1. NAME OF THE MEDICINALPRODUCT

Tamsulosin Hydrochloride Modified-Release Capsules 400 mcg

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each hard gelatin capsule contains:

Tamsulosin Hydrochloride USP..... .400 mcg

(As modified-release pellets)

Excipients ..... q.s.

Approved colours used in empty capsule

For complete list of excipients refer section 6.1

3. PHARMACEUTICAL FORM

Oral Solid Dosage Form- Capsules.

4. CLINICAL PARTICULARS

4.1 Therapeuticindications

Lower urinary tract symptoms (LUTS) associated with Benign Prostatic Hyperplasia (BPH).

4.2 Posology and method ofadministration

Posology

Oral use.

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

The capsule must be swallowed whole and should not be crunched or chewed as this interferes with the modified release of the 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

There is no relevant indication for use of this medicine product in children.

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 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 foruse

As with other α 1-adrenoceptors 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 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 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 cataract surgery. The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract surgery is scheduled is not recommended.

During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract 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).

Allergic reactions to the presence of colouring agents azorubine (E122), ponceau 4R (E124) and sunset yellow (E110) may occur.

4.5 Interaction with other medicinal products and other forms ofinteraction

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, whereasfurosemide a fall, but as levels remain within the normal range, posology need not be adjusted.

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, 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 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 usemachines

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 Undesirableeffects

Tamsulosin prolonged-release tablets were evaluated in two double-blind placebo controlled trials. Adverse events were mostly mild and their incidence was generally low. The most commonly reported ADR was abnormal ejaculation occurring in approximately 2% of patients.

Suspected adverse reactions reported with Tamsulosin prolonged release tablets or an alternative formulation of tamsulosin, were:

Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000) and Very rare (<1/10,000), including isolated reports , not known (frequency cannot be estimated from the available data).

Nervous systems disorders
Common: dizziness (1.3%)
Uncommon: headache
Rare: syncope
Eye disorders
Not known: vision blurred*, visual impairment*
Cardiac disorders
Uncommon: palpitations
Vascular disorders
Uncommon: orthostatic hypotension
Respiratory, thoracic and mediastinal disorders
Uncommon: rhinitis
Not known: epistaxis*
Gastrointestinal disorders
Uncommon: nausea, vomiting, constipation, diarrhoea
Not known: dry mouth*

Skin and subcutaneous tissue disorders
Uncommon: rash, pruritus, urticaria
Rare: angioedema
Very rare: Stevens-Johnson syndrome
Not known: erythema multiforme*, dermatitis exfoliative*
Reproductive system and breast disorders
Common: ejaculation disorders including retrograde ejaculation and ejaculation failure
Very rare: priapism
General disorders and administration site conditions
Uncommon: asthenia
*observed post-marketing

As with other alpha-blockers, drowsiness, blurred vision, dry mouth 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.

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 can be 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. PHARMACOLOGICALPROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists.

ATC code: G04C A02.

Preparations for the exclusive treatment of prostatic disease.

Mechanism of action:

Tamsulosin binds selectively and competitively to postsynaptic α_1-adrenoceptors, in particular to the subtypes α_{1A} and $\alpha_{1D.}$ It brings about relaxation of prostatic and urethral smooth muscle.

Pharmacodynamic effects:

Tamsulosin increases the maximum urinary flow rate. It relieves obstruction by relaxing the smooth muscle in the 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 catheterization is significantly delayed.

α_1-adrenoceptors 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 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 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 hydrochloride is absorbed from the intestine and is almost completely bioavailable.

Absorption of tamsulosin hydrochloride is reduced by a recent meal. Uniformity of absorption can be promoted by the patient always taking Tamsulosin Ranbaxy 0.4 mg Prolonged release capsules after the same meal.

Tamsulosin shows linear kinetics.

After a single dose of tamsulosin 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, Cmax in patients is about two thirds higher than that reached after a single dose.

Although this was seen in the older 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 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 metabolized 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 with about 9% of a dose being present in the form of unchanged active substance.

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

5.3 Preclinical safety data

Single and repeat dose toxicity were performed in mice, rats and dogs.

In addition, reproduction toxicity studies 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 α1-adrenoceptors 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 incidence 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. PHARMACEUTICALPARTICULARS

6.1 List ofexcipients

Hard Gelatin Capsules Shells Size ‘2’ (brown cap and White body).

6.2 Incompatibilities

Not Applicable

6.3 Shelflife

24 months from the date of Manufacture.

6.4 Special precautions forstorage

Storage in cool, place below 30°C. Protect From Light.

Keep the medicine out of reach of children.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

10 capsules in Aluminium– PVDC Blister along with a leaflet.

6.6 Special precautions for disposal <and otherhandling>

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

7. APPLICANT/MANUFACTURER>

Name of the Applicant:

SAI SAGAR PHARMA LIMITED

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Manufactured by:

S Kant
HEALTHCARE Ltd.

1802-1805, G.I.D.C., Phase III,

Vapi - 396 195. Gujarat, INDIA.

8. WHO PREQUALIFICATION REFERENCE NUMBER-
Not applicable

9. DATE OF PREQUALIFICATION / RENEWAL OF PREQUALIFICATION-
Not applicable

10. DATE OF REVISION OF THE TEXT-
Not applicable