studies presented by the applicant compare the pharmacokinetic profiles of Pinexel PR 400 micrograms Prolonged-Release Hard Capsules (test), and Omnic® MR 0.4 mg capsules sourced from the Netherlands (reference). The test and reference products were identical for all three studies. The studies were of an appropriate design and were conducted to principles of Good Clinical Practice (GCP).
Study A - single dose, fasted

This was a randomised, open-label, two-treatment, two-period, two-sequence, single dose crossover bioavailability and bioequivalence study. The study was conducted in 44 (40 + 4 standby) healthy adult male subjects between the ages of 18 to 45 years old, under fasting conditions. Following an overnight fast, a single dose of the investigational products was administered orally, with 240 ml water, to each subject in each period. A satisfactory washout period of 8 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 72.0 hours after administration of test or reference product. Plasma levels of tamsulosin were detected by a validated HPLC-MS method.

The primary pharmacokinetic parameters for this study were $C_{\text{max}}$, $\text{AUC}_0-t$, and $\text{AUC}_0-\infty$.

Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed $C_{\text{max}}$, $\text{AUC}_0-t$, and $\text{AUC}_0-\infty$.

**Assessor's comment:**
A standard BE study was conducted. The study design was adequate to address the BE. None of the pre-dose samples contained detectable levels of tamsulosin; the length of the washout period was adequate. The blood collection time of 72h was sufficient, $\text{AUC}$ extrapolated area was <10% of $\text{AUC}_0-\text{inf}$ for most of the individuals after both treatments. The analytical part of the study adhered to the GLP requirements. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

**Results:**
Forty-four subjects entered the trial and 39 of these completed both study periods. Withdrawals were explained satisfactorily. There were 13 adverse events (AEs) reported in 12 subjects. All were abnormal blood results recorded during the post study assessment after the administration of both reference and test product. Five subjects were found to be anaemic, 4 subjects showed eosinophilia, 1 subject showed both anaemia and eosinophilia. One subject had a rise in total leucocyte count and 1 subject had a low platelet count. All AEs were categorised as mild and the relationship with the study medication was defined as unlikely. There were no serious or significant adverse events reported in the study.

The summary of the results of the bioequivalence study are tabulated below:

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Geometric Least Squares Mean</th>
<th>90 % Confidence Interval</th>
<th>Intra-subject variability CV (%)</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (A)</td>
<td>Reference (B)</td>
<td>% Ratio (A/B)</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>18.83</td>
<td>19.53</td>
<td>96.38 %</td>
<td>91.15 % -101.91 %</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ (ng.hr/mL)</td>
<td>233.62</td>
<td>226.12</td>
<td>103.32 %</td>
<td>97.89 % -109.04 %</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (ng.hr/mL)</td>
<td>244.53</td>
<td>236.85</td>
<td>103.24 %</td>
<td>98.05 % -108.70 %</td>
</tr>
</tbody>
</table>

**Conclusion**
The 90% confidence intervals for the ln-transformed AUC and $C_{\text{max}}$ lie within the acceptance criteria of 80.00-125.00%. Bioequivalence has been demonstrated, under fasting conditions.
Study B - single dose, fed

This was a randomised, open-label, two-treatment, two-period, two-sequence, single dose crossover bioavailability and bioequivalence study. The study was conducted in 40 (36 + 4 standby) healthy adult male subjects between the ages of 18 to 45 years old, under fed conditions. Following an overnight fast the volunteers were given a high fat breakfast. After a 30 minute gap, a single dose of the investigational products was then administered orally, with 240 ml water, to each subject in each period. A satisfactory washout period of 8 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 72.0 hours after administration of test or reference product. Plasma levels of tamsulosin were detected by a validated HPLC-MS method. The primary pharmacokinetic parameters for this study were $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$.

