1. **Name of the Medicinal Product :**
   1.1 **Product Name :** Tamsulosin Hydrochloride Prolonged Release Tablets 0.4 mg
   1.2 **Strength :** 0.4 mg
   1.3 **Pharmaceutical Dosage Form :** Prolonged Release Tablet

2. **Quality and Quantitative Composition :**
   2.1 Qualitative Declaration
   INN Name: Tamsulosin Hydrochloride
   IUPAC Name: R(-)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzene sulfonamide, monohydrochloride

Ingredients	**Reference**
Tamsulosin Hydrochloride	Ph.Eur
Hypromellose	Ph.Eur
Cellulose, microcrystalline	Ph.Eur
Carbomer	Ph.Eur
Silica colloidal anhydrous	Ph.Eur
Iron oxide red	Regulation 231/2012
Magnesium stearate	Ph.Eur
Purified water	Ph.Eur

2.2 Quantitative Declaration

Ingredients	**Reference**	**Mg/tablet**
Inner core tablet		
Hypromellose	Ph.Eur	36.00
Cellulose, microcrystalline	Ph.Eur	20.37
Carbomer	Ph.Eur	3.00
Silica colloidal anhydrous	Ph.Eur	0.30
Iron oxide red	Regulation 231/2012	0.03
Magnesium stearate	Ph.Eur	0.3
Inner core mass		***60.00***
Outer core tablet		
Tamsulosin Hydrochloride[1]	Ph.Eur	0.40
Cellulose, microcrystalline[2]	Ph.Eur	71.00
Purified water[3]	Ph.Eur	q.s.
Hypromellose	Ph.Eur	126.84
Carbomer	Ph.Eur	10.50
Silica colloidal anhydrous	Ph.Eur	1.05
Magnesium stearate[4]	Ph.Eur	0.21
Outer core mass		***210.00***
Total tablet mass		**270.00**

[1] Prior to manufacturing, a correction factor is calculated to compensate for water content (H2O in %) and assay (assay, by HPLC) using the following equation.

$$F = \frac{100}{100 - H2O} \times \frac{100}{\text{assay (in \%)}}$$

When the assay is >100.0%, then 100.0% has to be used in the equation above.

[2] Microcrystalline cellulose (outer core) is used to compensate for the mass change of the theoretical amount of Tamsulosin hydrochloride. The compensation mass of microcrystalline cellulose © is defined as:

C = [Theoretical mass of TSL.HCl] x [F-1]

The amount of C is deducted from the theoretical mass of microcrystalline cellulose.

[3] Purified water is removed during drying step.

[4] Vegetable origin

3. Pharmaceutical Form: White, un-scored, 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:

Oral use.

One tablet daily.

Tarnsulosin 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.

No dose adjustment is warranted in renal impairment.

No dose adjustment is warranted in patients with mild to moderate hepatic insufficiency.

Paediatric population

The safety and efficacy of tamsulosine in children and adolescents have not been established. There is no relevant indication for use of tamsulosin in children.

4.3 Contraindications :

- Hypersensitivity to tamsulosin hydrochloride, including drug-induced angioedema or to any of the excipients.
- A history of orthostatic hypotension.
- Severe hepatic insufficiency.

4.4 Special warning and precautions for use :

As with other α_{1a} 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 surgery in some patients on or previously treated with tamsulosin. IFIS may lead to increased procedural complications during the operation. The initiation of therapy with tamsulosin in patients for whom cataract surgery is scheduled is not recommended. Discontinuing tamsulosin 1-2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of stopping the therapy prior to cataract surgery has not yet been established.

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. 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 Interactions:

Interaction studies have only been performed in adults. No interactions have been seen when tamsulosin 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.

No interactions at the level of hepatic metabolism have been seen during in vitro studies with liver microsomal fractions (representative of the cytochrome P_{450}-linked drug metabolising enzyme system), involving amitriptyline, salbutamol, glibenclamide and finasteride. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin. Concurrent administration of other α_1 drenoceptor antagonists could lead to hypotensive effects.

4.6 Pregnancy and lactation:

Not applicable, as tamsulosin is intended for male patients only.

4.7 Effects on ability to drive and use machine:

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 Adverse reactions :

MedDRA system organ class	Common (≥/100 to <1/10)	Uncommon (≥/1,000 to <1/100)	Rare (≥/10,000 to <1/1,000)	Very rare (<1/10,000)
Nervous systems disorders	Dizziness (1.3%)	Headache	Syncope	
Cardiac disorders		Palpitations		
Vascular disorders		Orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders		Rhinitis		
Gstro-intestinal disorders		Constipation, diarrhoea, nausea, vomiting		
Skin and subcutaneous tissue disorders		Rash, pruritus, urticaria	Angioedema	Stevens Johnson syndrome
Reproductive system and breast disorders	Ejaculation disorders			Priapism
General disorders and administration site conditions		Asthenia		

During cataract surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been associated with therapy of tamsulosin during post-marketing surveillance..

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.

4.9 Overdose and special antidotes :

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.

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_1-adrenoceptor antagonist
Preparations for the exclusive treatment of prostatic disease.

ATC code:
G04C A02

Mechanism of action
Tamsulosin binds selectively and competitively to the postsynaptic αl 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.
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.

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 administered as Tamsulosin prolonged release tablets is absorbed from the intestine. Of the administered dose, approximately 57% is estimated to be absorbed.
The rate and extent of absorption of tamsulosin administered as Tamsulosin prolonged release tablets are not affected by food.
Tamsulosin shows linear pharmacokinetics.

After a single dose of tamsulosin 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 Tamsulosin prolonged release 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 man, tamsulosin is about 99% bound to plasma proteins. 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 unchanged active substance. It is metabolised in the liver.
In rats, hardly any induction of microsomal liver enzymes was seen to be caused by tamsulosin.
No dose adjustment is warranted in hepatic insufficiency.
None of the metabolites is more active than the original compound.
Excretion
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 Tamsulosin prolonged release tablets.
After a single dose of Tamsulosin prolonged release tablets and in steady state, elimination half-lives of about 19 and 15 hours, respectively, have been measured.
No dose adjustment is warranted in renal impairment.

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:
Hypromellose Ph.Eur, Cellulose microcrystalline Ph.Eur, Carbomer Ph.Eur, Silica colloidal anhydrous Ph.Eur, Iron oxide red (E 172), Magnesium stearate Ph.Eur.

6.2 Incompatibilities: None

6.3 Shelf life: 36 months

6.4 Special precautions for storage:
Keep out of reach of children
Protect from light and moisture
Store below 30°C in a dry place.

6.5 Nature and contents of container:
Alu alu pack containing 3 blisters of 10 tablets each.

6.6 Special precautions for disposal and other handling:
No special requirements

7. Marketing Authorization Holder and manufacturing site address:
Marketing Authorization Holder:
Mega Lifesciences Public Company Limited
384 Moo 4, Pattana 3 Road,
Bangpoo Industrial Estate,
Soi 6, Preaksa, Muang Samutprakarn,
Samutprakarn 10280, Thailand

Manufacturing site address:
Synthon Hispania S.L.
C/Castello, n°1,
Pol. Las Salinas Sant Boi de
Llobregat
Barcelona, 08830
Spain

8. Marketing Authorization Number:

9. Date of first authorization / renewal of the authorization :

10. Date of revision of the text: