For the use of a Registered Medical Practitioner or a Hospital or a Laboratory.

PRESCRIPTION DRUG

VELTAM 0.2/0.4

(Tamsulosin Hydrochloride Modified Release Tablets 0.2 mg and 0.4 mg)

DESCRIPTION

Tamsulosin hydrochloride is an antagonist of alpha 1A adrenoceptors in the prostate. Tamsulosin HCl is (-)-(R)-5-[2-[[2- (0-ethoxyphenoxy) ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride. The empirical formula of tamsulosin HCl is $C_{20}H_{28}N_2O_5S.HCl$. The molecular weight tamsulosin HCl is 444.98.

COMPOSITION

VELTAM 0.2

(1) Tamsulosin hydrochloride modified release tablets 0.2 mg
Each film coated modified release tablet contains:
Tamsulosin hydrochloride USP ..... 0.2 mg

VELTAM 0.4

(2) Tamsulosin hydrochloride modified release tablets 0.4 mg
Each film coated modified release tablet contains:
Tamsulosin hydrochloride USP..... 0.4 mg

CLINICAL PHARMACOLOGY

Tamsulosin hydrochloride is an $alpha_1$ -adrenoceptor antagonist Tamsulosin binds selectively and competitively to postsynaptic $alpha_1$-receptors, in particular to the subtype $alpha_{1A}$, which bring about relaxation of the smooth muscle of the prostate, whereby tension is reduced.

Tamsulosin increases maximum urinary flow rate by reducing smooth muscle tension in prostate and urethra and thereby relieving obstruction. It also improves the complex of irritative and obstructive symptoms in which bladder instability and tension of the smooth muscles of the lower urinary tract play an important role. $Alpha_1$-blockers can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with tamsulosin.

PHARMACOKINETICS

The pharmacokinetics of tamsulosin HCl have been evaluated in adult healthy volunteers and patients with BPH after single and/or multiple administration with doses ranging from 0.1 mg to 1 mg.

Absorption

Absorption of tamsulosin HCl from tamsulosin 0.4 mg tablets is essentially complete (>90%) following oral administration under fasting conditions. Tamsulosin HCl exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of once-a-day dosing.

Effect of Food: The time to maximum concentration (T_{max}) is reached by four to five hours under fasting conditions and by six to seven hours when tamsulosin tablets are administered with food. Taking tamsulosin tablets under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentrations (C_{max}) compared to fed conditions.

Distribution

The mean steady-state apparent volume of distribution of tamsulosin HCl after intravenousadministration to ten healthy male adults was 16L, which is suggestive of distribution into extracellular fluids in the body. Tamsulosin HCl is extensively bound to human plasma proteins (94% to 99%), primarily $alpha_1$ acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600 ng/mL). The results of two-way in *vitro studies* indicate that the binding of tamsulosin HCl to human plasma proteins is not affected by amitriptyline, diclofenac, glyburide, simvastatin plus simvastatin-hydroxy acid metabolite, warfarin, diazepam, propranolol, trichlormethiazide, or chlormadinone. Likewise, tamsulosin HCl had no effect on the extent of binding of these drugs.

Metabolism

There is no enantiometric bioconversion from tamsulosin HCl [R(-) isomer] to the S(+) isomer in humans. Tamsulosin HCl is extensively metabolized by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. The metabolites of tamsulosin HCl undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Excretion

On administration of the radiolabeled dose of tamsulosin HCl to four healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to feces (21%) over 168 hours. Following intravenous or oral administration of an immediate-release formulation, the elimination half-life of tamsulosin HCl in plasma range from five to seven hours. Because of absorption rate-controlled pharmacokinetics with tamsulosin tablets, the apparent half-life of tamsulosin HCl is approximately 9 to 13 hours in healthy volunteers and 14 to 15 hours in the target population. Tamsulosin HCl undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h).

Special Populations

Geriatrics (Age)

Cross-study comparison of tamsulosin tablets overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin HCl may be slightly prolonged in geriatric males compared to young, healthy male volunteers. Intrinsic clearance is independent of tamsulosin HCl binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects of age 55 to 75 years compared to subjects of age 20 to 32 years.

In Renal impairment patients

The pharmacokinetics of tamsulosin HCl have been compared in 6 subjects with mild-moderate (3 CLcr<70 mL/min/1.73m^2) or moderate-severe (1CLcr < 30 mL/min/1.73m^2) renal impairment and 6 normal subjects (CLcr<90 mL/min/1.73m^2). While a change in the overall plasma concentration of tamsulosin HCl was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin HCl, as well as the intrinsic clearance, remained relatively constant.

Therefore, patients with renal impairment do not require an adjustment in tamsulosin dosing. However, patients with endstage renal disease (CLcr < 10 mL/min/1.73m^2) have not been studied.

In Hepatic Impairment patients

The pharmacokinetics of tamsulosin HCl have been compared in 8 subjects with moderate hepatic dysfunction and 8 normal subjects. While a change in the overall plasma concentration of tamsulosin HCl was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin HCl does not change significantly with only a modest (32%) change in intrinsic clearance of unbound tamsulosin HCl.

Therefore, patients with moderate hepatic dysfunction do not require an adjustment in tamsulosin tablets dosage.

INDICATIONS AND USAGE

Tamsulosin HCl tablets are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Tamsulosin tablets are not indicated for the treatment of hypertension.

DOSAGE AND ADMINISTRATION

Tamsulosin tablets 0.4 mg once daily is recommended as the dose for the treatment of the signs and symptoms of BPH. It should be administered approximately one-half hour following the same meal each day. For those patients who fail to respond to the 0.4-mg dose after two to four weeks of dosing, the dose of tamsulosin tablets can be increased to 0.8 mg once daily. If tamsulosin tablets administration is discontinued or interrupted for several days at either the 0.4-mg or 0.8-mg dose, therapy should be started again with the 0.4-mg once daily dose.

