CONTIFLO OD 0.4 mg

(Tamsulosin Hydrochloride Extended Release Capsules)
(For oral administration)

COMPOSITION
Contiflo OD 0.4 mg
Active Ingredients
Each capsule contains
Tamsulosin Hydrochloride 0.4 mg
Excipients
Microcrystalline cellulose, Magnesium stearate, Methacrylic acid-ethyl acrylate copolymer dispersion, Methacrylic acid-ethyl acrylate copolymer, Sodium hydroxide, Triacetin, Titanium dioxide, Purified talc & Purified water*
*Lost during processing

PHARMACEUTICAL FORM AND CONTENTS
Contiflo OD 0.4 mg: Box containing blister strip of 10 capsules.

THERAPEUTIC CLASS/ACTIVITY
The symptoms associated with benign prostatic hyperplasia (BPH) are related to bladder outlet obstruction, which is comprised of two underlying components: static and dynamic.
The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of α_1 adrenoceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenoceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH.
Tamsulosin, an α_1 adrenoceptor blocking agent, exhibits selectivity for α_1 receptors in the human prostate. At least three discrete α_1-adrenoceptor subtypes have been identified: α_{1a}, α_{1b} & α_{1d}; their distribution differs between human organs and tissue. Approximately 70% of the α_1-receptors in human prostate are of the α_{1a} subtype
Tamsulosin hydrochloride is not intended for use as an antihypertensive drug.

THERAPEUTIC INDICATIONS
Contiflo OD capsules are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

CONTRAINDICATIONS
Contiflo OD capsules are contraindicated in patients known to be hypersensitive to tamsulosin hydrochloride or to any of the inactive ingredients of the drug product; with a history of orthostatic hypotension or severe hepatic insufficiency.

PRECAUTIONS
General
Contiflo OD capsules are not indicated for the treatment of hypertension.
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 start of tamsulosin hydrochloride therapy to rule out presence of carcinoma of the prostate.
Drug-Drug Interactions: The pharmacokinetic and pharmacodynamic interactions between tamsulosin hydrochloride and other α-adrenergic blocking agents have not been determined. However, interactions may be expected and tamsulosin hydrochloride capsules should NOT be used in combination with other α-adrenergic blocking agents.
The pharmacokinetic interaction between cimetidine and tamsulosin hydrochloride was investigated. The results indicate significant changes in tamsulosin hydrochloride clearance (26% decrease) and AUC (44% increase). Therefore, tamsulosin hydrochloride 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 hydrochloride and warfarin are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and tamsulosin hydrochloride.
Laboratory Tests: No laboratory test interactions with tamsulosin hydrochloride capsules are known. Treatment with tamsulosin hydrochloride for up to 12 months had no significant effect on prostate-specific antigen (PSA).

WARNINGS
The signs and symptoms of orthostasis (postural hypotension, dizziness and vertigo) were detected more frequently in tamsulosin hydrochloride treated patients than in placebo recipients. As with other α-adrenergic blocking agents there is a potential risk of syncope (see **ADVERSE REACTIONS**).
Patients beginning treatment with tamsulosin hydrochloride 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 α_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.
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 hydrochloride 0.4 mg for seven days followed by tamsulosin hydrochloride 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 hydrochloride is administered concomitantly with nifedipine, atenolol, or enalapril.
Warfarin: A definitive drug-drug interaction study between tamsulosin hydrochloride 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 hydrochloride.
Digoxin and Theophylline: In two studies in healthy volunteers (n= 10 per study, age range 19-39 years) receiving tamsulosin hydrochloride 0.4 mg/day for two days, followed by tamsulosin hydrochloride 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 a tamsulosin hydrochloride is administered concomitantly with digoxin or theophylline.
Furosemide: The pharmacokinetic and pharmacodynamic interaction between tamsulosin hydrochloride 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 hydrochloride had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced an 11% to 12% reduction in tamsulosin hydrochloride C_{max} and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the tamsulosin hydrochloride 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 hydrochloride 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 hydrochloride which resulted in a moderate increase in tamsulosin hydrochloride AUC (44%). Therefore, tamsulosin hydrochloride should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.
Carcinogenicity/Mutagenicity - Rats administered doses up to 43 mg/kg/day in males and 52 mg/kg/day in females had no increases in tumor incidence with the exception of a modest increase in the frequency of mammary gland fibroadenomas in female rats receiving doses $\geq$ 5.4 mg/kg ($P<0.015$). The highest doses of tamsulosin hydrochloride evaluated in the rat carcinogenicity study produced systemic exposures (AUC) in rats 3 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.
Mice were administered doses up to 127 mg/kg/day in males & 158 mg/kg/day in females. There were no significant tumor findings in male mice. Female mice treated for 2 years with the two highest doses of 45 and 158 mg/kg/day had statistically significant increases in the incidence of mammary gland fibroadenomas ($P< 0.0001$) and adenocarcinomas ($P< 0.0075$). The highest dose levels of tamsulosin hydrochloride evaluated in the mice carcinogenicity study produced systemic exposures (AUC) in mice 8 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.
The increased incidences of mammary gland neoplasms in female rats and mice were considered secondary to tamsulosin hydrochloride induced hyperprolactinemia. It is not known if tamsulosin hydrochloride elevate prolactin in humans. The relevance for human risk of the findings of prolactinmediated endocrine tumors in rodents is not known.
Tamsulosin hydrochloride produced no evidence of mutagenic potential *in vitro* in the Ames reverse mutation test, mouse lymphoma thymidine kinase assay, unscheduled DNA repair synthesis assay, and chromosomal aberration assays in Chinese hamster ovary cells or human lymphocytes. There were no mutagenic effects in the in vivo sister chromatid exchange and mouse micronucleus assay.
Use in Children - Tamsulosin hydrochloride is not indicated for use in pediatric populations.
Use in Pregnancy and Lactation - Tamsulosin hydrochloride is not indicated for use in women.
Use in Elderly - Cross-study comparison of tamsulosin hydrochloride overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin hydrochloride may be slightly prolonged in geriatric males compared to young, healthy male volunteers. Intrinsic clearance is independent of tamsulosin hydrochloride 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.
Effect on Driving/Machine operating ability - No data is available on whether tamsulosin hydrochloride adversely affects the ability to drive or operate machines. However, in this respect patients should be aware of the fact that drowsiness, blurred vision, dizziness and syncope can occur.

THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you . Follow strictly the doctors prescription, the method of use and the instructions of the pharmacist who sold the medicament.
The doctor and the pharmacist are the experts in medicines, their benefits and risks.
Do not by yourself interrupt the period of treatment prescribed.
Do not repeat the same prescription without consulting your doctor.
Keep all medicaments out of reach of children.
Council of Arab Health Ministers, Union of Arab Pharmacists.

DOSAGE AND ADMINISTRATION
For Benign prostate hyperplasia
The usual recommended dose is one **Contiflo OD** 0.4 mg capsule once daily. It should be administered approximately one-half hour following the same meal each day. The capsule should be swallowed whole and should not be crunched or chewed.
For those patients who fail to respond to the 0.4 mg dose after two to four weeks of dosing, the dose of tamsulosin hydrochloride can be increased to 0.8 mg once daily. If tamsulosin hydrochloride 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.

WITHDRAWAL EFFECTS, IF ANY
The termination of treatment with tamsulosin hydrochloride is unlikely to be associated with withdrawal effects; however, treatment should be discontinued only on the advice of the treating physician.

OVERDOSAGE AND ITS MANAGEMENT
Should overdosage of tamsulosin hydrochloride lead to hypotension (see **WARNINGS** and **ADVERSE REACTIONS**), support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, then administration of intravenous fluids should be considered. If necessary, vasopressors should then be used and renal function should be monitored and supported as needed. Laboratory data indicate that tamsulosin hydrochloride is 94% to 99% protein bound; therefore, dialysis is unlikely to be of benefit.
One patient reported an overdose of thirty 0.4 mg tamsulosin hydrochloride capsules. Following the ingestion of the capsules, the patient reported a severe headache.

MISSED DOSE INSTRUCTIONS
In case a dose is missed, it should be taken as soon as possible unless it is almost time for the next dose. If several doses are missed, the pharmacist/physician must be informed.

ADVERSE REACTIONS
The incidence of treatment-emergent adverse events has been ascertained from six short-term U.S. and European placebo-controlled clinical trials in which daily doses of 0.1 to 0.8 mg tamsulosin hydrochloride were used. These studies evaluated safety in 1783 patients treated with tamsulosin hydrochloride and 798 patients administered placebo. Table below summarizes the treatment emergent adverse events that occurred in $\geq$ 2% of patients receiving either tamsulosin hydrochloride 0.4 mg, or 0.8 mg and at an incidence numerically higher than that in the placebo group during two 13-week U.S. trials conducted in 1487 men.

Table. Treatment Emergent[1] Adverse Events Occurring In $\geq$2% Of Tamsulosin hydrochloride Or Placebo Patients In Two U.S. Short- Term Placebo Controlled Clinical Studies

Body system/adverse events	Tamsulosin hydrochloride 0.4 mg	Tamsulosin hydrochloride 0.8 mg	Placebo
Body as whole			
Headache	97 (19.3%)	104 (21.1%)	99 (20.1%)
Infection	45 (9.0%)	53 (10.8%)	37 (7.5%)
Asthenia	39 (7.8%)	42 (8.5%)	27 (5.5%)
Back pain	35 (7.0%)	41 (8.3%)	27 (5.5%)
Chest Pain	20 (4.0%)	20 (4.1%)	18 (3.7%)
Nervous system			
Dizziness	75 (14.9%)	84 (17.1%)	50 (10.1%)
Somnolence	15 (3.0%)	21 (4.3%)	8 (1.6%)
Insomnia	12 (2.4%)	7 (1.4%)	3 (0.6%)
Libido Decreased	5 (1.0%)	10 (2.0%)	6 (1.2%)
Respiratory system			
Rhinitis	66 (13.1%)	88 (17.9%)	41 (8.3%)
Pharyngitis	29 (5.8%)	25 (5.1%)	23 (4.7%)
Cough Increased	17 (3.4%)	22 (4.5%)	12 (2.4%)
Sinusitis	11 (2.2%)	18 (3.7%)	8 (1.6%)
Digestive system			
Diarrhea	31 (6.2%)	21 (4.3%)	22 (4.5%)
Nausea	13 (2.6%)	19 (3.9%)	16 (3.2%)
Tooth Disorder	6 (1.2%)	10 (2.0%)	7 (1.4%)
Urogenital system			
Abnormal Ejaculation	42 (8.4%)	89 (18.1%)	1 (0.2%)
Special senses			
Amblyopia	1 (0.2%)	10 (2.0%)	2 (0.4%)

