Public Assessment Report

Decentralised Procedure

FLECTONE XL 400 MICROGRAM PROLONGED-RELEASE TABLETS

(Tamsulosin hydrochloride)

Procedure No: UK/H/1518/001/DC

UK Licence No: PL 00289/1142.

TEVA UK LIMITED
LAY SUMMARY

On 20 April 2011, the Czech Republic, Germany, Spain, France, Hungary, Italy, the Netherlands, Poland, Romania, and the UK agreed to grant a Marketing Authorisation to Teva UK Limited for the medicinal product Flectone XL 400 microgram prolonged-release tablets (PL 00289/1142, UK/H/1518/001/DC). This licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 23 May 2011. This is a prescription-only medicine (POM) intended for use in men to treat lower urinary tract symptoms caused by benign prostatic hyperplasia (BPH), which is an enlargement of the prostate gland.

Flectone XL 400 microgram prolonged-release tablets contain the active ingredient tamsulosin. Tamsulosin is an alpha1 receptor blocker which reduces the tension in the muscles of the prostate and urethra (the tube that carries urine to the outside). As a result, the urethra, which runs through the prostate, is less contracted and urination is easier.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Flectone XL 400 microgram prolonged-release tablets outweigh the risks.
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## Module 1

<table>
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<tr>
<th><strong>Product Name</strong></th>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Flectone XL 400 microgram prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One prolonged-release tablet contains 0.40 mg tamsulosin hydrochloride equivalent to 0.367 mg tamsulosin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Prolonged-release tablet
Yellow, biconvex, oval, film-coated tablet, debossed 'T04' on one side and plain on the other.

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
One prolonged-release (PR) tablet daily. The tablet can be taken independently of food and must be swallowed whole and not crunched or chewed as this interferes with the prolonged release of the active substance.
No dose adjustment is warranted in renal impairment.
No dose adjustment is warranted in patients with mild to moderate hepatic insufficiency (see also section 4.3).
There is no relevant indication for use of tamsulosin hydrochloride in children.

4.3 Contraindications
- Hypersensitivity to tamsulosin, including drug-induced angioedema, or to any of the excipients.
- History of orthostatic hypotension.
- Severe hepatic insufficiency.

4.4 Special warnings and precautions for use
The use of tamsulosin may lower blood pressure, which in rare cases may cause fainting. If initial symptoms of orthostatic hypotension start to appear (dizziness, weakness), then the patient should sit or lie down until the symptoms have gone.

The patient should be examined before commencement of therapy with tamsulosin to exclude the presence of other conditions that can produce similar symptoms to those of BPH. The prostate should be examined via the rectum and, if necessary, the PSA count determined prior to commencement of treatment and again later at regular intervals.

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

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

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 requirement of stopping the therapy 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.

4.5 Interaction with other medicinal products and other forms of interaction
Interactions studies have only been performed in adults. No interactions have been observed when tamsulosin has been given concomitantly with atenolol, enalapril, nifedipine or theophylline. Concomitant cimetidine raises, and concomitant furosemide lowers, plasma concentrations of tamsulosin but, as the concentration of tamsulosin remains within the normal range, posology need not be altered.

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

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

Concurrent administration with another α1-adrenoreceptor antagonist may lower blood pressure.

4.6 Pregnancy and lactation
Tamsulosin is intended for males only.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, patients should be aware of the fact that dizziness can occur.

4.8 Undesirable effects

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<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000)</th>
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<td>Cardiac disorders</td>
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<td>Palpitations</td>
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<td>Vascular disorders</td>
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<td>Skin and subcutaneous tissue disorders</td>
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<td>Rash, itching, urticaria</td>
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<td>Stevens-Johnson syndrome</td>
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<td>Ejaculation disorders</td>
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<td>General disorders and administration site conditions</td>
<td>Asthenia</td>
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</table>

Post-marketing experience
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).

