Tadalafil
Tamsulosin hydrochloride

Rx

Gugutams®
5 mg/400 mcg Capsule
Alpha-adrenoreceptor Antagonist

【Pharmacologic Category】
Tadalafil: Phosphodiesterase Type-5 (PDE-5) Inhibitor
Tamsulosin hydrochloride: Alpha$_1$ Adrenoreceptor Antagonist

【Product Description】
Upper orange and lower white hard capsule containing a yellow round shaped film-coated tablet and pale yellow prolonged release pellets.

【Formulation】
Each capsule contains:
Tadalafil (EP) …… 5 mg
Tamsulosin hydrochloride (EP) …… 400 mcg
Additives (tar color): FD&C Red No. 3, FD&C Yellow No. 6

【Pharmacology】
TADALAFIL
Mechanism of Action
Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cGMP. Tadalafil inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by tadalafil has no effect in the absence of sexual stimulation.
The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum and pulmonary arteries is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The mechanism for reducing BPH symptoms has not been established.
Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in the smooth muscle of the corpus cavernosum, prostate, and bladder as well as in vascular and visceral smooth muscle, skeletal muscle, urethra, platelets, kidney, lung, cerebellum, heart, liver, testis, seminal vesicle, and pancreas.
In vitro studies have shown that the effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. These studies have shown that tadalafil is >10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, leukocytes, skeletal muscle, and other organs. Tadalafil is >10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. Additionally, tadalafil is 700-fold more potent for PDE5 than for PDE6, which is found in the retina and is responsible for phototransduction. Tadalafil is >9,000-fold more potent for PDE5 than for PDE8, PDE9, and PDE10. Tadalafil is 14-fold more potent for PDE5 than for PDE11A1 and 40-fold more potent for PDE5 than for PDE11A4, two of the four known forms of PDE11. PDE11 is an enzyme found in human prostate, testes, skeletal muscle and in other tissues (e.g., adrenalcortex). *In vitro*, tadalafil inhibits human recombinant PDE11A1 and, to a lesser degree, PDE11A4 activities at concentrations within the therapeutic range. The physiological role and clinical consequence of PDE11 inhibition in humans have not been defined.

TAMSULOSIN HYDROCHLORIDE
Mechanism of Action
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 alpha$_1$ 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 alpha$_1$ adrenoceptor blocking agent, exhibits selectivity for alpha$_1$ receptors in the human prostate. At least three discrete alpha$_1$ adrenoceptor subtypes have been identified: alpha$_{1A}$, alpha$_{1B}$, and alpha$_{1D}$; their distribution differs between human organs and tissue. Approximately 70% of the alpha$_1$ receptors in the human prostate are of the alpha$_{1A}$ subtype.
Tamsulosin is not intended for use as an antihypertensive drug.