Assessor's comment:
A standard BE study was conducted. The study design was adequate to address the BE. None of the pre-dose samples contained detectable levels of tamsulosin; the length of the washout period was adequate. The blood collection time of 72h was sufficient, $AUC_{\infty}$ extrapolated area was <10% of $AUC_{0-t}$ for most of the individuals after both treatments. The analytical part of the study adhered to the GLP requirements. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

Results:
Forty subjects entered the trial and 33 of these completed both study periods. Withdrawals were explained satisfactorily. There were 11 AEs reported in 8 subjects. Nine AEs were abnormal blood results recorded during the post study assessment after the administration of both reference and test product. Three subjects were found to be anaemic, 2 subjects showed eosinophilia, 1 subject showed both anaemia and eosinophilia. One subject had a rise in total leucocyte count and anemia. All of these 9 AEs were categorised as mild and the relationship with the study medication was defined as unlikely. One subject suffered from nausea and 2 episodes of vomiting after taking the test product on the dosing day. This event was categorised as mild and probably related to the study drug. The subject was withdrawn from the study. There were no serious or significant adverse events reported in the study.

The summary of the results of the bioequivalence study are tabulated below:

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Geometric Least Squares Mean N = 33</th>
<th>90 % Confidence Interval</th>
<th>Intra-subject variability CV(%)</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (A)</td>
<td>Reference (B)</td>
<td>$%$ Ratio (A/B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>10.22</td>
<td>9.26</td>
<td>110.33 %</td>
<td>100.63 - 120.96 %</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng hr/mL)</td>
<td>173.01</td>
<td>162.48</td>
<td>106.48 %</td>
<td>99.19 - 114.32 %</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng hr/mL)</td>
<td>188.75</td>
<td>173.36</td>
<td>108.88 %</td>
<td>101.77 - 116.49 %</td>
</tr>
</tbody>
</table>

Conclusion
The 90% confidence intervals for the ln-transformed AUC and $C_{\text{max}}$ lie within the acceptance criteria of 80.00-125.00%. Bioequivalence has been demonstrated, under fed conditions.
Study C - multiple dose, steady state

This was a randomised, open-label, two-treatment, two-period, two-sequence, multiple dose crossover, steady state bioavailability and bioequivalence study. The study was conducted in 28 (24 + 4 standby) healthy adult male subjects between the ages of 18 to 45 years old, under fasted conditions. Study drug was administered orally once daily, with 240ml water, after an overnight fast, followed by an additional fasting time of 4 hours. A satisfactory washout period of 8 days was maintained between the seven dosing days in each group.

Blood samples were taken pre-dose (0.0) on each of the 7 days and at specified time points up to 72.0 hours after administration of the 7th dose of test or reference product. Plasma levels of tamsulosin were detected by a validated HPLC-MS method.

The primary pharmacokinetic parameters for this study were C\text{max}, AUC\text{0-\text{t}}, and AUC\text{0-\infty}.

Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed C\text{max}, AUC\text{0-\text{t}}, and AUC\text{0-\infty}.

Assessor's comment:

A standard BE study was conducted. The study design was adequate to address the BE. None of the pre-dose samples contained detectable levels of tamsulosin; the length of the washout period was adequate. The blood collection time of 72h was sufficient, AUC extrapolated area was <10% of AUC\text{0-\text{t}} for most of the individuals after both treatments.

The SPC states that modified-release tamsulosin should be taken after the same meal each day, reflecting the fact that there is a food effect in the absorption of the drug. In this case a steady state study should be carried out in a fed state after a light breakfast. The steady state study was done after fasting. If modified-release tamsulosin is taken without food, the AUC and C\text{max} is higher and T\text{max} is earlier and the fluctuation in serum concentrations is higher than after a meal. The SPC of tamsulosin recommends intake with food in order to minimize the risk for orthostatic hypotension. However, the inter-individual variability is reduced when taken with food. The effect of food on release characteristics was studied after a single dose and was shown to be similar for the test and reference product. On these grounds, multiple dose study under fasting conditions is acceptable.