In addition to the adverse events listed above, the following have been reported in association with tamsulosin use: Cardiac disorders: atrial fibrillation, arrhythmia, tachycardia Respiratory, thoracic and mediastinal disorders: dyspnoea

Since these spontaneously reported events are from worldwide post marketing experience, their frequency and the role of tamsulosin in their causation cannot be reliably determined.
4.9 **Overdose**

Acute overdose with 5 mg tamsulosin hydrochloride has been reported. Acute hypotension (systolic blood pressure 70 mmHg), vomiting and diarrhoea were observed, which were treated with fluid replacement and the patient could be discharged the same day. In the event of acute hypotension, 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. If large quantities of the medicinal product are involved, gastric lavage may be performed and activated charcoal and an osmotic laxative, such as sodium sulphate, may be given.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists

ATC code: G04CA02

The medicinal product is only used for the treatment of prostatic conditions.

*Mechanism of action*

Tamsulosin binds selectively and competitively to post-synaptic $\alpha_1$-adrenoreceptors, in particular to the subtypes $\alpha_{1A}$ and $\alpha_{1D}$, which brings about relaxation of prostatic and urethral smooth muscle.

*Pharmacodynamic effects*

Tamsulosin increases the maximum urinary flow rate by relaxing prostatic and urethral smooth muscle, thus relieving obstruction.

The medicinal product also improves the irritative and obstructive symptoms in which the contraction of smooth muscle in the lower urinary tract plays an important role.

Alpha-blockers can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with tamsulosin in normotensive patients.

The medicinal product’s effect on storage and voiding symptoms are also maintained during long-term therapy. Observational data indicate that use of tamsulosin may lead to a delay in the need for surgery or catheterization.

5.2 **Pharmacokinetic properties**

*Absorption*

Tamsulosin administered as prolonged-release tablets is absorbed from the intestine. Of the administered dose, approximately 57% is estimated to be absorbed. The rate and extent of absorption of tamsulosin administered as prolonged-release tablets are not affected by food.

Tamsulosin shows linear kinetics.

After a single dose of tamsulosin prolonged-release tablets in the fasted state, plasma concentrations of tamsulosin peak at a median time of 6 hours. In steady-state, which is reached by day 4 of multiple dosing, plasma concentrations of tamsulosin peak at 4 to 6 hours, in the fasted and fed state. Peak plasma concentrations increase from approximately 6 ng/ml after the first dose to 11 ng/ml in steady-state. As a result of the prolonged-release characteristics of these tablets the trough concentration of tamsulosin in plasma amounts to 40% of the peak plasma concentration under fasted and fed conditions.

There are huge inter-patient variations in plasma levels of tamsulosin, both after single as well as multiple dosing.
**Distribution**

In humans, tamsulosin is more than 99% bound to plasma proteins and the volume of distribution is small (about 0.2 l/kg).

**Biotransformation**

Tamsulosin has a low first-pass metabolic effect. Most tamsulosin is found unaltered in plasma. The substance is metabolised in the liver.

In studies on rats, tamsulosin was found to cause only a slight induction of microsomal liver enzymes.

The metabolites are not as effective and toxic as the active medicinal product itself.

**Excretion**

Tamsulosin and its metabolites are mainly excreted in the. The amount excreted as unchanged active substance is estimated to be about 4-6% of the dose, administered as prolonged-release tablets.

After a single dose of tamsulosin as prolonged-release tablets and in steady-state, elimination half-lives of about 19 and 15 hours, respectively, have been measured.

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 pharmacological actions of alpha-adrenergic blocking agents.

At very high dose levels, the ECG was altered in dogs. This response is not considered to be clinically relevant. Tamsulosin showed no relevant genotoxic properties.

Increased incidences of proliferative changes in the 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**

Core: Cellulose microcrystalline
Polyethylene oxide
Silica, colloidal anhydrous
Magnesium stearate

Film-coating: Hypromellose 6cP
Titanium dioxide (E171)
Macrogol 8000
Iron oxide, yellow (E172)
Iron oxide, red (E172)

6.2 **Incompatibilities**

Not applicable

6.3 **Shelf life**

36 months

6.4 **Special precautions for storage**

This medicinal product does not require any special storage conditions.

