

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tamsulosine HCl Sandoz retard capsule 0,4 mg, capsules met gereguleerde afgifte, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard modified-release capsule contains 0.4 mg of tamsulosin hydrochloride.

For the full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Hard modified-release capsule.

Light green/yellow hard modified-release capsules filled with white to slightly yellowish pellets.

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 capsule a day after breakfast or the first meal of the day. The capsule is swallowed whole with a glass of water while standing or sitting (not lying down). The capsule should not be broken or pulled apart as this may have an effect on the release of the long-acting active ingredient.

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

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, including drug-induced angio-oedema, or to any of the excipients listed in section 6.1.

Orthostatic hypotension observed earlier (history of orthostatic hypotension).

Severe hepatic insufficiency.

4.4 Special warnings and precautions for use

As with other α 1-blockers the use of tamsulosin may lower blood pressure, which in rare cases may cause fainting. If initial symptoms of orthostatic hypotension start to appear (dizziness, weakness), then the patient should sit or lie down until the symptoms have gone.

The patient should be examined before commencement of therapy with tamsulosin to exclude the presence of other conditions that can produce similar symptoms to those of BPH. The prostate should be examined via the rectum and, if necessary, the PSA count determined prior to commencement of treatment and again later at regular intervals.

The treatment of severely renally impaired patients (creatinine clearance of < 10 ml/min) should be approached with caution as these patients have not been studied.

Angio-oedema has been rarely reported after the use of tamsulosin. Treatment should be discontinued immediately, the patient should be monitored until disappearance of the oedema, and tamsulosin should not be re-administered.

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. 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 and duration of requirement of stopping the therapy prior to cataract surgery 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 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 should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype.

Tamsulosin should be used with caution in combination with strong and moderate inhibitors of CYP3A4 (see section 4.5).

[Nationally completed name] contains sodium.

This medicinal product contains less than 1 mmol sodium (23 mg) per hard modified-release capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

No interactions have been observed when tamsulosin has been given concomitantly with atenolol, enalapril, or theophylline. Concomitant cimetidine raises, and concomitant furosemide lowers, plasma concentrations of tamsulosin but, as the concentration of tamsulosin remains within the normal range, posology need not be altered.

In vitro, neither diazepam nor propranolol, trichlormethiazide, chlormadinon, 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 chlormadinon.

Diclofenac and warfarin may increase the elimination rate of tamsulosin.

Concomitant administration of tamsulosin with strong inhibitors of CYP3A4 may lead to increased exposure to tamsulosin. Concomitant administration with ketoconazole (a known strong CYP3A4 inhibitor) resulted in an increase in AUC and C_{max} of tamsulosin 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 should be used with caution in combination with strong and moderate inhibitors of CYP3A4.

Concomitant administration of tamsulosin with paroxetine, a strong inhibitor of CYP2D6, resulted in a C_{max} 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 with another α_1 -adrenoreceptor antagonist may lower blood pressure.

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 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

	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
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	Angio- oedema	Stevens- Johnson syndrome	Erythema multiforme*, dermatitis exfoliative*
Reproductive systems and breast disorders	ejaculation disorders, including retrograde ejaculation and ejaculation failure			Priapism	
General disorders and administration site		Asthenia			

conditions					
-------------------	--	--	--	--	--

*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 the national reporting system listed in Appendix V*.

4.9 Overdose

Symptoms

Overdosage with tamsulosin 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. If large quantities of the medicinal product are involved, gastric lavage may be performed and activated charcoal and an osmotic laxative, such as sodium sulphate, may be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

α_{1A} adrenoreceptor antagonist, ATC code: G04CA02.

The medicinal product is only used for the treatment of prostatic conditions.

Mechanism of action

Tamsulosin binds selectively and competitively to postsynaptic α_{1A} adrenoreceptors, which convey smooth muscle contraction, thereby relaxing prostatic and urethral smooth muscle.

Pharmacodynamic effects

Tamsulosin increases the maximum urinary flow rate by relaxing prostatic and urethral smooth muscle, thus relieving obstruction.

The medicinal product also improves the irritative and obstructive symptoms in which the contraction of smooth muscle in the lower urinary tract plays an important role.

Alpha-blockers can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with tamsulosin in normotensive patients.

The medicinal product's effect on storage and voiding symptoms are also maintained during long-term therapy, as a result of which the need for surgical treatment is significantly postponed.

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

Absorption

Tamsulosin is rapidly absorbed from the intestines and its bioavailability is almost complete. Absorption is slowed down if a meal has been eaten before taking the medicinal product. Uniformity of absorption can be assured by always taking tamsulosin after breakfast. Tamsulosin shows linear kinetics.

Peak plasma levels are achieved at approximately six hours after a single dose of tamsulosin taken after a full meal. The steady state is reached by day five of multiple dosing, when C_{max} in patients is about two-thirds higher than that reached after a single dose. Although this has been demonstrated only in the elderly, the same result would also be expected in younger patients.

There are huge inter-patient variations in plasma levels of tamsulosin, both after single as well as multiple dosing.

Distribution

In humans, tamsulosin is about 99% bound to plasma proteins and volume of distribution is small (about 0.2 l/kg).

Biotransformation

Tamsulosin has a low first pass metabolic effect. Most tamsulosin is found unaltered in plasma. The substance is metabolised in the liver.

In studies on rats, tamsulosin was found to cause only a slight induction of microsomal liver enzymes.

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 with about 9% of a dose being present in the form of unchanged active substance.

The elimination half-life of tamsulosin in patients is approximately 10 hours (when taken after a meal) and 13 hours in the steady state.

5.3 Preclinical safety data

Toxicity after a single dose and multiple dosing has been investigated in mice, rats and dogs. Reproductive toxicity has also been investigated in rats, carcinogenicity in mice and rats, and genotoxicity *in vivo* and *in vitro*.

The common toxicity profile found with large doses of tamsulosin is equivalent to the pharmacological effect associated with alpha adrenergic antagonists. Changes in ECG readings were found with very large doses in dogs. This is not, however, assumed to be of any clinical significance. Tamsulosin has not been found to have any significant genotoxic properties.

Greater proliferative changes in the mammary glands of female rats and mice have been discovered on exposure to tamsulosin. These findings, which are probably indirectly linked to hyperprolactinaemia and only occur as a result of large doses having been taken, are considered clinically insignificant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Content of capsule

Microcrystalline cellulose (E 460)
Polyacrylate dispersion 30%
Metacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30%
Polysorbate 80 (E 433)
Sodium laurylsulfate
Talc (E 553b)
Colloidal anhydrous silica (E 551)

Capsule shell

Gelatin (E 441)
Patent Blue V (E 131)
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Red iron oxide (E 172)
Black iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

The hard modified-release capsules are packed in ALU/PVC/TE/PVDC blisters and inserted in a carton.

Pack sizes:

10, 20, 28, 30, 50, 56, 60, 90, 100 hard modified-release capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Sandoz B.V.
Veluwezoom 22
1327 AH Almere
Nederland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 33747

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van de eerste verlening van de vergunning: 8 mei 2008
Datum laatste verlenging: 30 maart 2012

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft rubrieken 4.4, 6.1, 6.5 en 6.6: 2 juli 2020