[1]A treatment-emergent adverse event was defined as any event satisfying one of the following criteria:
- The adverse event occurred for the first time after initial dosing with double-blind study medication.
- The adverse event was present prior to or at the time of initial dosing with double-blind study medication and subsequently increased in severity during double-blind treatment; or
- The adverse event was present prior to or at the time of initial dosing with double-blind study medication, disappeared completely, and then reappeared during double-blind treatment.

Signs and Symptoms of Orthostasis: In the two U.S. studies, symptomatic postural hypotension was reported by 0.2% of patients (1 of 502) in the 0.4 mg group, 0.4% of patients (2 of 492) in the 0.8 mg group, and by no patients in the placebo group. Syncope was reported by 0.2% of patients (1 of 502) in the 0.4 mg group, 0.4% of patients (2 of 492) in the 0.8 mg group and 0.6% of patients (3 of 493) in the placebo group. Dizziness was reported by 15% of patients (75 of 502) in the 0.4 mg group, 17% of patients (84 of 492) in the 0.8 mg group, and 10% of patients (50 of 493) in the placebo group. Vertigo was reported by 0.6% of patients (3 of 502) in the 0.4 mg group, 1% of patients (5 of 492) in the 0.8 mg group and by 0.6% of patients (3 of 493) in the placebo group.
Multiple testing for orthostatic hypotension was conducted in a number of studies. Such a test was considered positive if it met one or more of the following criteria: (1) a decrease in systolic blood pressure of $\geq$20 mmHg upon standing from the supine position during the orthostatic tests; (2) a decrease in diastolic blood pressure $\geq$10mmHg upon standing, with the standing diastolic blood pressure <65 mmHg during the orthostatic test; (3) an increase in pulse rate of $\geq$20 bpm upon standing with a standing pulse rate $\geq$100 bpm during the orthostatic test; and (4) the presence of clinical symptoms (faintness, lightheadedness/lightheaded, dizziness, spinning sensation, vertigo, or postural hypotension) upon standing during the orthostatic test.
Following the first dose of double-blind medication, a positive orthostatic test result at 4 hours post-dose was observed in 7% of patients (37 of 498) who received tamsulosin hydrochloride 0.4 mg once daily and in 3% of the patients (8 of 253) who received placebo. At 8 hours post-dose, a positive orthostatic test result was observed for 6% of the patients (31 of 498) who received tamsulosin hydrochloride 0.4 mg once daily and 4% (9 of 250) who received placebo.
At least one positive orthostatic test result was observed during the course of the studies for 81 of the 502 patients (16%) in the tamsulosin hydrochloride 0.4 mg once daily group, 92 of the 491 patients (19%) in the tamsulosin hydrochloride 0.8 mg once daily group and 54 of the 493 patients (11%) in the placebo group.
Because orthostasis was detected more frequently in tamsulosin hydrochloride treated patients than in placebo recipients, there is a potential risk of syncope (see **WARNINGS**).
Abnormal Ejaculation: Abnormal ejaculation includes ejaculation failure, ejaculation disorder, retrograde ejaculation and ejaculation decrease. As shown in Table above, abnormal ejaculation was associated with tamsulosin hydrochloride administration and was dose-related.
Withdrawal from these clinical studies of tamsulosin hydrochloride because of abnormal ejaculation was also dose-dependent with 8 of 492 patients (1.6%) in the 0.8 mg group, and no patients in the 0.4 mg or placebo groups discontinuing treatment due to abnormal ejaculation.
Post-Marketing Experience: Allergic-type reactions such as skin rash, pruritus, angioedema of tongue, lips and face and urticaria have been reported with positive rechallenge in some cases.
Priapism has been reported rarely. Infrequent reports of palpitations, constipation and vomiting have been received during the post-marketing period.

Expiry Date with Warning
The product should not be used after the expiry date mentioned on the pack.

STORAGE
Store below 25°C, protected from moisture.

SHELF LIFE
24 Months

Date of Last Revision of Package Leaflet
February 2005

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

MARKETING AUTHORIZATION HOLDER:
Ranbaxy Laboratories Limited
19, Nehru Place
New Delhi, India

MANUFACTURER
Ranbaxy Laboratories Limited
Industrial Area-3
Dewas 455 001 (M.P.),India