6.5 **Nature and contents of container**

OPA/Alu/PVC-aluminium blister

Pack sizes: 10, 14, 20, 28, 30, 50, 56, 60, 90, 100, 200 Tablets and 50x1 (hospital pack) prolonged-release tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited
Brampton Road
Hampden Park
Eastbourne
BN22 9AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1142

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/05/2011

10 DATE OF REVISION OF THE TEXT
23/05/2011
Module 3

FLECTONE XL 400 microgram PROLONGED-RELEASE TABLETS

Tamsulosin hydrochloride

PACKAGE LEAFLET INFORMATION FOR THE USER

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

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

1. WHAT FLECTONE XL IS AND WHAT IT IS USED FOR

The active ingredient of Flectone XL is tamsulosin. Tamsulosin is an alpha, receptor blocker which reduces the tension in the muscles of the prostate and urethra (the tube that carries urine to the outside). As a result, the urethra, which runs through the prostate, is less constricted and urination is easier.

Flectone XL is intended for use in men to treat lower urinary tract symptoms caused by benign prostatic hyperplasia (BPH), which is an enlargement of the prostate gland.

2. BEFORE YOU TAKE FLECTONE XL

Do NOT take Flectone XL

- If you are allergic (hypersensitive) to tamsulosin or any of the other ingredients listed in section 6. Further Information.
- If you have serious liver disease.
- If you suffer from orthostatic hypotension (feeling dizzy because of low blood pressure when sitting or standing).

Take special care with Flectone XL

- If you have serious kidney disease.
- In rare cases, Flectone XL may cause fainting when sitting down or standing up. If you feel dizzy or weak, lie or sit down until these symptoms disappear.
- Before you start taking Flectone XL, your doctor will examine you to make sure you do not have another illness likely to cause symptoms similar to those of a non-cancerous enlargement of the prostate. Your doctor will examine your prostate manually to look for possible abnormalities and will order tests for a chemical produced by the prostate (prostate specific antigen, PSA) in your blood before you start treatment, and at regular intervals afterwards.
- In rare cases, a serious allergic reaction may occur with swelling of the face, lips, tongue and throat, which may make it hard to breathe, talk or swallow (anaphylaxis). If this happens, stop taking Flectone XL immediately and consult your doctor.
- If you are undergoing eye surgery because of cloudiness of the lens (cataract), please inform your eye specialist that you have been or are taking Flectone XL. The specialist can then take appropriate precautions with respect to medication and surgical techniques to be used.

Consult your doctor if any of these warnings apply or would have applied to you in the past.

Taking other medicines

No interactions have been reported, but using Flectone XL at the same time as other medicines belonging to the same class may lead to a drop in blood pressure.

Diclofenac (an anti-inflammatory medicine used to treat pain) and warfarin (used to prevent blood clotting) may influence the speed with which Flectone XL is removed from the body.

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

Taking Flectone XL with food and drink

You may take your Flectone XL independently of food.

Pregnancy and breast feeding

Flectone XL is only intended for use by men.

Driving and using machines

Flectone XL may cause dizziness. If you experience this symptom, do not drive or use any tools or machinery the handling of which requires concentration.

3. HOW TO TAKE FLECTONE XL

Always take Flectone XL exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is one tablet per day, by mouth. No dose adjustment is required if you have impaired kidney function or mild to moderate liver disease (see also 'Do not take Flectone XL' in section 2 above).

Swallow the tablet whole with a glass of water, without crushing or chewing.

Do not forget to take your medicine. Your doctor will tell you how long you need to keep taking Flectone XL.

If you take more Flectone XL than you should

If you take too much Flectone XL, contact your doctor or pharmacist or go to the nearest hospital casualty department immediately. Take along this leaflet and any remaining tablets with you. An overdose of Flectone XL may cause dizziness, fainting and headache.

If you forget to take Flectone XL

If you forget to take your daily tablet of Flectone XL, you may take it later on the same day. If you forget to take it at all one day, continue with your treatment the next day with the normal dose at the usual time. Do not take a double dose to make up for a forgotten one.

If you stop taking Flectone XL

If you stop taking Flectone XL earlier than your doctor recommends, the initial symptoms may reappear. You must therefore keep taking Flectone XL for as long as your doctor tells you to, even if your symptoms have gone. Always talk to your doctor if you are considering stopping treatment.

