Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

1.1 (Invented) Name of the medicinal product
FLOWEL (TAMSULOSIN HYDROCHLORIDE CAPSULES USP 0.4 MG)

1.2 Strength
Each hard gelatin capsule contains:

Tamsulosin Hydrochloride USP (As sustained release pellets)	0.4 mg
Excipients	Q.S.
Approved colored used for capsules	

1.3 Pharmaceutical Form
Oral Hard Gelatin Capsule

2. Qualitative and Quantitative Formula
Batch Size: 100,000 Capsules

Sr. No.	Name of Ingredient	Specification	Quantity/ capsule in mg	Quantity/ Batch in kg	Functions
1.	Tamsulosin Hydrochloride USP* (as sustained release pellets)	In house	300.75	30.075 kg	Active/α_1-adreno receptor antagonist
Total Weight of Pellets			**300.75 mg**	**30.075 kg**	
2.	A purple/ purple colored hard gelatin capsules size '2'	In house	1 No.	100,000 Nos.	Capsule Shell

*Tamsulosin Hydrochloride USP (as sustained release pellets) corresponds to 0.4 mg of Tamsulosin Hydrochloride:

$$\text{Calculated By} = \frac{0.4 \times 100 \text{ (Label claim per capsule x100)}}{0.133 \quad \text{(Strength of pellets)}}$$

= 300.75 mg Tamsulosin Sustained Release Pellets for Tamsulosin Hydrochloride USP 0.4 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION OF TAMSULOSIN HYDROCHLORIDE PELLETS 0.133%

(Reference: Spansules Formulations)

Approved Name (INN)	Chemical Name /Molecular Formula	Quantity In mg in one gram of pellets
Tamsulosin HCl USP	(--)-(R)-5-[2-[[2-(o-Ethoxy phenoxy)ethyl]amino]propyl]-2-methoxybenzene sulfonamide mono hydrochloride	1.33mg

Inactive Ingredient	Specification or Reference	Quantity In mg in one gram of pellets
Hypromellose (HPMC E5)	BP	50.00
Mannitol	BP	479.27
Sucrose	BP	394.40
Crospovidone	BP	20.00
Ethyl cellulose	BP	50.00
Diethyl Pthalate	BP	5.000
Isopropyl alcohol*	BP	NA*
Dichloromethane*	BP	NA*

NA*: Not present in final product.

3. Pharmaceutical form

A purple/purple colored hard gelatin capsules of size ‘2’ containing white to off white spherical sustained release pellets.

4. Clinical particulars:

4.1 Therapeutic Indication:

FLOWEL is indicated that Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration:

Male 45 to 75 years.

One capsule daily, to be taken after the same meal each day.

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

4.3 Contraindications

FLOWEL is contraindicated that

- Hypersensitivity to the active substance including drug-induced angioedema.
- Orthostatic hypotension observed earlier (history of orthostatic hypotension).
- Severe hepatic insufficiency.

4.4 Special warnings and precautions for use:

As with other α1 adrenoceptors antagonists, a reduction in blood pressure can occur in individual cases during treatment with Tamsulosin hydrochloride 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 hydrochloride 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.

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 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 metabolize CYP2D6 phenotype.

Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4.

4.5 Interaction with other medicinal products and other forms of interaction

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, whereas furosemide 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 C_{max} 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 metabolize 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 $\alpha_1$adrenoreceptor antagonists could lead to hypotensive effects.

4.5 Adverse Drug Reactions

System Organ Class	**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 (cannot be estimated from the available data)
Nervous system disorders	Dizziness (1.3%)	Headache	Syncope		
Cardiac disorders		Palpitations			
Vascular disorders		Orthostatic hypotension			
Eye disorders					Vision blurred, visual impairment
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 system and breast disorders				Priapism	Ejaculation disorder, retrograde ejaculation, ejaculation failure
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.

4.7 Fertility, Pregnancy and lactation

Pregnancy

Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.

Breastfeeding

Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

4.8 Effects on ability to drive and use machines:

Omeprazole is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machinery.

4.9 Overdose:

Symptoms

Over dosage 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 over dosage 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 sulphate, can be administered.

5. Pharmacological properties

5.1 Pharmacotherapeutic Group

Pharmacotherapeutic Group: Urological, alpha-adrenoreceptor antagonist

ATC code: G04CA02

Mechanism of action

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

5.2 Pharmacodynamic properties

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 catheterization and number of times wet at time of catheterization as recorded in catheterization 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.

5.3 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 Cmax 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 more than 99% bound to plasma proteins and the 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 metabolized in the liver.

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

The metabolites are not as effective and toxic as the active medicinal product itself.

Elimination

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

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

5.4 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

Not Applicable

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precautions for storage

Store below 30°C. Keep medicines out of reach of children.

6.5 Nature and contents of container

3 X 10 Capsules Alu - Alu blister pack in a printed carton along with package insert.

6.6 Special precautions for disposal

No special requirements.

7. REGISTRANT

ANTILA LIFESCIENCES PVT. LTD.
Mfg. At: C-1B 305/2, 3, 4 & 5, G.I.D.C, Kerala (Bavla),
Dist.: Ahmedabad, Gujarat, India.

8. DATE OF REVISION OF THE TEXT

----

9. NAME AND ADDRESS OF MANUFACTURER

ANTILA LIFESCIENCES PVT. LTD.
Mfg. At: C-1B 305/2, 3, 4 & 5, G.I.D.C, Kerala (Bavla),
Dist.: Ahmedabad, Gujarat, India.