	Checked by				Approved by
Department	PMQC	R.A.	Packing Dev.	Q.A.	Head Q.A.
Signature					
Date					

Product Name : Veltam-0.4
Size : 140 x 210 (mm)
Folding Size : 140 x 30 (mm)
No. of Col. : 1
Date : 03/12/15

File name : 80 1175 0 8610284-Veltam-0.4-PIL
Col. Shade No.: Pantone Black

CONTRAINDICATIONS

Tamsulosin tablets are contraindicated in patients known to be hypersensitive to tamsulosin HCl or any component of tamsulosin tablets.

WARNINGS

The signs and symptoms of orthostasis (postural hypotension, dizziness and vertigo) were detected more frequently in tamsulosin tablets treated patients than in placebo recipients. As with other alpha-adrenergic blocking agents there is a potential risk of syncope. Patients beginning treatment with tamsulosin tablets should be cautioned to avoid situations where injury could result should syncope occur.

Rarely (probably less than one in fifty thousand patients), tamsulosin, like other alpha$_1$ antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Because this condition can lead to permanent impotence if not properly treated, patients must be advised about the seriousness of the condition.

PRECAUTIONS

General

1) Carcinoma of the prostate: Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently co-exist. Patients should be evaluated prior to the start of tamsulosin tablets therapy to rule out the presence of carcinoma of the prostate.
2) Drug-Drug Interactions: The pharmacokinetic and pharmacodynamic interactions between tamsulosin tablets and other alpha-adrenergic blocking agents have not been determined. However, interactions may be expected and tamsulosin tablets should not be used in combination with other alpha-adrenergic blocking agents.

   The pharmacokinetic interaction between cimetidine and tamsulosin tablets was investigated. The results indicate significant changes in tamsulosin HCl clearance (26% decrease) and AUC (44% increase). Therefore, tamsulosin tablets should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

   Results from limited *in vitro* and *in vivo* drug-drug interaction studies between tamsulosin HCl and warfarin are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and tamsulosin tablets.

Pregnancy

Not applicable as tamsulosin tablets is intended for male patients only. Tamsulosin tablets are not indicated for use in women.

Nursing Mothers

Tamsulosin tablets are not indicated for use in women.

Pediatric Use

Tamsulosin tablets are not indicated for use in pediatric populations.

Drug-Drug Interactions

Nifedipine, Atenolol, Enalapril: In three studies in hypertensive subjects (age range 47-79 years) whose blood pressure was controlled with stable doses of nifedipine, atenolol, or enalapril for at least three months, tamsulosin tablets 0.4 mg for seven days followed by tamsulosin tablets 0.8 mg for another seven days (n=8 per study) resulted in no clinically significant effects on blood pressure and pulse rate compared to placebo (n=4 per study). Therefore, dosage adjustments are not necessary when tamsulosin tablets are administered concomitantly with nifedipine, atenolol, or enalapril.

Warfarin: A definitive drug-drug interaction study between tamsulosin HCl and warfarin was not conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and tamsulosin tablets.

Digoxin and Theophylline: In two studies in healthy volunteers (n=10 per study; age range 19-39 years) receiving tamsulosin tablets 0.4 mg/day for two days, followed by tamsulosin tablets 0.8 mg/day for five to eight days, single intravenous doses of digoxin 0.5 mg or theophylline 5 mg/kg resulted in no change in the pharmacokinetics of digoxin or theophylline. Therefore, dosage adjustments are not necessary when tamsulosin capsule is administered concomitantly with digoxin or theophylline.

Furosemide: The pharmacokinetic and pharmacodynamic interaction between tamsulosin tablets 0.8 mg/day (steady-state) and furosemide 20 mg intravenously (single dose) was evaluated in ten healthy volunteers (age range 21-40 years). Tamsulosin tablets had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced an 11% to 12% reduction in tamsulosin HCl Cmax and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the tamsulosin tablets dosage.

Cimetidine: The effects of cimetidine at the highest recommended dose (400 mg every six hours for six days) on the pharmacokinetics of a single tamsulosin tablets 0.4 mg dose was investigated in ten healthy volunteers (age range 21-38 years). Treatment with cimetidine resulted in a significant decrease (26%) in the clearance of tamsulosin HCl which resulted in a moderate increase in tamsulosin HCl AUC (44%). Therefore, tamsulosin tablets should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

ADVERSE EFFECTS

The following adverse reactions have been reported during the use of tamsulosin: dizziness, abnormal ejaculation and, less frequently (1-2%) headache, asthenia, postural hypotension, palpitations and rhinitis.

Gastrointestinal reactions such as nausea, vomiting, diarrhoea, and constipation can occasionally occur. Hypersensitivity reactions such as rash, pruritus, and urticaria can occur occasionally. As with other alpha-blockers, drowsiness, blurred vision, dry mouth or oedema can occur.Syncope has been reported rarely, and there have been very rare reports of angioedema and priapism.

OVERDOSAGE

No cases of acute overdosage have been reported. However, acute hypotension could theoretically occur after overdosage in which case 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 functions 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.

STORAGE

Store in a cool & dry place.

PRESENTATION

VELTAM 0.2 & VELTAM 0.4 are available in blister pack of 10 tablets.

Manufactured by:

INTAS

INTAS PHARMACEUTICALS LTD.

Selaqui, Dehradun-248 197. INDIA

80 1175 0 8610284

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