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

Flectone XL is not intended for use in children.
POSSIBLE SIDE EFFECTS

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

See your doctor or go to a hospital immediately if you experience any of the following rare side effects (you may be experiencing an allergic reaction):
- Rash, itching, inflamed or red skin (especially if your whole body is affected)
- Swelling of the face, lips, tongue or throat, which may cause difficulty swallowing or breathing (angioedema).

The following side effects have been observed with Tamsulosin:

Common side effects (affecting 1 to 10 users in 100):
- Headache
- Dizziness
- Ejaculation disorders.

Uncommon side effects (affecting 1 to 10 users in 1,000):
- Pounding heart beat (palpitations)
- Orthostatic hypotension (feeling dizzy because of low blood pressure when sitting or standing)
- Runny or stuffy nose (rhinitis)
- Feeling or being sick (nausea or vomiting), diarrhoea, constipation
- Allergic reactions such as rash, itching and local inflammation
- Weakness.

Rare side effects (affecting 1 to 10 users in 10,000):
- Painful
- Nettle rash (hives) on the whole body with swelling of the hands, feet, lips, tongue, throat, airways (angioedema).

Very rare side effects (affecting less than 1 user in 10,000):
- A severe skin rash which develops with flu-like symptoms (Stevens-Johnson syndrome)
- Priapism (persistent painful erection in the absence of sexual stimulation; this side effect requires immediate treatment).

If you are undergoing eye surgery because of cloudiness of the lens (cataract) and have been or are taking Flectone XL, your pupil may not dilate right and your iris (the coloured part of the eye) may become floppy during the operation (see also “Take special care with Flectone XL” above).

Abnormal heart rhythms and breathlessness have also been reported by people taking tamsulosin, but the frequency at which they occur is not known. It has also not been established that tamsulosin was responsible.

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

HOW TO STORE FLECTONE XL

Keep out of the reach and sight of children.

Do not use Flectone XL after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

There are no special precautions for storage.

Medicines should not be disposed of via wastewater or household wastes. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
Module 4
Labelling

Carton:

Each prolonged-release tablet contains 0.4 mg tamsulosin hydrochloride equivalent to 0.367 mg tamsulosin.

**Dosage:**
Oral use. Please read the package leaflet before use. Use as directed by your doctor.

**Warning:** Do not crush or chew.
Keep out of the reach and sight of children.

There are no specific storage instructions.

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Flectone XL 400 microgram
Prolonged-Release Tablets
tamsulosin hydrochloride

Oral Use

30 Tablets

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Flectone XL 400 microgram Prolonged-Release Tablets
tamsulosin hydrochloride

400 microgram

30 Tablets
Blister:

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Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Flectone XL 400 microgram prolonged-release tablets (PL 00289/1142, UK/H/1518/001/DC) could be approved. This application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and the Czech Republic, Germany, Spain, France, Hungary, Italy, the Netherlands, Poland and Romania, as Concerned Member States (CMS).

Flectone XL 400 microgram prolonged-release tablets is a prescription-only medicine (POM) indicated for lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

This is an application made according to Article 10.1 of 2001/83/EC, as amended, claiming to be a generic medicinal product of Flomaxtra XL 400 micrograms film-coated prolonged release tablets (Astell Pharma Ltd., UK). The originator product is Omnic 0.4mg capsules which was originally granted a licence to Astella Pharma Europe B.V, the Netherlands on 11 April 1995.

Tamsulosin belongs to a group of medicines called alpha-adrenoreceptor antagonists. Tamsulosin binds selectively and competitively to post-synaptic $\alpha_1$-adrenoreceptors, in particular to the subtypes $\alpha_{1A}$ and $\alpha_{1D}$, which brings about relaxation of prostatic and urethral smooth muscle.

No new non-clinical studies were conducted, which is acceptable given that the applications were for products that are being considered as generic medicinal products of an originator product that have been licensed for over 10 years.

