

# New Zealand Datasheet

## 1 PRODUCT NAME

Tamsulosin capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tamsulosin 0.4 mg

## 3 PHARMACEUTICAL FORM

Tamsulosin capsules are size 2 hard gelatin capsules with a brown cap and off-white opaque body.

Each capsule contains 0.4mg tamsulosin hydrochloride equivalent to 0.367mg tamsulosin presented as off-white modified release pellets.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of functional symptoms of benign prostatic hyperplasia (BPH).

### 4.2 Dose and method of administration

One capsule daily, to be taken after breakfast, or the first meal of the day.

The capsule should be swallowed whole and should not be crushed or chewed as this will interfere with the modified release of the active ingredient.

### 4.3 Contraindications

Hypersensitivity to tamsulosin hydrochloride or any other component of the product.

A history of orthostatic hypotension.

Severe hepatic insufficiency.

Severe renal impairment with creatinine clearance of less than 10ml/min

Concurrent use of another  $\alpha_1$ -adrenoceptor inhibitor.

### 4.4 Special warnings and precautions for use

As with other alpha1-blockers, reduction in blood pressure can occur in individual cases during treatment with tamsulosin capsules, as a result of which, very 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 capsules 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 severely renally impaired patients (creatinine clearance of < 10ml/min) should be approached with caution as these patients have not been studied.

### **Intra-operative Floppy Iris Syndrome**

'Intra-operative Floppy Iris Syndrome' (IFIS) has been observed during cataract surgery in some patients taking or who have previously been treated with  $\alpha_1$ -adrenoceptor antagonists. This variant of small pupil syndrome is characterised by the combination of a flaccid iris that billows in response to intra-operative irrigation currents, progressive intra-operative miosis despite pre-operative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phaco-emulsification incisions. The patient's ophthalmologist should be prepared for possible modifications to their surgical technique, such as the utilisation of iris hooks, iris dilator rings, or visco-elastic substances. There does not appear to be a benefit of stopping  $\alpha_1$ -adrenoceptor antagonist therapy prior to cataract surgery.

### **Myocardial ischaemia**

Patients with myocardial infarction or angina pectoris within the preceding six months were excluded from the Phase III clinical studies. As a result, the safety of tamsulosin in these patients has not been formally assessed.

#### **General**

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 interactions).

#### **Effects on fertility**

$\alpha_1$ -adrenoceptor antagonists are known to reduce male fertility by affecting penile erection, emission and/or ejaculation. In male rats, a severe reduction in male copulation rate and fertility was observed after a single dose or after repeated oral doses of tamsulosin. Spermatogenesis was not affected in the rat studies, and the effect on fertility was reversible. The no effect dose on male rat fertility was associated with plasma tamsulosin levels (AUC) at least 50% of those expected in human males treated with tamsulosin.

Treatment of female rats with tamsulosin caused disruption of the oestrus cycle and a severe reduction in fertility, due to interference of fertilisation with the ova. These effects were shown to be reversible.

### **Renal impairment**

Severe renal impairment, with creatinine clearance of less than 10ml/min. is a Contraindication, as these patients have not been studied.

### **Hepatic impairment**

No dose adjustment for tamsulosin capsules is expected in patients with mild to moderate hepatic impairment. Severe hepatic impairment (Child-Pugh scores >9) is a Contraindication.

## **4.5 Interaction with other medicines and other forms of interaction**

### **Drugs known to interact with tamsulosin**

Concomitant cimetidine leads to a rise in plasma levels of tamsulosin, while furosemide leads to a fall (about 12% following a single 20 mg intravenous dose). However, as levels remain within the normal range, dosage need not be adjusted.

Concurrent administration of tamsulosin capsules with other  $\alpha_1$ -adrenoceptor antagonists is contraindicated because of the potential for hypotensive effects – see Contraindications.

### **Drugs which may interact with tamsulosin**

Tamsulosin binds extensively to plasma proteins and may displace other protein-bound drugs. No interactions at the level of hepatic metabolism have been seen during *in vitro* studies with liver microsomal fractions (representative of the cytochrome P450-linked drug metabolising enzyme system), involving amitriptyline, salbutamol, glibenclamide and finasteride. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin.