【Pharmacodynamics】
TADALAFIL
Effects on Blood Pressure
Tadalafil 20 mg administered to healthy male subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (difference in the mean maximal decrease of 1.6/0.8 mmHg, respectively) and in standing systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6 mmHg, respectively). In addition, there was no significant effect on heart rate.
Effects on Blood Pressure When Administered with Nitrates
In clinical pharmacology studies, tadalafil (5 to 20 mg) was shown to potentiate the hypotensive effect of nitrates. Therefore, the use of Tadalafil in patients taking any form of nitrates is contraindicated [see Contraindications].
A study was conducted to assess the degree of interaction between nitroglycerin and tadalafil, should nitroglycerin be required in an emergency situation after tadalafil was taken. This was a double-blind, placebo-controlled, crossover study in 150 male subjects at least 40 years of age (including subjects with diabetes mellitus and/or controlled hypertension) and receiving daily doses of tadalafil 20 mg or matching placebo for 7 days. Subjects were administered a single dose of 0.4 mg sublingual nitroglycerin (NTG) at pre-specified time points, following their last dose of tadalafil (2, 4, 8, 24, 48, 72, and 96 hours after tadalafil). The objective of the study was to determine when, after tadalafil dosing, no apparent blood pressure interaction was observed. In this study, a significant interaction between tadalafil and NTG was observed at each time point up to and including 24 hours. At 48 hours, by most hemodynamic measures, the interaction between tadalafil and NTG was not observed, although a few more tadalafil subjects compared to placebo experienced greater blood-pressure lowering at this time point. After 48 hours, the interaction was not detectable.
Therefore, Tadalafil administration with nitrates is contraindicated. In a patient who has taken Tadalafil, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of Tadalafil before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring [see Contraindications].
Effect on Blood Pressure When Administered with Alpha-Blockers
Six randomized, double-blinded, crossover clinical pharmacology studies were conducted to investigate the potential interaction of tadalafil with alpha-blocker agents in healthy male subjects [see Dosage and Mode/Route of Administration; Precautions]. In four studies, a single oral dose of tadalafil was administered to healthy male subjects taking daily (at least 7 days duration) an oral alpha-blocker. In two studies, a daily oral alpha-blocker (at least 7 days duration) was administered to healthy male subjects taking repeated daily doses of tadalafil.
Doxazosin: Three clinical pharmacology studies were conducted with tadalafil and doxazosin, an alpha [1] - adrenergic blocker.
In the first doxazosin study, a single oral dose of tadalafil 20 mg or placebo was administered in a 2-period, crossover design to healthy subjects taking oral doxazosin 8 mg daily (N=18 subjects). Doxazosin was administered at the same time as tadalafil or placebo after a minimum of seven days of doxazosin dosing.
Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after tadalafil or placebo administration. Outliers were defined as subjects with a standing systolic blood pressure of <85 mmHg or a decrease from baseline in standing systolic blood pressure of >30 mmHg at one or more time points. There were nine and three outliers following administration of tadalafil 20 mg and placebo, respectively. Five and two subjects were outliers due to a decrease from baseline in standing systolic BP of >30 mmHg, while five and one subject were outliers due to standing systolic BP <85 mmHg following tadalafil and placebo, respectively. Severe adverse events potentially related to blood-pressure effects were assessed. No such events were reported following placebo. Two such events were reported following administration of tadalafil. Vertigo was reported in one subject that began 7 hours after dosing and lasted about 5 days. This subject previously experienced a mild episode of vertigo on doxazosin and placebo. Dizziness was reported in another subject that began 25 minutes after dosing and lasted 1 day. No syncope was reported.
In the second doxazosin study, a single oral dose of tadalafil 20 mg was administered to healthy subjects taking oral doxazosin, either 4 or 8 mg daily. The study (N=72 subjects) was conducted in three parts, each a 3-period crossover.
In part A (N=24), subjects were titrated to doxazosin 4 mg administered daily at 8 a.m. Tadalafil was administered at either 8 a.m., 4 p.m., or 8 p.m. There was no placebo control.
In part B (N=24), subjects were titrated to doxazosin 4 mg administered daily at 8 p.m. Tadalafil was administered at either 8 a.m., 4 p.m., or 8 p.m. There was no placebo control.
In part C (N=24), subjects were titrated to doxazosin 8 mg administered daily at 8 a.m. In this part, tadalafil or placebo were administered at either 8 a.m. or 8 p.m.
Blood pressure was measured by ABPM every 15 to 30 minutes for up to 36 hours after tadalafil or placebo. Subjects were categorized as outliers if one or more systolic blood pressure readings of <85 mmHg were recorded or one or more decreases in systolic blood pressure of >30 mmHg from a time-matched baseline occurred during the analysis interval.
Of the 24 subjects in part C, 16 subjects were categorized as outliers following administration of tadalafil and 6 subjects were categorized as outliers following placebo during the 24-hour period after 8 a.m. dosing of tadalafil or placebo. Of these, 5 and 2 were outliers due to systolic BP <85 mmHg, while 15 and 4 were outliers due to a decrease from baseline in systolic BP of >30 mmHg following tadalafil and placebo, respectively.
During the 24-hour period after 8 p.m. dosing, 17 subjects were categorized as outliers following administration of tadalafil and 7 subjects following placebo. Of these, 10 and 2 subjects were outliers due to systolic BP <85 mmHg, while 15 and 5 subjects were outliers due to a decrease from baseline in systolic BP of >30 mmHg, following tadalafil and placebo, respectively.
Some additional subjects in both the tadalafil and placebo groups were categorized as outliers in the period beyond 24 hours.
Severe adverse events potentially related to blood-pressure effects were assessed. In the study (N=72 subjects), 2 such events were reported following administration of tadalafil (symptomatic hypotension in one subject that began 10 hours after dosing and lasted approximately 1 hour, and dizziness in another subject that began 11 hours after dosing and lasted 2 minutes). No such events were reported following placebo. In the period prior to tadalafil dosing, one severe event (dizziness) was reported in a subject during the doxazosin run-in phase.
In the third doxazosin study, healthy subjects (N=45 treated; 37 completed) received 28 days of once per day dosing of tadalafil 5 mg or placebo in a two-period crossover design. After 7days, doxazosin was initiated at 1 mg and titrated up to 4 mg daily over the last 21 days of each period (7 days on 1 mg; 7 days of 2 mg; 7 days of 4 mg doxazosin).
Blood pressure was measured manually pre-dose at two time points (-30 and -15 minutes) and then at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hours post dose on the first day of each doxazosin dose, (1 mg, 2 mg, 4 mg), as well as on the seventh day of 4 mg doxazosin administration.
Following the first dose of doxazosin 1 mg, there were no outliers on tadalafil 5 mg and one outlier on placebo due to a decrease from baseline in standing systolic BP of >30 mmHg.
There were 2 outliers on tadalafil 5 mg and none on placebo following the first dose of doxazosin 2 mg due to a decrease from baseline in standing systolic BP of >30 mmHg.
There were no outliers on tadalafil 5 mg and two on placebo following the first dose of doxazosin 4 mg due to a decrease from baseline in standing systolic BP of >30 mmHg. There was one outlier on tadalafil 5 mg and three on placebo following the first dose of doxazosin 4mg due to standing systolic BP <85 mmHg. Following the seventh day of doxazosin 4 mg, there were no outliers on tadalafil 5 mg, one subject on placebo had a decrease >30 mmHg in standing systolic blood pressure, and one subject on placebo had standing systolic blood pressure <85 mmHg. All adverse events potentially related to blood pressure effects were rated as mild or moderate. There were two episodes of syncope in this study, one subject following a dose of tadalafil 5 mg alone, and another subject following coadministration of tadalafil 5 mg and doxazosin 4 mg.
Tamsulosin: tamsulosin study, a single oral dose of tadalafil 10, 20 mg, or placebo was administered in a 3 period, crossover design to healthy subjects taking 0.4 mg once per day tamsulosin, a selective alpha[1A]- adrenergic blocker (N=18 subjects). Tadalafil or placebo was administered 2 hours after tamsulosin following a minimum of seven days of tamsulosin dosing.
Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after tadalafil or placebo dosing. There were 2, 2, and 1 outliers (subjects with a decrease from baseline in standing systolic blood pressure of >30 mmHg at one or more time points) following administration of tadalafil 10 mg, 20 mg, and placebo, respectively. There were no subjects with a standing systolic blood pressure <85 mmHg. No severe adverse events potentially related to blood-pressure effects were reported. No syncope was reported.
Healthy subjects (N=39 treated; and 35 completed) received 14 days of once per day dosing of tadalafil 5 mg or placebo in a two-period crossover design. Daily dosing of tamsulosin 0.4 mg was added for the last seven days of each period.
Blood pressure was measured manually pre-dose at two time points (-30 and -15 minutes) and then at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours post dose on the first, sixth and seventh days of tamsulosin administration. There were no outliers (subjects with a decrease from baseline in standing systolic blood pressure of >30 mmHg at one or more time points). One subject on placebo plus tamsulosin (Day 7) and one subject on tadalafil plus tamsulosin (Day 6) had standing systolic blood pressure <85 mmHg. No severe adverse events potentially related to blood pressure were reported. No syncope was reported.
Alfuzosin: A single oral dose of tadalafil 20 mg or placebo was administered in a 2-period, crossover design to healthy subjects taking once-daily alfuzosin HCl 10 mg extended-release tablets, an alpha[1]-adrenergic blocker (N=17 completed subjects). Tadalafil or placebo was administered 4 hours after alfuzosin following a minimum of seven days of alfuzosin dosing.
Blood pressure was measured manually at 1, 2, 3, 4, 6, 8, 10, 20, and 24 hours after tadalafil or placebo dosing. There was 1 outlier (subject with a standing systolic blood pressure <85mmHg) following administration of tadalafil 20 mg. There were no subjects with a decrease from baseline in standing systolic blood pressure of >30 mmHg at one or more time points. No severe adverse events potentially related to blood pressure effects were reported. No syncope was reported.
Effects on Blood Pressure When Administered with Antihypertensives
Amlodipine: A study was conducted to assess the interaction of amlodipine (5 mg daily) and tadalafil 10 mg. There was no effect of tadalafil on amlodipine blood levels and no effect of amlodipine on tadalafil blood levels. The mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking amlodipine was 3/2 mmHg, compared to placebo. In a similar study using tadalafil 20 mg, there were no clinically significant differences between tadalafil and placebo in subjects taking amlodipine.
Angiotensin II receptor blockers (with and without other antihypertensives): A study was conducted to assess the interaction of angiotensin II receptor blockers and tadalafil 20 mg. Subjects in the study were taking any marketed angiotensin II receptor blocker, either alone, as a component of a combination product, or as part of a multiple antihypertensive regimen. Following dosing, ambulatory measurements of blood pressure revealed differences between tadalafil and placebo of 8/4 mmHg in systolic/diastolic blood pressure.
Bendrofluazide: A study was conducted to assess the interaction of bendrofluazide (2.5 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking bendrofluazide was 6/4 mmHg, compared to placebo.
Enalapril: A study was conducted to assess the interaction of enalapril (10 to 20 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking enalapril was 4/1 mmHg, compared to placebo.
Metoprolol: A study was conducted to assess the interaction of sustained-release metoprolol (25 to 200 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking metoprolol was 5/3mmHg, compared to placebo.
Effects on Blood Pressure When Administered with Alcohol
Alcohol and PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. The interaction of tadalafil with alcohol was evaluated in 3 clinical pharmacology studies. In 2 of these, alcohol was administered at a dose of 0.7 g/kg, which is equivalent to approximately 6 ounces of 80-proof vodka in an 80-kg male, and tadalafil was administered at a dose of 10 mg in one study and 20 mg in another. In both these studies, all patients imbibed the entire alcohol dose within 10 minutes of starting. In one of these two studies, blood alcohol levels of 0.08% were confirmed. In these two studies, more patients had clinically significant decreases in blood pressure on the combination of tadalafil and alcohol as compared to alcohol alone. Some subjects reported postural dizziness, and orthostatic hypotension was observed in some subjects. When tadalafil 20 mg was administered with a lower dose of alcohol (0.6 g/kg, which is equivalent to approximately 4ounces of 80-proof vodka, administered in less than 10 minutes), orthostatic hypotension was not observed, dizziness occurred with similar frequency to alcohol alone, and the hypotensive effects of alcohol were not potentiated.
Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.
Effects on Exercise Stress Testing
The effects of tadalafil on cardiac function, hemodynamics, and exercise tolerance were investigated in a single clinical pharmacology study. In this blinded crossover trial, 23 subjects with stable coronary artery disease and evidence of exercise-induced cardiac ischemia were enrolled. The primary endpoint was time to cardiac ischemia. The mean difference in total exercise time was 3 seconds (tadalafil 10 mg minus placebo), which represented no clinically meaningful difference. Further statistical analysis demonstrated that tadalafil was non-inferior to placebo with respect to time to ischemia. Of note, in this study, in some subjects who received tadalafil followed by sublingual nitroglycerin in the post-exercise period, clinically significant reductions in blood pressure were observed, consistent with the augmentation by tadalafil of the blood-pressure-lowering effects of nitrates.
Effects on Vision
Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green), using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. In a study to assess the effects of a single dose of tadalafil 40 mg on vision (N=59), no effects were observed on visual acuity, intraocular pressure, or pupilometry. Across all clinical studies with tadalafil, reports of changes in color vision were rare (<0.1% of patients).
Effects on Sperm Characteristics
Three studies were conducted in men to assess the potential effect on sperm characteristics of tadalafil 10 mg (one 6 month study) and 20 mg (one 6 month and one 9 month study) administered daily. There were no adverse effects on sperm morphology or sperm motility in any of the three studies. In the study of 10 mg tadalafil for 6 months and the study of 20 mg tadalafil for 9 months, results showed a decrease in mean sperm concentrations relative to placebo, although these differences were not clinically meaningful. This effect was not seen in the study of 20 mg tadalafil taken for 6 months. In addition, there was no adverse effect on mean concentrations of reproductive hormones, testosterone, luteinizing hormone or follicle stimulating hormone with either 10 or 20 mg of tadalafil compared to placebo.
Effects on Cardiac Electrophysiology
The effect of a single 100-mg dose of tadalafil on the QT interval was evaluated at the time of peak tadalafil concentration in a randomized, double-blinded, placebo, and active (intravenous ibutilide)-controlled crossover study in 90 healthy males aged 18 to 53 years. The mean change in QT$_c$ (Fridericia QT correction) for tadalafil, relative to placebo, was 3.5 milliseconds (two-sided 90% CI=1.9, 5.1). The mean change in QT$_c$ (Individual QT correction) for tadalafil, relative to placebo, was 2.8 milliseconds (two-sided 90% CI=1.2, 4.4). A 100-mg dose of tadalafil (5 times the highest recommended dose) was chosen because this dose yields exposures covering those observed upon coadministration of tadalafil with potent CYP3A4 inhibitors or those observed in renal impairment. In this study, the mean increase in heart rate associated with a 100-mg dose of tadalafil compared to placebo was 3.1 beats per minute.

