SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Tamsulosin hydrochloride 0.4 mg prolonged-release capsules
Tamsumac 0.4

2. Qualitative and quantitative composition
Each tablet contains 0.4 mg of tamsulosin hydrochloride.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Prolonged release capsule.

Olive green opaque/orange opaque, size '2', hard gelatin capsules, containing free-flowing white to off-white spheroids with 'CL 23' on the cap and '0.4' on the body imprinted with black ink.

4. Clinical particulars

4.1 Therapeutic indications
Tamsulosin is indicated in adults for the treatment of functional symptoms of benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

Posology
One tablet daily, to be taken with or without food.

Paediatric Population
The safety and efficacy of tamsulosin in children <18 years have not been established. Currently available data are described in Section 5.1.

Method of administration
For oral use.

The tablet should be swallowed whole and should not be crunched or chewed as this will interfere with the prolonged release of the active ingredient.

4.3 Contraindications
A history of orthostatic hypotension; and severe hepatic insufficiency.
Hypersensitivity to the active substance, or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
As with other alpha$_1$ blockers, a reduction in blood pressure can occur in individual cases during treatment with tamsulosin prolonged-release tablets, 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 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 severely renally impaired patients (creatinine clearance of less than 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 the 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 (e.g., ketoconazole) in patients with poor metaboliser CYP2D6 phenotype.

Tamsulosin hydrochloride should be used with caution in combination with strong (e.g., ketoconazole) and moderate (e.g., erythromycin) inhibitors of CYP3A4 (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

No interactions have been seen when tamsulosin was given concomitantly with atenolol, enalapril, or theophylline. Concomitant cimetidine brings about a rise in plasma levels of tamsulosin, and furosemide a fall, but as levels remain within the normal range, posology need not be changed.

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

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 (e.g., ketoconazole) in patients with poor metaboliser CYP2D6 phenotype.

Tamsulosin hydrochloride should be used with caution in combination with strong (e.g., ketoconazole) and moderate inhibitors (e.g., erythromycin) 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.

There is a theoretical risk of enhanced hypotensive effect when given concurrently with drugs which may reduce blood pressure, including anaesthetic agents and other α_1-adrenoceptor antagonists.

4.6 Fertility, pregnancy and lactation

Tamsulosin 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-authorisation phase.

4.7 Effects on the ability to drive and use machines

No data is available on whether tamsulosin adversely affects the ability to drive or operate machines. However, in this respect, patients should be aware of the fact that drowsiness, blurred vision, dizziness and syncope can occur.

4.8 Undesirable effects

Tabulated list of adverse reactions

System Organ Class	Common >1/100, <1/10	Uncommon >1/1000, <1/100	Rare >1/10,000, <1/1000	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, pruritis, 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

As with other alpha-blockers, drowsiness, blurred vision or oedema can occur. 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 the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose

Symptoms
Overdosage with tamsulosin hydrochloride can potentially result in severe hypotensive effects, dizziness and malaise. Severe hypotensive effects have been observed at different levels of overdosing.

Treatment
In case of acute hypotension occurring after an overdose, 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 sulfate, can be administered.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacological classification: 12.3.1 Vasodilators.

Mechanism of action:
Tamsulosin binds selectively and competitively to postsynaptic alpha$_1$- receptors, in particular to the subtype alpha$_{1A}$, which brings about relaxation of the smooth muscle of the prostate, whereby tension is reduced.

Pharmacodynamic effects:
Tamsulosin increases the maximum urinary flow rate by reducing smooth muscle tension in the prostate and urethra, thereby relieving the obstruction.

It also improves the complex of irritative and obstructive symptoms in which bladder instability and tension of the smooth muscles of the lower urinary tract play an important role. Alpha$_1$-blockers 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 a number of patients who decreased their detrusor leak point pressure (LPP) to <40 cm H2O based on 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 a number of times wet at the 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
Tamsulosin is formulated as an Oral Controlled Absorption System (OCAS) and is a prolonged-release tablet of the non-ionic gel matrix type.

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. A consistent slow release of tamsulosin is maintained over the whole pH range encountered in the gastrointestinal tract with little fluctuation over 24 hours. The extent of absorption is increased by 64% and 149% (AUC and Cmax respectively) by a high-fat meal compared to fasting.

After a single dose of tamsulosin in the fasted state, plasma levels of tamsulosin peak at a median time of 6 hours. In a steady state, which is reached by day 4 of multiple dosing, plasma levels of tamsulosin peak at 4 to 6 hours in the fasted and fed state. Peak plasma levels increase from approximately 6 ng/ml after the first dose to 11 ng/ml in a steady state.

As a result of the prolonged release characteristics of tamsulosin, 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 and the volume of distribution is small (about 0.2 l/kg).

Metabolism
Tamsulosin has a low first-pass effect, being metabolised slowly. Most tamsulosin is present in plasma in the form of an unchanged drug. 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 sections 4.4 and 4.5).

No dose adjustment is warranted in hepatic insufficiency. 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 the unchanged drug is estimated to be about 4 - 6% of the dose, administered as tamsulosin. After a single dose of tamsulosin, and in a steady state, elimination half-lives of about 19 and 15 hours,

respectively, have been measured. No dose adjustment is necessary in patients with renal impairment.

Linearity/non-linearity
Tamsulosin shows linear kinetics.

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 known pharmacological actions of the alpha-adrenergic blocking agents. 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 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
Microcrystalline cellulose
Polysorbate 80
Methacrylic acid copolymer dispersions
Triacetin
Purified water
Calcium stearate
Sodium lauryl sulfate
Gelatin capsule shell

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of the container
The tablets are packed in PVC/PE/PVDC/Alu blisters.

Pack sizes: 1 x 10 capsules and 3 x 10 capsules.

6.6 Special precautions for disposal and handling

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

7. APPLICANT

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8. MANUFACTURERS

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9. REGISTRATION DETAILS

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10. DATE OF REVISION OF TEXT

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