### **Drugs which do not interact significantly with tamsulosin**

Tamsulosin did not affect the pharmacokinetics of a single intravenous dose of digoxin 0.5 mg. No interactions have been seen when tamsulosin hydrochloride was given concomitantly with either atenolol, enalapril, nifedipine or theophylline.

### **General**

Tamsulosin is metabolised in the liver, and may be expected to interact with other hepatically metabolised drugs. Pharmacokinetic studies in healthy volunteers revealed that concomitant administration with strong inhibitors of CYP3A4 or CYP2D6 may lead to increased exposure to tamsulosin. Concomitant administration with ketoconazole (a known CYP3A4 inhibitor) resulted in an increased  $C_{max}$  and AUC of tamsulosin. Tamsulosin should not be used in combination with strong inhibitors of CYP3A4 in patients known to be CYP2D6 poor metabolizers.

Concomitant administration with paroxetine (a known CYP2D6 inhibitor) resulted in an increased  $C_{max}$  and AUC of tamsulosin. Tamsulosin should therefore be used with caution in patients who are taking other drugs, particularly those which undergo hepatic metabolism.

### **Other in vitro findings**

*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.

An *in vitro* study using human liver microsomal fractions showed no effect of amitriptyline, salbutamol, glibenclamide and finasteride on the rate of disappearance of tamsulosin. The clinical relevance of these findings is uncertain.

## **4.6 Fertility, pregnancy and lactation**

### **Pregnancy**

Category B2. Not applicable as tamsulosin capsules are intended for male patients only.

### **Breast feeding**

Not applicable as tamsulosin capsules are intended for male patients only.

### **Fertility**

Not applicable as tamsulosin capsules are intended for male patients only.

## **4.7 Effects on ability to drive and use machines**

Tamsulosin may cause dizziness, patients should be warned to take care whilst operating machinery or driving.

## **4.8 Undesirable effects**

### **Priapism**

Rarely, tamsulosin, like other alpha-1 antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Patients should be informed that this reaction is extremely rare, but if not brought to immediate medical attention, can lead to permanent erectile dysfunction.

### **Abnormal ejaculation**

Patients should be advised on the potential for abnormal ejaculation to occur upon commencement of tamsulosin treatment. Retrograde ejaculation is the most commonly reported abnormal ejaculation event associated with the use of tamsulosin.

The following treatment-related adverse events were reported from clinical trials, where Common is  $\geq 1\%$  and  $< 10\%$ ; Uncommon is  $\geq 0.1\%$  and  $< 1\%$ ; Rare is  $\geq 0.01\%$  and  $< 0.1\%$ ; and Very rare is  $< 0.01\%$ .

### **Cardiac disorders**

Uncommon: palpitations.

### **Gastro-intestinal disorders**

Uncommon: constipation, diarrhoea, nausea, vomiting, dry mouth.

### **General disorders**

*Uncommon:* asthenia.

### **Nervous system disorders**

Common: dizziness (1.3%).

*Uncommon:* headache.

Rare: syncope.

### **Reproductive system disorders**

Common: ejaculation disorder.

Very rare: priapism.

### **Respiratory, thoracic and mediastinal disorders**

Uncommon: rhinitis.

### **Skin and subcutaneous tissue disorders**

Uncommon: rash, pruritus, urticaria.

Rare: angioedema.

### **Vascular disorders**

Uncommon: postural hypotension.

Post-marketing experience

The following events have also been reported during the post-marketing period. These events are reported voluntarily from a population of uncertain size, therefore it is not possible to reliably estimate their frequency.

Vision disorders: blurred vision, vision impairment.

During cataract and glaucoma surgery, a variant of small pupil syndrome known as Intraoperative Floppy Iris Syndrome (IFIS) has been reported in association with  $\alpha_1$ -adrenoceptor antagonist therapy (See Warnings and Precautions).

Skin and subcutaneous tissue disorders: skin desquamation, dermatitis exfoliative, erythema

multiforme.

Respiratory, thoracic and mediastinal disorders: epistaxis.

