

# 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 0.4 mg tamsulosin hydrochloride.

Excipients:

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated, prolonged release tablet.

(Oral Controlled Absorption System, OCAS).

Approximately 9 mm in diameter, round, bi-convex, yellow, film-coated and debossed with the code '04'.

## 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 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  $\alpha_1$ -adrenoceptor 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 (see 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 interactions

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 C<sub>max</sub> 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 C<sub>max</sub> 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  $\alpha_1$ -adrenoceptor antagonists could lead to hypotensive effects.

#### 4.6 Fertility, pregnancy and lactation

Omnexel is not indicated for use in women.

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)
<b>Nervous systems disorders</b>	Dizziness (1.3%)	Headache	Syncope		
<b>Eye disorders</b>					Vision blurred * Visual impairment*
<b>Cardiac disorders</b>		Palpitations			
<b>Vascular disorders</b>		Orthostatic hypotension			
<b>Respiratory, thoracic and mediastinal disorders</b>		Rhinitis			Epistaxis*
<b>Gastro-intestinal disorders</b>		Constipation, diarrhoea, nausea, vomiting			Dry mouth*
<b>Skin and subcutaneous tissue disorders</b>		Rash, pruritus, urticaria	Angioedema	Stevens-Joh nson syndrome	Erythema multiforme* Dermatitis exfoliative*
<b>Reproductive system and breast disorders</b>	Ejaculation disorders including retrograde ejaculation and ejaculation failure			Priapism	
<b>General disorders and administration site conditions</b>		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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: [www.hpra.ie](http://www.hpra.ie).

**4.9 Overdose****Symptoms**

Overdosage 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**

$\alpha_1$ -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  $\alpha_1$ -adrenoceptors, in particular to subtypes  $\alpha_{1A}$  and  $\alpha_{1D}$ . 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.

$\alpha_1$ -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, randomized, 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 randomized 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<sub>2</sub>O based upon two evaluations on the same day. Secondary endpoints were: Actual and percent change from baseline in detrusor leak point pressure, improvement or stabilization 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<sub>max</sub> 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 4.5).

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  $\alpha$ -adrenoceptor 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).

Colloidal silica anhydrous (E551).

Hypromellose (E464).

Iron oxide yellow (E172).

### **6.2 Incompatibilities**

Not applicable.

### **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**

Aluminium / aluminium foil blister packs containing 10, 14, 18, 20, 28, 30, 45, 50, 56, 60, 90, 100, 200 tablets.  
Not all pack sizes may be marketed.

### **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 MARKETING AUTHORISATION HOLDER**

Astellas Pharma Co. Ltd  
5 Waterside  
Citywest Business Campus  
Naas Road  
Dublin 24  
Ireland

### **8 MARKETING AUTHORISATION NUMBER**

PA1241/006/001

### **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of First Authorisation: 18 March 2005

Renewal of Authorisation: 12 July 2006

### **10 DATE OF REVISION OF THE TEXT**

May 2020