The analytical part of the study adhered to the GLP requirements. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

Results:

Twenty-eight subjects entered the trial and 24 of these completed both study periods. Withdrawals were explained satisfactorily. There were 10 AEs reported in 6 subjects. One subject suffered from fever, raised leucocyte count and a decrease in platelet count. The same subject suffered from vomiting after study drug ingestion and was withdrawn. The AEs were categorised as mild and the vomiting as likely related to the study drug, whereas fever and blood abnormalities were categorised as unlikely to be related. Two events were considered mild and probably related to the study drug: 1 subject suffered from vomiting after test drug and 1 subject from giddiness after the reference drug. Four AEs were abnormal blood results recorded during the post study assessment after the administration of both reference and test product. Three subjects showed eosinophilia, 1 subject showed elevated SGPT. All of these 4 adverse events were categorised as mild and the relationship with the study medication was defined as unlikely. There were no serious or significant adverse events reported in the study.
The summary of the results of the bioequivalence study are tabulated below:

Summary pharmacokinetic data for a randomised, open-label, two-way, multiple dose, crossover, steady state study between the test and reference products. n=24 healthy subjects, dosed fasted; t=72 hours. Wash-out period: 8 days. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD) – tamsulosin

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Geometric Least Squares Mean N = 24</th>
<th>90 % Confidence Interval</th>
<th>Intra-subject variability CV (%)</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>Test (A) 25.37 Reference (B) 27.17</td>
<td>% Ratio (A/B) 97.07 %</td>
<td>88.02 % -107.04 %</td>
<td>19.85 %</td>
</tr>
<tr>
<td>C_{min} (ng/mL)</td>
<td>4.14      4.01</td>
<td>103.16 %</td>
<td>93.24 % -114.14 %</td>
<td>20.54 %</td>
</tr>
<tr>
<td>AUC_{r} (ng hr/mL)</td>
<td>271.61   264.66</td>
<td>102.63 %</td>
<td>94.95 % -110.93 %</td>
<td>15.72 %</td>
</tr>
</tbody>
</table>

Conclusion
The 90% confidence intervals for the ln-transformed AUC and C_{max} lie within the acceptance criteria of 80.00-125.00%. Bioequivalence has been demonstrated, under fasted conditions.

**Conclusion on Bioequivalence**
The results of the bioequivalence studies show that the test and reference products are bioequivalent under fasting, fed and steady state conditions as the confidence intervals for C_{max} and AUC for tamsulosin fall within the acceptance criteria range of 80-125% in line with current guidelines.

**Clinical efficacy**
No new data have been submitted and none are required. The reference product is established and the application depends upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of tamsulosin hydrochloride is well-established from its extensive use in clinical practice.

**Clinical safety**
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of tamsulosin hydrochloride is well-known.

**PRODUCT INFORMATION:**
**Summary of Product Characteristics (SmPC)**
The approved SmPC is consistent with that for the reference product, and is acceptable.

**Patient Information Leaflet**
The final PIL is in line with the approved SmPC and is satisfactory.

**Labelling**
The labelling is satisfactory.
Expert report
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

Post marketing experience
No post-marketing data are available. The medicinal product has not been marketed in any country. Tamsulosin has a recognised efficacy and an acceptable level of safety in the approved indication.

CONCLUSIONS
All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Pinexel PR 400 micrograms Prolonged-Release Hard Capsules) and reference (Omnic® MR 0.4 mg capsules) products within general acceptance limits. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the reference medicinal product, Omnic® MR, 400 micrograms, modified release capsule, hard.

Sufficient clinical information has been submitted to support this application. A Marketing Authorisation was therefore granted.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Pinexel PR 400 micrograms Prolonged-Release Hard Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Pinexel PR 400 micrograms Prolonged-Release Hard Capsules, and the reference product, Omnic® MR 0.4 mg capsules (sourced from the Netherlands).

No new or unexpected safety concerns arise from these applications.

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

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence studies and their conclusions support the claim that the applicant’s Pinexel PR 400 micrograms Prolonged-Release Hard Capsules is a generic version of Omnic® MR, 400 micrograms, modified release capsule, hard (PL 00166/0171, Astellas Pharma Ltd). Extensive clinical experience with tamsulosin hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
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<tr>
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</table>