TAMSULOSIN HYDROCHLORIDE
Urologic pharmacodynamic effects have been evaluated in neurologically impaired pediatric patients and in adults with BPH.
Neurologically Impaired Pediatric Patients
Efficacy and positive benefit/risk of tamsulosin hydrochloride was not demonstrated in two studies conducted in patients 2 years to 16 years of age with elevated detrusor leak point pressure (>40 cm H_2O) associated with known neurological disorder (e.g., spina bifida). Patients in both studies were treated on a weight-based mg/kg schema (0.025 mg, 0.05 mg, 0.1 mg, 0.2 mg, or 0.4 mg tamsulosin hydrochloride) for the reduction in detrusor leak point pressure below 40 cm H_2O.
In a randomized, double-blind, placebo-controlled, 14-week, pharmacokinetic, safety and efficacy study in 161 patients,

no statistically significant difference in the proportion of responders was observed between groups receiving tamsulosin hydrochloride and placebo. In an open-label, 12-month safety study, 87 patients were treated with tamsulosin hydrochloride. The most frequently reported adverse events (≥5%) from the pooled data of both studies were urinary tract infection, vomiting, pyrexia, headache, nasopharyngitis, cough, pharyngitis, influenza, diarrhea, abdominal pain, and constipation.

Adults with BPH

Four placebo-controlled clinical studies and one active-controlled clinical study enrolled a total of 2296 patients (1003 received tamsulosin capsules 0.4 mg once daily, 491 received tamsulosin capsules 0.8 mg once daily, and 802 were control patients) in the U.S. and Europe.

In the two U.S. placebo-controlled, double-blind, 13-week, multicenter studies, 1486 men with the signs and symptoms of BPH were enrolled. In both studies, patients were randomized to either placebo, tamsulosin capsules 0.4 mg once daily, or tamsulosin capsules 0.8 mg once daily. Patients in tamsulosin capsules 0.8 mg once-daily treatment groups received a dose of 0.4 mg once daily for one week before increasing to the 0.8 mg once-daily dose. The primary efficacy assessments included: 1) total American Urological Association (AUA) Symptom Score questionnaire, which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms, where a decrease in score is consistent with improvement in symptoms; and 2) peak urine flow rate, where an increased peak urine flow rate value over baseline is consistent with decreased urinary obstruction.

Mean changes from baseline to Week 13 in total AUA Symptom Score were significantly greater for groups treated with tamsulosin capsules 0.4 mg and 0.8 mg once daily compared to placebo in both U.S. studies. The changes from baseline to Week 13 in peak urine flow rate were also significantly greater for the tamsulosin capsules 0.4 mg and 0.8 mg once-daily groups compared to placebo in Study 1, and for the tamsulosin capsules 0.8 mg once-daily group in Study 2.

Overall there were no significant differences in improvement observed in total AUA Symptom Scores or peak urine flow rates between the 0.4 mg and the 0.8 mg dose groups with the exception that the 0.8 mg dose in Study 1 had a significantly greater improvement in total AUA Symptom Score compared to the 0.4 mg dose.

Mean total AUA Symptom Scores for both Tamsulosin capsules 0.4 mg and 0.8 mg once-daily groups showed a rapid decrease starting at 1 week after dosing and remained decreased through 13 weeks in both studies. In Study 1, 400 patients (53% of the originally randomized group) elected to continue in their originally assigned treatment groups in a double-blind, placebo-controlled, 40-week extension trial (138 patients on 0.4 mg, 135 patients on 0.8 mg, and 127 patients on placebo). Three hundred twenty-three patients (43% of the originally randomized group) completed one year. Of these, 81% (97 patients) on 0.4 mg, 74% (75 patients) on 0.8 mg, and 56% (57 patients) on placebo had a response ≥25% above baseline in total AUA Symptom Score at one year.

【Pharmacokinetics】

TADALAFIL

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Steady-state plasma concentrations are attained within 5 days of once per day dosing and exposure is approximately 1.6-fold greater than after a single dose.

Absorption

After single oral-dose administration, the maximum observed plasma concentration(C_{max}) of tadalafil is achieved between 30 minutes and 6 hours (median time of 2 hours). Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food; thus tadalafil may be taken with or without food.

Distribution

The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins.

Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Metabolism

Tadalafil is predominantly metabolized by CYP3A4 isoform to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. *In vitro* data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Excretion

The mean oral clearance for tadalafil is 2.5 L/hr and the mean terminal half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36%of the dose).

