Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tamzeltos 400 micrograms prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 400 micrograms tamsulosin hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

White, unscored, round tablets with a diameter of 9 mm, debossed on one side with "T9SL" and "0.4" on the other side

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

Posology

One tablet daily.

Tamsulosin can be taken independently of food.

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 Tamzeltos in children.
The safety and efficacy of tamsulosine in children < 18 years have not been established. Currently available data are described in section 5.1.

Method of administration

Oral use.

The tablet must be swallowed whole and not be crunched or chewed as this interferes with the prolonged release of the active substance.

4.3 Contraindications

- Hypersensitivity to tamsulosin hydrochloride, including drug-induced angioedema or to any of the excipients listed in section 6.1.
- A history of orthostatic hypotension.
- Severe hepatic insufficiency.

4.4 Special warnings and precautions for use

As with other α_1-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with tamsulosin, 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 tamsulosin 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 surgery and glaucoma surgery in some patients on or previously treated with tamsulosin. IFIS may increase the risk of eye complications during and after the operation.

Discontinuing tamsulosin 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 surgery.

The initiation of therapy with tamsulosin 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 galucoma 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 combnation 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 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 α1-adrenoceptor antagonists could lead to hypotensive effects.

4.6 Fertility, pregnancy and lactation

Tamzeltos 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 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <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, retrograde ejaculation, 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 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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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: Urologicals, drugs used in benign prostatic hypertrophy; ATC code: G04CA02.

Mechanism of action
Tamsulosin binds selectively and competitively to the postsynaptic α1-adrenoceptors, in particular to subtypes α1A and α1D. It brings about relaxation of prostatic and urethral smooth muscle.

Pharmacodynamic effects
Tamsulosin 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 tamsulosin.

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 H2O 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

The Tamsulosin prolonged-release formulation provides consistent slow release of tamsulosin, resulting in an adequate exposure, with little fluctuation, over 24 hours.

Tamsulosin 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 Cmax respectively) by a high-fat meal compared to fasted.

Tamsulosin shows linear pharmacokinetics.

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 Tamsulosin prolonged-release tablets 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 Tamsulosin prolonged-release tablets.

After a single dose of tamsulosin 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 α-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

Inner core tablet:
Hypromellose (E464)
Microcrystalline cellulose (E460)
Carbomer
Colloidal anhydrous silica (E551)
Red iron oxide (E172)
Magnesium stearate (E470b)

Outer tablet:
Microcrystalline cellulose (E460)
Hypromellose (E464)
Carbomer
Colloidal anhydrous silica (E551)
Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

OPA/Alu/PVC/Alu blisters in boxes containing 30 and 90 prolonged-release tablets.
PVC/PE/PVDC/Alu blisters in boxes containing 30 and 90 prolonged-release tablets.
PVC/PVDC/Alu blisters in boxes containing 30 and 90 prolonged-release tablets.
PVC/PCTFE/Alu blister in boxes containing 30 and 90 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Krka, d.d.
Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/087/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th November 2019

10 DATE OF REVISION OF THE TEXT