Three bioequivalence studies (two single dose and one multiple dose) were submitted to support this application, comparing the test product Flectone XL 400 microgram prolonged-release tablets with the reference product Omnic Ocas® 0.4 mg tablets (Astellas Pharma Europe B.V, the Netherlands).

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications were for products that are being considered as generic medicinal products of an originator product that have been licensed for over 10 years. The bioequivalence study was 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 these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the application could be approved, with the end of procedure (Day 210) on 20 April 2011. After a subsequent national phase, the licence was granted in the UK on 23 May 2011.
**II. ABOUT THE PRODUCT**

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<td>Tamsulosin hydrochloride</td>
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<td>United Kingdom</td>
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<td>PL 00289/1142</td>
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<tr>
<td><strong>Name and address of the authorisation holder</strong></td>
<td>Teva UK Limited, Brampton Road, Hampden Park Eastbourne, BN22 9AG, UK.</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Tamsulosin hydrochloride
Chemical name: 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy benzene sulfonamide hydrochloride

Structure:

![Structure of Tamsulosin Hydrochloride](image)

Molecular formula: C_{20}H_{29}ClN_{2}O_{5}S
Molecular weight: 445.0
Appearance: Tamsulosin hydrochloride is a white or almost white powder which is slightly soluble in water and anhydrous ethanol and freely soluble in formic acid.

Tamsulosin hydrochloride was the subject of a European Pharmacopoeia monograph at the time of assessment.

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 specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the following pharmaceutical excipients cellulose microcrystalline, polyethylene oxide, silica, colloidal anhydrous, magnesium stearate and Opadry yellow 03F32784 [(consisting of hypromellose 6cP, titanium dioxide (E171), macrogol 8000, iron oxide, yellow (E172) and iron oxide, red (E172)].

All excipients comply with their respective European Pharmacopoeia monograph with the exception of Opadry yellow 03F32784 which is compliant with suitable in-house
specifications. In addition, the specifications for Opadry yellow 03F32784 are in compliance with Directive 78/25/EC (concerning use of colouring agents in foodstuff). Satisfactory Certificates of Analysis have been provided for all excipients.

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

**Pharmaceutical Development**

The objective of the development programme was to formulate robust, stable tablets containing 0.4 mg tamsulosin hydrochloride that could be considered a generic medicinal product of Omnic Ocas® 0.4 mg tablets (Astellas Pharma Europe B.V, the Netherlands). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**

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

**Container-Closure System**

The finished product is packaged in oriented polyamide/aluminium/ polyvinyl chloride-aluminium blisters and is available in pack sizes of 10, 14, 20, 28, 30, 50, 56, 60, 90, 100, 200 prolonged-release tablets and also 50 x 1 (hospital pack) prolonged-release tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the Product**

Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months, with no special storage conditions.
Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

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

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Forms
The MAA form is satisfactory.

Expert Report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of tamsulosin hydrochloride are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of this product from a non-clinical viewpoint.
III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of this application, the marketing authorisation holder has submitted the following three bioequivalence studies:

STUDY 1
A blinded, single dose, randomised, three-period, six-sequence, three-treatment, crossover study to compare the pharmacokinetics of the test product Flectone XL 400 microgram prolonged-release tablets (Teva UK Limited) versus the reference products Omnic Ocas® 0.4 mg tablets (Astellas Pharma Europe BV, the Netherlands) and Flomax® CR 0.4 mg tablets (Boehringer Ingelheim Ltd, Canada) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or one of the reference products administered with 240 ml of water after an overnight fast of 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 60 hours post dose. The washout period between treatment periods was at least 7 days.

