Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Omnexel, 400 micrograms, prolonged release tablets, film-coated

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release film-coated tablet contains 400 micrograms tamsulosin hydrochloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated, prolonged release tablet.
(Oral Controlled Absorption System, OCAS).

Product imported from The Netherlands, Poland, and the United Kingdom:
Round, bi-convex, yellow, film-coated and debossed with the code '04' 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

Oral use.
One tablet daily.
Omnexel can be taken independently of food.
The tablet must be swallowed whole and not be 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 4.3. Contraindications).

Paediatric population
There is no relevant indication for use of Omnexel, 400 micrograms, in children.
The safety and efficacy of tamsulosin in children <18 years have not been established. Currently available data are described in section 5.1.

4.3 Contraindications

Hypersensitivity to tamsulosin hydrochloride, including drug-induced angioedema or to any of the excipients.
A history of orthostatic hypotension.
Severe hepatic insufficiency.

4.4 Special warnings and precautions for use

As with other α1adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with Omnexel, 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 Omnexel 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 patients with severe renal impairment (creatinine clearance of < 10 ml/min) should be approached with caution, as these patients have not been studied.
The 'Intraoperative Floppy Iris Syndrome' (IFIS), a variant of small pupil syndrome, has been observed during cataract and glaucoma surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation. Discontinuing tamsulosin hydrochloride 1-2 weeks prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not been established. IFIS has also been reported in patients who had discontinued tamsulosin for a longer period prior to the surgery.
The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract or glaucoma surgery is scheduled is not recommended. During pre-operative assessment, surgeons and ophthalmic teams should consider whether patients scheduled for cataract or glaucoma 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.
Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4 (section 4.5)
It is possible that a remnant of the tablet is observed in the faeces.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.
No interactions have been seen when tamsulosin hydrochloride was given concomitantly with either atenolol, enalapril, or theophylline.
Concomitant cimetidine brings about a rise in plasma levels of tamsulosin, whereas furosemide a fall, but as levels remain within the normal range, posology need not be adjusted.
In vitro, neither diazepam nor propranolol, trichlormethiazide, chlormadinone, amitriptyline, 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 chlormadinone.
Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin.
Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4 may lead to increased exposure to tamsulosin hydrochloride. Concomitant administration with ketoconazole (a known strong CYP3A4 inhibitor) resulted in an increase in AUC and Cmax of tamsulosin hydrochloride by a factor of 2.8 and 2.2, respectively. Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4.
Concomitant administration of tamsulosin hydrochloride with paroxetine, a strong inhibitor of CYP2D6, resulted in a Cmax and AUC of tamsulosin that had increased by a factor of 1.3 and 1.6, respectively, but these increases are not considered clinically relevant.
Concurrent administration of other α_1-adrenoceptor antagonists could lead to hypotensive effects.

4.6 Fertility, pregnancy and lactation

Omnexel is not indicated for use in women.
Omnexel
Ejaculation disorders have been observed in short and long term clinical studies with tamsulosin. Events of ejaculation disorder, retrograde ejaculation and ejaculation failure have been reported in the post authorization phase.

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

MedDRA system organ class	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1,000)	Very rare (<1/10,000)	Not Known (Cannot be estimated from the available data)
Nervous systems disorders	Dizziness (1.3%)	Headache	Syncope		
Eye disorders					Vision blurred* Visual Impairment*
Cardiac disorders		Palpitations			
Vascular disorders		Orthostatic hypotension			
Respiratory, thoracic and mediastinal disorders		Rhinitis			Epistaxis*
Gastro-intestinal disorders		Constipation, diarrhoea, nausea, vomiting			Dry Mouth*
Skin and subcutaneous tissue disorders		Rash, pruritus, urticaria	Angioedema	Stevens-Johnson syndrome	Erythema Multiforme* Dermatitis Exfoliative*
Reproductive system and breast disorders	Ejaculation disorders including retrograde ejaculation and ejaculation failure			Priapism	
General disorders and administration site conditions		Asthenia			

*observed post-marketing

During cataract and glaucoma 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).
Post-marketing experience: In addition to the adverse events listed above, atrial fibrillation, arrhythmia, tachycardia and dyspnoea have been reported in association with tamsulosin use. Because these spontaneously reported events are from the worldwide post-marketing experience, the frequency of events and the role of tamsulosin in their causation cannot be reliably determined.

