SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tamsulosine HCl ratiopharm 0,4 mg, tabletten met verlengde afgifte

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

One tablet daily.
No dose adjustment is warranted in renal impairment.
No dose adjustment is warranted in patients with mild to moderate hepatic insufficiency (see section 4.3).

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

Method of administration
Oral use.
Tamsulosin 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.

4.3 Contraindications

- Hypersensitivity to the active substance, 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 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 yet 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 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

Tamusolsin 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

Adverse drug reactions are listed in the table below by system organ class and frequency.

Frequencies are defined as: very common (≥1/10); 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).

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 system 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*
Gastrointestinal 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 section 4.4).

Post-marketing experience
In addition to the adverse events listed above, the following adverse reactions have been reported in association with tamsulosin use.

Cardiac disorders
Not known: Atrial fibrillation, arrhythmia, tachycardia

Respiratory, thoracic and mediastinal disorders
Not known: Dyspnoea

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 the national reporting system listed in Appendix V.

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: Drugs used in benign prostatic hypertrophy, alpha-adrenoreceptor antagonists, ATC code: G04CA02. 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
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.
Observational data indicate that use of tamsulosin may lead to a delay in the need for surgery or catheterization.
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. A response was defined as a primary endpoint with patients who decrease 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 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 differences were found between the placebo group and any of the 3 tamsulosin dose groups for either the primary or any secondary endpoints. Additional

exploratory analyses in subgroups confirmed these findings (e.g. age, anti-cholinergic use, weight, geographic regions). No dose response was observed for any dose level.

5.2 Pharmacokinetic properties

Absorption
The tamsulosin prolonged-release formulation provides consistent slow release of tamsulosin, resulting in an adequate exposure, with little fluctuation, over 24 hours.
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 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 is a considerable inter-patient variation in plasma levels both after single and multiple dosing.

Distribution
In humans, 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 studies on 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 metabolising enzymes may lead to increased exposure to tamsulosin hydrochloride (see sections 4.4 and 4.5).
None of the metabolites are more active than the original active 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 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 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 α_1-adrenoceptor antagonists.

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 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

Inner core tablet
Hypromellose
Cellulose microcrystalline
Carbomer
Silica colloidal anhydrous
Iron oxide red (E 172)
Magnesium stearate

Outer tablet
Cellulose microcrystalline
Hypromellose
Carbomer
Silica colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package to protect from light.

6.5 Nature and contents of container

PVC/PVDC:Al blister packs containing
10, 18, 20, 28, 30, 50, 60, 90, 98 and 100 tablets

PVC/Aclar:Al blíster packs containing
10, 18, 20, 28, 30, 50, 60, 90, 98 and 100 tablets

oPA/Al/PVC/Al blíster packs containg
10, 18, 20, 28, 30, 50, 60, 90, 98 and 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORIZATION HOLDER

Ratiopharm GmbH
Graf-Arco-Str. 3
89079 Ulm
Duitsland

8 MARKETING AUTHORIZATION NUMBER(S)

RVG 106172

9 DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Datum van eerste verlening van de vergunning: 15 februari 2011
Datum van laatste hernieuwing: 31 maart 2015

10 DATE OF REVISION OF THE TEXT

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