Geriatrics

Healthy male elderly subjects (65 years or over), had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) with no effect on C_{max} relative to that observed in healthy subjects 19 to 45 years of age. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered.

Patients with Diabetes Mellitus

In male patients with diabetes mellitus after a 10 mg tadalafil dose, exposure (AUC) was reduced approximately 19% and C_{max} was 5% lower than that observed in healthy subjects. No dose adjustment is warranted.

Patients with BPH

In patients with BPH following single and multiple-dose of 20 mg tadalafil, no statistically significant differences in exposure (AUC and C_{max}) were observed between elderly (70 to 85 years) and younger (≤60 years of age) subjects. No dose adjustment is warranted.

TAMSULOSIN HYDROCHLORIDE

The pharmacokinetics of tamsulosin hydrochloride 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 hydrochloride capsule 0.4 mg is essentially complete (>90%) following oral administration under fasting conditions. Tamsulosin hydrochloride 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 4 to 5 hours under fasting conditions and by 6 to 7 hours when tamsulosin hydrochloride capsules are administered with food. Taking tamsulosin hydrochloride capsules 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 hydrochloride after intravenous administration to 10 healthy male adults was 16 L, which is suggestive of distribution into extracellular fluids in the body.

Tamsulosin hydrochloride 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 hydrochloride 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 hydrochloride had no effect on the extent of binding of these drugs.

Metabolism

There is no enantiomeric bioconversion from tamsulosin hydrochloride [R(-) isomer] to the S(+) isomer in humans. Tamsulosin hydrochloride 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. Tamsulosin is extensively metabolized, mainly by CYP3A4 and CYP2D6 as well as via some minor participation of other CYP isoenzymes. Inhibition of hepatic drug-metabolizing enzymes may lead to increased exposure to tamsulosin [see Precautions; Interactions]. The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Incubations with human liver microsomes showed no evidence of clinically significant metabolic interactions between tamsulosin hydrochloride and amitriptyline, albuterol (beta agonist), glyburide (glibenclamide) and finasteride (5-alpha-reductase inhibitor for treatment of BPH). However, results of the *in vitro* testing of the tamsulosin hydrochloride interaction with diclofenac and warfarin were equivocal.

Excretion

On administration of the radiolabeled dose of tamsulosin hydrochloride to 4 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 hydrochloride in plasma ranged from 5 to 7 hours. Because of absorption rate-controlled pharmacokinetics with tamsulosin hydrochloride capsules, the apparent half-life of tamsulosin hydrochloride is approximately 9 to 13 hours in healthy volunteers and 14 to 15 hours in the target population.

Tamsulosin hydrochloride undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h).

Pediatric Use

Tamsulosin hydrochloride capsules are not indicated for use in pediatric populations.

Geriatric (age) use

Cross-study comparison of tamsulosin hydrochloride capsules overall exposure (AUC) and half-life indicates 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.

Renal Impairment

The pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate (30≤ CL_{cr} ≤70 mL/min/1.73 m^2) or moderate-severe (10≤ CL_{cr} ≤30 mL/min/1.73 m^2) renal impairment and 6 normal subjects (CL_{cr} >90 mL/min/1.73 m^2). While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in tamsulosin hydrochloride capsules dosing. However, patients with end-stage renal disease (CL_{cr} <10 mL/min/1.73 m^2) have not been studied.

Hepatic Impairment

The pharmacokinetics of tamsulosin hydrochloride have been compared in 8 subjects with moderate hepatic impairment (Child-Pugh's classification: Grades A and B) and 8 normal subjects. While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride does not change significantly, with only a modest (32%) change in intrinsic clearance of unbound tamsulosin hydrochloride. Therefore, patients with moderate hepatic impairment do not require an adjustment in tamsulosin hydrochloride capsules dosage. Tamsulosin hydrochloride capsules has not been studied in patients with severe hepatic impairment.

【Therapeutic indication(s)】

Gugutams is indicated for the treatment of Erectile Dysfunction (ED) and Benign Prostatic Hyperplasia (BPH) as a substitution for co-administration of Tadalafil and Tamsulosin hydrochloride.

The therapeutic indication for each active ingredient of Gugutams is as follows.

TADALAFIL

- Tadalafil is indicated for the treatment of erectile dysfunction (ED).
- Tadalafil is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).
- Tadalafil is indicated for the treatment of ED and the signs and symptoms of BPH (ED/BPH).
- If Tadalafil is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of Tadalafil decreases from 4 weeks until 26 weeks, and the incremental benefit of Tadalafil beyond 26 weeks is unknown.

TAMSULOSIN HYDROCHLORIDE

- Tamsulosin hydrochloride is indicated for the treatment of the signs and symptoms of BPH.
- Tamsulosin hydrochloride is not indicated for the treatment of hypertension.

【Dosage and Mode/Route of Administration】

For medication convenience, male adult patients who have been on concomitant treatment with Tadalafil 5 mg and Tamsulosin hydrochloride 400 mcg may be switched to this drug (a fixed dose combination therapy containing the same doses of the individual active ingredients) to be administered once daily after meal.

Administer Gugutams orally around the same time of each day, regardless of time of sexual activity.

Eligibility for therapy should be periodically re-evaluated or as prescribed by the physician. This drug should be swallowed whole and should not be crushed or chewed.

The dosage and administration for each active ingredient of Gugutams is as follows.

TADALAFIL

Tadalafil for Once Daily Use for Erectile Dysfunction

The recommended dose is 5 mg taken once a day at approximately the same time every day.

Tadalafil for Once Daily Use for Benign Prostatic Hyperplasia

The recommended dose of Tadalafil for once daily use is 5 mg, taken at approximately the same time every day.

When therapy for BPH is initiated with Tadalafil and finasteride, the recommended dose of Tadalafil for once daily use is 5 mg, taken at approximately the same time every day for up to 26 weeks.

Tadalafil for Once Daily Use for Erectile Dysfunction and Benign Prostatic Hyperplasia

The recommended dose of Tadalafil for once daily use is 5 mg, taken at approximately the same time every day, without regard to timing of sexual activity.

Use with Food

Tadalafil may be taken without regard to food.

Use in Specific Populations

Renal impairment: Erectile Dysfunction: Creatinine clearance less than 30 mL/min or on hemodialysis: Tadalafil for once daily use is not recommended.

Benign Prostatic Hyperplasia and Erectile Dysfunction/Benign Prostatic Hyperplasia: Creatinine clearance less than 30 mL/min to 50 mL/min: Use of 5 mg may be considered based on individual response.

Creatinine clearance less than 30 mL/min or on hemodialysis: Tadalafil for once daily use is not recommended.

Hepatic Impairment: Mild or moderate (Child Pugh Class A or B): Tadalafil for once daily use has not been extensively evaluated in patients with hepatic impairment. Therefore, caution is advised if Tadalafil for once daily use is prescribed to these patients.

Severe (Child Pugh Class C): The use of Tadalafil is not recommended.

Geriatric Use: No dose adjustment is warranted based on age alone. However, a greater sensitivity to medications in some older individuals should be considered.

Pediatric Use: Tadalafil is not indicated for use in pediatric patients. Safety and efficacy in patients below the age of 18 years have not been established.

Concomitant Medications

Alpha-Blockers: ED: When Tadalafil is co-administered with an alpha-blocker in patients being treated for ED, patients should be stable on alpha-blocker therapy prior to initiating treatment, and Tadalafil should be initiated at the lowest recommended dose.

BPH: Tadalafil is not recommended for use in combination with alpha-blockers for the treatment of BPH.