4.9 Overdose

Overdose with tamsulosin hydrochloride can potentially result in severe hypotensive effects. Severe hypotensive effects have been observed at different levels of overdosing.
Treatment
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: α_1-adrenoceptor antagonists.
ATC code: G04C A02. Preparations for the exclusive treatment of prostatic disease.

Mechanism of action
Tamsulosin binds selectively and competitively to the postsynaptic α_1-adrenoceptors, in particular to subtypes α_{1A} and α_{1D}. It brings about relaxation of prostatic and urethral smooth muscle.

Pharmacodynamic effects
Omnexel increases the maximum urinary flow rate. It relieves obstruction by relaxing smooth muscle in prostate and urethra thereby improving voiding symptoms.
It also improves the storage symptoms in which bladder instability plays an important role.
These effects on storage and voiding symptoms are maintained during long-term therapy. The need for surgery or catheterisation is significantly delayed.
α_1-adrenoceptor antagonists can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with Omnexel.

Paediatric population
A double-blind, randomised, placebo-controlled, dose ranging study was performed in children with neuropathic bladder. A total of 161 children (with an age of 2 to 16 years) were randomised and treated at 1 of 3 dose levels of tamsulosin (low [0.001 to 0.002 mg/kg], medium [0.002 to 0.004 mg/kg], and high [0.004 to 0.008 mg/kg]), or placebo. The primary endpoint was number of patients who decreased their detrusor leak point pressure (LPP) to <40 cm H_2O based upon two evaluations on the same day. Secondary endpoints were: Actual and percent change from, baseline in detrusor leak point pressure, improvement or stabilisation of hydronephrosis and hydroureter and change in urine volumes obtained by catheterisation and number of times wet at time of catheterisation as recorded in catheterisation diaries. No statistically significant difference was found between the placebo group and any of the 3 tamsulosin dose groups for either the primary or any secondary endpoints. No dose response was observed for any dose level.

5.2 Pharmacokinetic properties

Absorption
Omnexel is a prolonged release tablet of the non-ionic gel matrix type. The Ocas formulation provides slow release of tamsulosin, resulting in an adequate exposure over 24 hours, with little fluctuation.
Tamsulosin hydrochloride administered as prolonged release tablets is absorbed from the intestine. Under fasting conditions approximately 57% of the administered dose is estimated to be absorbed.
The rate and extent of absorption of tamsulosin hydrochloride administered as prolonged release tablets are not affected by a low fat meal.
The extent of absorption is increased by 64% and 149% (AUC and C_{max} respectively) by a high-fat meal compared to

fasted.
Tamsulosin shows linear pharmacokinetics.
After a single dose of Omnexel 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 Omnexel the trough concentration of tamsulosin in plasma amounts to 40% of the peak plasma concentration under fasted and fed conditions.
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. The 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 active substance. It is metabolised in the liver.
In rats, hardly any induction of microsomal liver enzymes was seen to be caused by tamsulosin.
In vitro results suggest that CYP3A4 and also CYP2D6 are involved in metabolism, with possible minor contributions to tamsulosin hydrochloride metabolism by other CYP isozymes. Inhibition of CYP3A4 and CYP2D6 drug metabolizing enzymes may lead to increased exposure to tamsulosin hydrochloride (see section 4.4 and 4.4).
None of the metabolites are more active than the original compound.

Elimination
Tamsulosin and its metabolites are mainly excreted in the urine. The amount excreted as unchanged active substance is estimated to be about 4 – 6% of the dose, administered as Omnexel.
After a single dose of Omnexel 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 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 αadrenoceptor antagonists.
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 hyperprolactinemia and only occurred at high dose levels, are regarded as irrelevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 7,000,000
Macrogol 8,000
Magnesium stearate (E470b)
Butylhydroxytoluene (E321)
Hypromellose (E464)
Iron oxide yellow (E172)
Product sourced from Poland and from The Netherlands also contains: Colloidal anhydrous silica (E551)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Store in the original pack.

6.5 Nature and contents of container

Cardboard outer containing blister strips.
Pack size: 30 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1151/020/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 14th September 2007

10 DATE OF REVISION OF THE TEXT

May 2014