The serum tamulosin hydrochloride results presented below are those for the test product and the EU reference product Omnic Ocas® 0.4 mg tablets (Astellas Pharma Europe B.V, the Netherlands). The results for Flomax® CR 0.4 mg tablets (Boehringer Ingelheim Ltd, Canada) are not relevant to this submission, as this reference product is sourced from outside the EU.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-∞} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>113.27</td>
<td>119.99</td>
<td>5.50</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>121.47</td>
<td>130.27</td>
<td>5.30</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>98.47 (91.11-106.44%)</td>
<td>97.78 (90.33-105.85%)</td>
<td>97.63 (90.97-104.79%)</td>
</tr>
</tbody>
</table>

C_{max} maximum plasma concentration
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity
*ln-transformed values

STUDY 2
An open-label, randomised, four-treatment, four-sequence, four-period crossover single-dose bioavailability study to compare the pharmacokinetics of three alternative formulations of the test product Flectone XL 400 microgram prolonged-release tablets (Teva UK Limited) versus the reference product Omnic Ocas® 0.4 mg tablets (Astellas Pharma Europe B.V, the Netherlands) in healthy adult volunteers under fed conditions.

All volunteers fasted overnight for at least 10 hours prior to being given a high-fat, high-calorie breakfast. After a period of 30 minutes, volunteers then received a single oral dose of either one of the test formulations or the reference product administered with 240 ml of water. Volunteers were required to fast for at least 4 hours after drug administration, until a controlled meal was served. Further standardised meals were provided at appropriate times thereafter in each period. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 60 hours post dose. The washout period between treatment periods was at least 7 days.
The serum tamsulosin hydrochloride results presented below are those for the formulation of the test product that has been submitted for this product licence application and the EU reference product Omnic Ocas® 0.4 mg tablets (Astellas Pharma Europe B.V, the Netherlands). The results for the other two formulations of test product are not relevant to this submission.

Serum tamsulosin (non-transformed values; arithmetic mean ± standard deviation and ratios, 90% confidence intervals):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ) (ng/ml/h)</th>
<th>( \text{AUC}_{0-\infty} ) (ng/ml/h)</th>
<th>( \text{C}_{\text{max}} ) (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>174.42 (95.10-120.88%)</td>
<td>182.49 (93.41-120.32%)</td>
<td>9.8560 (93.95-120.88%)</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>166.63 (93.41-120.32%)</td>
<td>176.42 (93.41-120.32%)</td>
<td>9.2987 (93.95-120.88%)</td>
</tr>
</tbody>
</table>

*ln-transformed values

STUDY 3

An open-label, randomised, two-treatment, two-sequence crossover multiple-dose bioavailability study to compare the pharmacokinetics of the test product Flectone XL 400 microgram prolonged-release tablets (Teva UK Limited) versus the reference product Omnic Ocas® 0.4 mg tablets (Astellas Pharma Europe B.V, the Netherlands) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product administered with 240 ml of water after an overnight fast of 10 hours on days 1 to 6 (Period 1) and days 7 to 10 (Period 2) of the study. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 24 hours post dose. There was no washout interval between the two periods.

Serum tamsulosin (non-transformed values; arithmetic mean ± standard deviation and ratios, 90% confidence intervals):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{\text{tau}} ) (ng/ml/h)</th>
<th>( \text{C}_{\text{min}} ) (ng/ml)</th>
<th>( \text{C}_{\text{max}} ) (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>139.18 (93.80-105.41%)</td>
<td>3.1434 (82.97-99.28%)</td>
<td>9.7556 (92.24-105.71%)</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>139.55 (93.80-105.41%)</td>
<td>3.4764 (82.97-99.28%)</td>
<td>9.6598 (92.24-105.71%)</td>
</tr>
</tbody>
</table>

*ln-transformed values

The 90% confidence intervals for \( \text{AUC} \), \( \text{C}_{\text{max}} \) and \( \text{C}_{\text{min}} \) (where appropriate) for test versus reference products are within predefined acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1). Thus, the data support the claim that the test product is bioequivalent to the reference product.

Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for these applications.
Efficacy
No new efficacy data were submitted and none were required for these applications.

Safety
With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were raised by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of this application from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Flectone XL 400 microgram prolonged-release tablets 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. The pharmacodynamic, pharmacokinetic and toxicological properties of tamsulosin are well-known.

EFFICACY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Flectone XL 400 microgram prolonged-release tablets and its respective reference product (Omnic Ocas® 0.4 mg tablets).

SAFETY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type. As the safety profile of tamsulosin is well-known, no
additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference product, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s product and the originator product are interchangeable. Extensive clinical experience with tamsulosin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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