CYP3A4 Inhibitors: For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, use of 5 mg Tadalafil is not recommended.

TAMSULOSIN HYDROCHLORIDE

Tamsulosin hydrochloride capsules 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. Tamsulosin hydrochloride capsules should not be crushed, chewed or opened.

For those patients who fail to respond to the 0.4 mg dose after 2 to 4 weeks of dosing, the dose of Tamsulosin hydrochloride capsules can be increased to 0.8 mg once daily. Tamsulosin hydrochloride capsules 0.4 mg should not be used in combination with strong inhibitors of CYP3A4 (e.g. ketoconazole)

If Tamsulosin hydrochloride capsules 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.

【Contraindications】

1) Patient with a history of hypersensitivity reactions (including angioedema) to this drug or any of its components.
2) Patient with severe hepatic impairment
3) Man with cardiac disease because of which sexual activity is not recommended
   - Drugs for the treatment of erectile dysfunction, including this drug, should not be used for men with cardiac diseases because of which sexual activity is not recommended. The physician should consider potential cardiac risk of sexual activity in patients with preexisting cardiovascular diseases.
4) This drug is contraindicated in the following patients with cardiovascular diseases because these populations were not included in clinical trials:
   - Patient with a history of myocardial infarction within the past 90 days
   - Patients with unstable angina or with a history of angina during sexual intercourse.
   - Patient with a history of New York Heart Association Class 2 or above heart failure within the past 6 months
   - Patient with uncontrolled arrhythmias, hypotension (<90/50mmHg), or uncontrolled hypertension (>170/100mmHg)
   - Patient with orthostatic hypotension
   - Patient with a history of stroke within the past 6 months
5) Patient with known inherited retinal degenerative disease including pigmentary retinitis
   - This drug is not recommended for this population because these patients were not included in clinical trials.
6) Co-administration of this drug with other erectile dysfunction therapy is not recommended because the safety and efficacy of this concomitant administration have not been studied.
7) Co-administration of this drug with other $alpha_1$-blockers is not recommended because the safety and efficacy of this concomitant administration have not been studied.
8) Because this drug contains lactose, it is contraindicated in patients with hereditary problems such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.
9) Patient with loss of vision in one eye caused by non-arthritic anterior ischemic optic neuropathy (NAION), regardless of prior treatment with PDE5 inhibitors

TADALAFIL

Nitrates

Administration of Tadalafil to patients, who are using any form of organic nitrate, either regularly and/or intermittently, is contraindicated. In clinical pharmacology studies, Tadalafil was shown to potentiate the hypotensive effect of nitrates [see Pharmacology; Pharmacodynamics].

Hypersensitivity Reactions

Tadalafil is contraindicated in patients with known serious hypersensitivity to Tadalafil. Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis [see Adverse Reactions].

Concomitant Guanylate Cyclase (GC) Stimulators

Do not use Tadalafil in patients who are using a GC stimulator. PDE5 inhibitors, including Tadalafil, may potentiate the hypotensive effects of GC stimulators.

TAMSULOSIN HYDROCHLORIDE

Tamsulosin hydrochloride capsules are contraindicated in patients known to be hypersensitive to tamsulosin hydrochloride or any component of the tamsulosin hydrochloride capsules. Reactions have included skin rash, urticaria, pruritus, angioedema, and respiratory symptoms [see Adverse Reactions].

【Precautions】

1) Treatment with this drug should be preceded by appropriate medical evaluation of erectile dysfunction and benign prostatic hyperplasia along with assessment of potential and underlying causes and appropriate therapeutic options as well as consideration of cautions, contraindications, and careful treatment sections.
2) Because of cardiac risk associated with sexual activity, the physician should consider the cardiovascular status of the patient before initiating treatment for erectile dysfunction. A patient who experiences cardiovascular disease related symptoms after initiation of sexual activity should refrain from further sexual activity and notify the physician.
3) Prolonged erections and priapism (erections with pain lasting for ≥6 hours) were rarely reported with phosphodiesterase type 5 (PDE5) inhibitors. The patient should be instructed to immediately seek medical assistance if he experiences an erection lasting for ≥4 hours. Without immediate treatment, priapism may result in damage to

penile tissues and permanent loss of erectile function.

4) Administration of any nitrates or NO donors (nitroglycerin, amyl nitrate, isosorbide dinitrate) before, during, or after treatment with this drug may result in excessive reduction in blood pressure due to enhanced blood pressure lowering effects. The physician should ensure that the patient did not administer nitrates or NO donors before prescribing this drug and should instruct the patient not to administer nitrates or NO donors during and after treatment with this drug.
5) Serious cardiovascular events including myocardial infarction, acute cardiac arrest, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitation, and tachycardia were reported in clinical trials and/or post-marketing surveillance (PMS) of Tadalafil. In addition, hypertension and hypotension (including postural hypotension) were also rarely observed in Tadalafil clinical trials. The majority of patients with these adverse events had preexisting cardiovascular risk factors. However, it remained unclear whether these adverse events were directly associated with cardiovascular factors or Tadalafil or sexual activity or a combination of these factors or other factors.
6) This drug is to be administered to patients who have been on stable treatment with Tamsulosin hydrochloride and Tadalafil and is not to be used for patients who have experienced hemodynamic instability, such as symptomatic hypotension, during concomitant treatment with alpha blockers and PDE5 inhibitors. For patients who experience orthostatic hypotension during treatment with this drug, this drug should be stopped and appropriate measures should be taken for blood pressure control. For the treatment of benign prostatic hyperplasia and erectile dysfunction, the physician should prescribe an appropriate drug through re-assessment of both diseases and patient consultation, based on the medical judgment that there is no concern over hypotension. Subsequently, the physician should consider potential risk of hypotension for the patient.
7) According from clinical trial, after administration of Tadalafil to dogs once daily for six (6) to twelve (12) months at a dose of ≥25mg/kg/day (resulting in >3 folds the exposures observed in humans given a single dose of 20 mg [ranging 3.7~18.6]), some of the dogs indicated regression of seminiferous tubular epithelium, resulting in reduced spermatogenesis.
   To evaluate the potential impact of Tadalafil on spermatogenesis, three (3) clinical trials were conducted in men who were treated with this drug at a daily dose of 10 mg for six (6) months or 20 mg for six (6) or nine (9) months. Of these, in two trials, reduced sperm counts and concentrations were observed, which appeared to have no clinical relevance to Tadalafil treatment. There were no changes in other parameters such as motility and morphology of sperms or follicle stimulating hormones (see Pharmacology; Pharmacodynamics)
8) Patients with left ventricular outflow obstruction (e.g., aortic stenosis and idiopathic hypertrophic sub aortic stenosis) may be sensitive to vasodilators including PDE5 inhibitors.

TADALAFIL

Evaluation of erectile dysfunction and BPH should include an appropriate medical assessment and to identify potential underlying causes, as well as treatment options.

Before prescribing Tadalafil, it is important to note the following.

Cardiovascular

Physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Therefore, treatments for erectile dysfunction, including Tadalafil should not be used in men for whom sexual activity is inadvisable as a result of their underlying cardiovascular status. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and seek immediate medical attention.

Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of Tadalafil. In such a patient, who has taken Tadalafil, where nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of Tadalafil before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Therefore, patients who experience anginal chest pain after taking Tadalafil should seek immediate medical attention [see Contraindications].

Patients with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) can be sensitive to the action of vasodilators, including PDE5 inhibitors.