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

## **4.9 Overdose**

Acute overdose with 5 mg tamsulosin hydrochloride has been reported. Acute hypotension (systolic blood pressure 70 mm Hg), vomiting and diarrhoea were observed, which were treated with fluid replacement and the patient could be discharged the same day.

If acute hypotension occurs after overdosage, cardiovascular support should be given and maintained. Blood pressure can be restored and heart rate brought back to normal by lying the patient down. If this is insufficient then volume expanders and, when necessary, vasopressors could be administered. 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 to impede absorption, such as emesis, can be taken. When large quantities of tamsulosin are involved, gastric lavage can be applied and activated charcoal and an osmotic laxative, such as sodium sulphate, can be administered.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Drugs used in benign prostatic hypertrophy, alpha adrenoreceptor antagonists, ATC code: G04CA02

Tamsulosin binds selectively and competitively to postsynaptic  $\alpha$ 1-adrenoceptors, in particular to subtypes alpha1A and alpha1D. It brings about relaxation of prostatic and urethral smooth muscle.

Tamsulosin increases the maximum urinary flow rate. It relieves obstruction by relaxing smooth muscle in prostate and urethra.

It also improves the irritative 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 surgical treatment is significantly delayed.

Alpha1-blockers can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with tamsulosin.

### **5.2 Pharmacokinetic properties**

#### **Absorption**

Tamsulosin is rapidly absorbed from the intestine and is almost completely bioavailable. Absorption of tamsulosin is reduced by a recent meal.

Uniformity of absorption can be promoted by the patient always taking tamsulosin capsules after the same meal.

Tamsulosin shows linear kinetics.

After a single dose of tamsulosin capsules in the fed state, plasma levels of tamsulosin peak at around 6 hours and in the steady state, which is reached by day 5 of multiple dosing, C<sub>max</sub> in patients is about two-thirds higher than that reached after a single dose. Although this was seen in elderly patients, the same finding would also be expected in young ones.

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 and the volume of distribution is small (about 0.2L/kg).

### **Biotransformation**

Tamsulosin capsules contain tamsulosin as the R(-) isomer. In humans, there is no *in vivo* conversion to the less active S(+) isomer. Tamsulosin has a low first pass effect, being metabolised slowly. Most tamsulosin is present in plasma in the form of unchanged drug. Tamsulosin is metabolised in the liver. *In vitro* results suggest that CYP3A4 and also CYP2D6 are involved in metabolism, with possible minor contributions to tamsulosin metabolism by other CYP isozymes. Inhibition of hepatic drug metabolising enzymes may lead to increased exposure to tamsulosin (see Interactions with other drugs). In rats, tamsulosin was seen to cause minimal induction of microsomal liver enzymes. No dose adjustment is warranted in hepatic insufficiency (see also Contraindications).

None of the metabolites are more active than tamsulosin itself.

### **Excretion**

Tamsulosin and its metabolites are mainly excreted in the urine with about 9% of a dose being present in the form of unchanged medicine.

After a single dose of tamsulosin capsules in the fed state, and in the steady state in patients, elimination half-lives of about 10 and 13 hours respectively have been measured.

The presence of renal impairment does not warrant lowering the dose.

## **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**

Tamsulosin capsules modified release capsules contain the following excipients:

Hypromellose, Methacrylic-acid copolymer, Triethyl citrate, Propylene glycol, Polysorbate 80, Talc, Ethyl cellulose, Colloidal silicon dioxide, Sugar, Gelatin

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

Shelf life is 24 months (2 years) from manufacture.

### **6.4 Special precautions for storage**

Store below 25°C.

### **6.5 Nature and contents of container**

30 or 100 capsules in foil blisters.

### **6.6 Special precautions for disposal and other handling**

Not applicable.

## **7 MEDICINE SCHEDULE**

Prescription Medicine

## **8 SPONSOR**

REX Medical Ltd  
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## **9 DATE OF FIRST APPROVAL**

6 March 2008

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

19 September 2018

## SUMMARY TABLE OF CHANGES

<b>Section changed</b>	<b>Summary of new information</b>
4.6	Fertility section added
4.8	Reporting of adverse events added
4.9	Poison information centre contact added
5.3	Section added