The following groups of patients with cardiovascular disease were not included in clinical safety and efficacy trials for Tadalafil, and therefore until further information is available, Tadalafil is not recommended for the following groups of patients: myocardial infarction within the last 90 days; unstable angina or angina occurring during sexual intercourse; New York Heart Association Class 2 or greater heart failure in the last 6 months; uncontrolled arrhythmias, hypotension (<90/50 mmHg), or uncontrolled hypertension; stroke within the last 6 months.

As with other PDE5 inhibitors, tadalafil has mild systemic vasodilatory properties that may result in transient decreases in blood pressure. In a clinical pharmacology study, tadalafil 20 mg resulted in a mean maximal decrease in supine blood pressure, relative to placebo, of 1.6/0.8 mmHg in healthy subjects. While this effect should not be of consequence in most patients, prior to prescribing Tadalafil, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.

TAMSULOSIN HYDROCHLORIDE

Orthostatis

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

Priapism

Rarely (probably less than 1 in 50,000 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.

Screening for Prostate Cancer

Prostate cancer and BPH frequently coexist; therefore, patients should be screened for the presence of prostate cancer prior to treatment with Tamsulosin capsules and at regular intervals afterwards.

Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract and glaucoma surgery in some patients on or previously treated with alpha$_1$ blockers, including Tamsulosin capsules [see Adverse Reactions].

Most reports were in patients taking the alpha$_1$ blocker when IFIS occurred, but in some cases, the alpha$_1$ blocker had been stopped prior to surgery. In most of these cases, the alpha$_1$ blocker had been stopped recently prior to surgery (2 to 14 days), but in a few cases, IFIS was reported after the patient had been off the alpha$_1$ blocker for a longer period (5 weeks to 9 months). IFIS is a variant of small pupil syndrome and is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs and potential prolapse of the iris toward the phacoemulsification incisions. The patient's ophthalmologist should be prepared for possible modifications to their surgical technique, such as the utilization of iris hooks, iris dilator rings, or viscoelastic substances.

IFIS may increase the risk of eye complications during and after the operation. The benefit of stopping alpha$_1$ blocker therapy prior to cataract or glaucoma surgery has not been established. The initiation of therapy with tamsulosin in patients for whom cataract or glaucoma surgery is scheduled is not recommended.

Sulfa Allergy

In patients with sulfa allergy, allergic reaction to Tamsulosin capsules has been rarely reported. If a patient reports a serious or life-threatening sulfa allergy, caution is warranted when administering Tamsulosin capsules.

【General Precautions】

TADALAFIL

1) In the event of sudden loss of vision in (one or both) eye(s) of the patient, the physician should recommend that the patient should stop treatment with PDE5 inhibitors including Tadalafil and should provide medical care. This symptom can be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a rare disease that may cause decreased visual acuity including permanent loss of vision, which was rarely reported in post-marketing surveillance and was considered potentially relevant. According to the published literature, annual incidence of NAION is 2.5-11.8 events per 100,000 men at the age of 50 or older. Results from an observational study to evaluate the relationship between recent use of PDE5 inhibitors and acute onset of NAION indicated that the risk of developing NAION was approximately two-fold higher within 5 half-lives of PDE5 inhibitors post-dose. These data did not prove whether these adverse events were directly associated with treatment with PDE5 inhibitors or other factors. The physician should consider if patients with preexisting NAION risk factors are susceptible to adverse effects due to treatment with PDE5 inhibitors. An individual who has experienced NAION is at a higher risk of recurrence of NAION. PDE5 inhibitors including this drug should to be administered to these patients with caution and only if expected benefits outweigh risks [See Adverse Reactions].
2) Tadalafil has not been administered to patients with bleeding disorders or active peptic ulcer. Although Tadalafil has not prolonged bleeding time in healthy volunteers, caution should be exercised and benefit/risk assessment should be performed when this drug is to be administered to patients with bleeding disorders or active peptic ulcer.
3) Since both Tadalafil and alcohol are minor vasodilators, co-administration of both may enhance blood pressure lowering effects. The physician should inform the patient that consumption of a large amount of alcohol concomitantly with this drug may result in orthostatic signs and symptoms such as increased heart rate, decreased blood pressure, dizziness, and headache.
4) In the event of sudden hearing decrease or hearing loss (with or without tinnitus and vertigo), the physician should recommend that the patient should discontinue PDE5 inhibitors including Tadalafil and should immediately provide medical care [see Adverse Reactions].
5) Tadalafil 5 mg once daily regimen has not been clinically used for more than 2 years and 6 months (for Tadalafil 5 mg monotherapy only).
6) Other urological conditions to be considered before initiation of benign prostatic hyperplasia treatment: Before treating benign prostatic hyperplasia with this drug, other urological conditions that may manifest similar symptoms should be considered. Additionally, prostate cancer and benign prostatic hyperplasia may occur concurrently.

TAMSULOSIN HYDROCHLORIDE

1) Tamsulosin hydrochloride overdose is expected to decrease blood pressure. Care should be taken for appropriate dose.
2) Standing up may lead to decreased blood pressure. Care should be taken for blood pressure change following postural change.
3) It should be noted that Tamsulosin hydrochloride is not a causal treatment but a symptomatic therapy. If expected effects are not obtained from Tamsulosin hydrochloride, other appropriate treatments such as surgery should be considered.
4) The patient may experience dizziness. Individuals whose work involves certain risks, such as working at a higher place or driving, should be reminded.
5) Antigenicity was reported in protein binding in animal experiments.
6) Because prostate cancer and prostatic hyperplasia manifest similar symptoms and occasionally occur concurrently, the patient should be assessed for prostate cancer before treatment with Tamsulosin hydrochloride.
7) The risk of fainting is comparable with that of other alpha-blockers.
8) As with other alpha$_1$-blockers, Tamsulosin hydrochloride is rarely associated with priapism. The physician should inform the patient of the seriousness of the status of prolonged erection which, without immediate treatment, may result in permanent loss of erectile function.
9) IFIS was observed during cataract or glaucoma operations in some patients who were being treated with or had previously been treated with alpha$_1$-blockers. The ophthalmologist should be prepared for possible alteration to routine surgical methods using iris hook, iris dilator ring, or viscoelastic substance.
10) Patient with a history of allergic reactions to sulfonamide (cases of allergic reactions to Tamsulosin hydrochloride have been reported. If a patient has experienced allergic reactions to sulfa drugs, caution should be exercised for treatment with this drug).

【Pregnancy and Lactation】

TADALAFIL

Pregnancy

Risk Summary: Tadalafil is not indicated for use in females.

There are no data with the use of Tadalafil in pregnant women to inform any drug-associated risks for adverse developmental outcomes. In animal reproduction studies, no adverse developmental effects were observed with oral administration of tadalafil to pregnant rats or mice during organogenesis at exposures up to 11 times the maximum recommended human dose (MRHD) of 20 mg/day.

Data: Animal Data: Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at exposures up to 11 times the maximum recommended human dose (MRHD) of 20 mg/day during organogenesis. In a prenatal/postnatal developmental study in rats, postnatal pup survival decreased following maternal exposure to tadalafil doses greater than 10 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 16 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.

In another rat prenatal and postnatal development study at doses of 60, 200, and 1000 mg/kg, a reduction in postnatal survival of pups was observed. The no observed effect level (NOEL) for maternal toxicity was 200 mg/kg/day and for developmental toxicity was 30 mg/kg/day. This gives approximately 16 and 10 fold exposure multiples, respectively, of the human AUC for the MRHD of 20 mg.

Tadalafil and/or its metabolites cross the placenta, resulting in fetal exposure in rats.

Lactation

Risk Summary: Tadalafil is not indicated for use in females.

There is no information on the presence of tadalafil and/or metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Tadalafil and/or its metabolites are present in the milk of lactating rats at concentrations approximately 2.4-fold greater than found in the plasma.

Females and Males of Reproductive Potential

Infertility: Based on the data from 3 studies in adult males, tadalafil decreased sperm concentrations in the study of 10 mg tadalafil for 6 months and the study of 20 mg tadalafil for 9 months. This effect was not seen in the study of 20 mg tadalafil taken for 6 months. There was no adverse effect of tadalafil 10 mg or 20 mg on mean concentrations of testosterone, luteinizing hormone or follicle stimulating hormone. The clinical significance of the decreased sperm concentrations in the two studies is unknown. There have been no studies evaluating the effect of tadalafil on fertility in men.

Based on studies in animals, a decrease in spermatogenesis was observed in dogs, but not in rats.

TAMSULOSIN HYDROCHLORIDE

Pregnancy

Risk Summary: Tamsulosin capsule is not indicated for use in women. There are no adequate data on the developmental risk associated with the use of Tamsulosin capsule in pregnant women. No adverse developmental effects were observed in animal studies in which tamsulosin hydrochloride was administered to rats or rabbits during the period of organogenesis (GD 7 to 17 in the rat and GD 6 to 18 in the rabbit).

In the U.S. general population, the estimated background risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Data: Administration of tamsulosin hydrochloride to pregnant female rats during the period of organogenesis at dose levels up to approximately 50 times the human therapeutic AUC exposure (300 mg/kg/day) revealed no evidence of harm to the fetus. Administration of tamsulosin hydrochloride to pregnant rabbits during the period of organogenesis at dose levels up to 50 mg/kg/day produced no evidence of fetal harm.

Lactation

Tamsulosin capsule is not indicated for use in women. There are no data on the presence of tamsulosin hydrochloride in human milk, the effects of tamsulosin hydrochloride on the breastfed infant, or the effects of tamsulosin hydrochloride on milk production. Tamsulosin hydrochloride is present in the milk of lactating rats.

Data: Oral administration of radiolabeled tamsulosin hydrochloride to rats demonstrated that tamsulosin hydrochloride and/or its metabolites are excreted into the milk of rats.

Females and Males of Reproductive Potential

Infertility: Males: Abnormal ejaculation including ejaculation failure, ejaculation disorder, retrograde ejaculation, and ejaculation decrease has been associated with Tamsulosin capsule [see Adverse Reactions]. Studies in rats revealed significantly reduced fertility in males considered to be due to impairment of ejaculation, which was reversible.

Females: Tamsulosin capsule is not indicated for use in women. Female fertility in rats was significantly reduced, considered to be due to impairment of fertilization.

【Interactions】

When the active ingredients of this drug, i.e. Tamsulosin hydrochloride 0.4 mg and Tadalafil 5 mg, were administered to healthy volunteers in a drug interaction study, no clinically significant pharmacokinetic interaction were observed. When the potential development of orthostatic hypotension was evaluated in healthy male adults in this clinical trial, orthostatic hypotension was reported in 46.67% (14/30 subjects, 16 events (7 events in the Tamsulosin hydrochloride/Tadalafil 0.4/5mg group, 4 events in the Tadalafil 5 mg group, 5 events in the Tamsulosin hydrochloride 0.4 mg group)).

The physician should provide the patient with appropriate clinical advice for potential development of orthostatic hypotension.

No drug-drug interaction studies were conducted between other drugs and Tamsulosin hydrochloride/Tadalafil fixed-combination therapy. However, Tamsulosin hydrochloride and Tadalafil were individually studied as follows.

TADALAFIL

Potential for Pharmacodynamic Interactions with Tadalafil

Nitrates: Administration of Tadalafil to patients who are using any form of organic nitrate is contraindicated. In clinical pharmacology studies, Tadalafil was shown to potentiate hypotensive effect of nitrates. In a patient who has taken Tadalafil, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapsed after the last dose of Tadalafil before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring [see Contraindications; Pharmacology].

Alpha-Blockers: Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including Tadalafil, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, tamsulosin or alfuzosin [see Dosage and Mode/Route of Administration; Precautions; Pharmacology].

Anti-hypertensives: PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo [see Precautions; Pharmacology].

Alcohol: Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g. 5 units or greater) in combination with Tadalafil can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness and headache. Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations [see Precautions; Pharmacology].

Potential for Other Drugs to Affect Tadalafil

Antacids: Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil.

H_2 Antagonists (e.g. Nizatidine): An increase in gastric pH resulting from administration of nizatidine had no significant effect on pharmacokinetics.

Cytochrome P450 Inhibitors: Tadalafil is a substrate of and predominantly metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase tadalafil exposure.

CYP3A4 (e.g., Ketoconazole): Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4, increased tadalafil 20 mg single-dose exposure (AUC) by 312% and C_{max} by 22%, relative to the values for tadalafil 20 mg alone. Ketoconazole (200 mg daily) increased tadalafil 10-mg single-dose exposure (AUC) by 107% and C_{max} by 15%, relative to the values for tadalafil 10 mg alone [see Dosage and Mode/Route of Administration].

Although specific interactions have not been studied, other CYP3A4 inhibitors, such as erythromycin, itraconazole, and grapefruit juice, would likely increase tadalafil exposure.

HIV Protease inhibitor: Ritonavir (500 mg or 600 mg twice daily at steady state), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil 20 mg single-dose exposure (AUC) by 32% with a 30% reduction in C_{max}, relative to the values for tadalafil 20 mg alone. Ritonavir (200 mg twice daily), increased tadalafil 20 mg single-dose exposure (AUC) by 124% with no change in C_{max}, relative to the values for tadalafil 20 mg alone. Although specific interactions have not been studied, other HIV protease inhibitors would likely increase tadalafil exposure [see Dosage and Mode/Route of Administration].

Cytochrome P450 inducers: Studies have shown that drugs that induce CYP3A4 can decrease tadalafil exposure.

CYP3A4 (e.g. Rifampicin): Rifampicin (600 mg daily), a CYP3A4 inducer, reduced tadalafil 10-mg-single-dose exposure (AUC) by 88% and C_{max} by 46%, relative to the values for tadalafil 10 mg alone. Although specific interactions have not been studied, other CYP3A4 inducers such as carbamazepine, phenytoin and phenobarbital, would likely decrease tadalafil exposure. No dose adjustment is warranted. The reduced exposure of tadalafil with the coadministration of rifampicin or other CYP3A4 inducers can be anticipated to decrease the efficacy of tadalafil for once daily use; the magnitude of decreased efficacy is unknown.

Potential for Tadalafil to Affect Other Drugs

Aspirin: Tadalafil did not potentiate the increase in bleeding time caused by aspirin.

Cytochrome P450 Substrates: Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms. Studies have shown that tadalafil does not inhibit or induce P450 isoforms CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

CYP1A2 (e.g. Theophylline): Tadalafil had no significant effect on the pharmacokinetics of theophylline. When tadalafil was administered to subjects taking theophylline, a small augmentation (3 beats per minute) of the increase in heart rate associated with theophylline was observed.

CYP2C9 (e.g. Warfarin): Tadalafil had no significant effect on exposure (AUC) to S-warfarin or R-warfarin, nor did tadalafil affect changes in prothrombin time induced by warfarin.

CYP3A4 (e.g. Midazolam or Lovastatin): Tadalafil had no significant effect on exposure (AUC) to midazolam or lovastatin.

P-glycoprotein (e.g. Digoxin): Coadministration of tadalafil (40 mg once per day) for 10 days did not have a significant effect on the steady-state pharmacokinetics of digoxin (0.25 mg/day) in healthy subjects.

TAMSULOSIN HYDROCHLORIDE

Cytochrome P450 Inhibition

Strong and Moderate Inhibitors of CYP3A4 or CYP2D6: Tamsulosin is extensively metabolized, mainly by CYP3A4 and CYP2D6.

Concomitant treatment with ketoconazole (a strong inhibitor of CYP3A4) resulted in an increase in the C_{max} and AUC of tamsulosin by a factor of 2.2 and 2.8, respectively [see Precautions; Pharmacology]. The effects of concomitant administration of a moderate CYP3A4 inhibitor (e.g., erythromycin) on the pharmacokinetics of tamsulosin capsule have not been evaluated [see Precautions; Pharmacology].

Concomitant treatment with paroxetine (a strong inhibitor of CYP2D6) resulted in an increase in the C_{max} and AUC of tamsulosin by a factor of 1.3 and 1.6, respectively [see Precautions; Pharmacology]. A similar increase in exposure is expected in CYP2D6 poor metabolizers (PM) as compared to extensive metabolizers (EM). Since CYP2D6 PMs cannot be readily identified and the potential for significant increase in tamsulosin exposure exists when tamsulosin capsule 0.4 mg is coadministered with strong CYP3A4 inhibitors in CYP2D6 PMs, tamsulosin capsules 0.4 mg should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole) [see Precautions; Pharmacology].

The effects of concomitant administration of a moderate CYP2D6 inhibitor (e.g., terbinafine) on the pharmacokinetics of tamsulosin capsule have not been evaluated [see Precautions; Pharmacology].

The effects of coadministration of both a CYP3A4 and a CYP2D6 inhibitor with tamsulosin capsules have not been evaluated. However, there is a potential for significant increase in tamsulosin exposure when tamsulosin capsule 0.4 mg is coadministered with a combination of both CYP3A4 and CYP2D6 inhibitors [see Precautions; Pharmacology].

Cimetidine: 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%) [see Precautions; Pharmacology].

Other Alpha Adrenergic Blocking Agents

The pharmacokinetic and pharmacodynamic interactions between tamsulosin capsules and other alpha adrenergic blocking agents have not been determined; however, interactions between tamsulosin capsules and other alpha adrenergic blocking agents may be expected [see Precautions; Pharmacology].

PDE5 Inhibitors

Caution is advised when alpha adrenergic blocking agents including tamsulosin capsule are coadministered with PDE5 inhibitors. Alpha-adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension [see Precautions; Pharmacology].

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. Caution should be exercised with concomitant administration of warfarin and Tamsulosin capsules [see Precautions; Pharmacology].

Nifedipine, Atenolol, Enalapril

Dosage adjustments are not necessary when Tamsulosin capsules are administered concomitantly with nifedipine, atenolol, or enalapril [see Pharmacology].

Digoxin and Theophylline

Dosage adjustments are not necessary when a Tamsulosin capsule is administered concomitantly with digoxin or theophylline [see Pharmacology].

Furosemide

Tamsulosin capsules 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 capsules dosage [see Pharmacology].

【Adverse Reactions】

The safety of this drug was assessed in a controlled clinical trial of Tadalafil in 500 patients with benign prostatic hyperplasia and erectile dysfunction. This clinical trial consisted of the 12-week treatment period and the 12-week extension period. The 12-week open-label extension treatment was performed in 440 patients who completed the 12-week treatment period.

1) Adverse events collected during the 12-week treatment period

Commonly reported adverse events in 163 subjects in the Tamsulosin hydrochloride/Tadalafil 0.4/5mg group included headache (5.52%), ocular hyperemia (3.07%), nasal congestion (3.07%), flushing (2.45%), dizziness (1.84%), myalgia (1.84%), and retrograde ejaculation (1.23%). Adverse drug reactions of this drug were eight (8) events of headache, five (5) of ocular hyperemia, five (5) events of nasal congestion, four (4) events of flushing, three (3) events of myalgia, two (2) events of dizziness, two (2) events of retrograde ejaculation, and one (1) event of conjunctival hyperemia, chest discomfort, laryngitis, rhinitis, vocal cord paresis, ejaculation disorder, dyspnea, and epistaxis, respectively.

The table below summarizes adverse events reported more frequently in the Tamsulosin hydrochloride/Tadalafil group than in the Tadalafil 5 mg group among those occurring in ≥1% of overall 500 subjects in this study (171 subjects in the Tadalafil 5 mg group, 166 subjects in the Tamsulosin hydrochloride/Tadalafil 0.2/5mg group, 163 subjects in the Tamsulosin hydrochloride/Tadalafil 0.4/5mg group).

Table 1. Adverse events collected during the 12-week treatment period in Tamsulosin hydrochloride/Tadalafil group than in the Tadalafil 5 mg group among those occurring in ≥1% of overall 500 subjects in this study

	Tadalafil / Tamsulosin hydrochloride group		Tadalafil 5mg group	Total
System organ class	**5/0.4mg (N=163) N(%)**	**5/0.2mg (N=166) N(%)**	**(N=171) N(%)**	**(N=500) N(%)**
Nervous system disorders				
headache	9 (5.52%)	3 (1.81%)	3 (1.75%)	15 (3.00%)
dizziness	3 (1.84%)	1 (0.60%)	1 (0.58%)	5 (1.00%)
Vascular system disorders				
flushing	4 (2.45%)	2 (1.20%)	1 (0.58%)	7 (1.40%)
hot flushing	0 (0%)	2 (1.20%)	0 (0%)	2 (0.40%)
Eye disorders				
ocular hyperemia	5 (3.07%)	1 (0.60%)	0 (0%)	6 (1.20%)
conjunctival hyperemia	1 (0.61%)	2 (1.20%)	0 (0%)	3 (0.60%)
Gastrointestinal disorders				
dyspepsia	1 (0.61%)	3 (1.81%)	1 (0.58%)	5 (1.00%)
epigastric pain	1 (0.61%)	2 (1.20%)	1 (0.58%)	4 (0.80%)
Respiratory, thoracic and mediastinal disorders				
nasal congestion	5 (3.07%)	1 (0.60%)	0 (0%)	6 (1.20%)
Musculoskeletal and connective tissue disorders				
myalgia	3 (1.84%)	0 (0%)	0 (0%)	3 (0.60%)
Reproductive system and breast disorders				
retrograde ejaculation	2 (1.23%)	1 (0.60%)	0 (0%)	3 (0.60%)
Cardiac disorders				
palpitation	0 (0%)	2 (1.20%)	0 (0%)	2 (0.40%)

2) Adverse events collected during the 12-week extension period

Adverse drug reactions of this drug were 2 events of headache, decreased volume of ejaculate, nasal congestion, and dry nasal mucous membrane, respectively and 1 event of tachycardia, ocular hyperemia, conjunctival hyperemia, epigastric pain, dyspepsia, functional gastrointestinal disturbance, peripheral edema, nasopharyngitis, and ejaculation disorder, respectively.

The table below summarizes the frequency of adverse events reported in ≥1% of overall 440 subjects in the 12-week extension period (150 subjects in the Tadalafil 5mg → Tamsulosin hydrochloride/Tadalafil 0.4/5mg group, 152 subjects in the Tamsulosin hydrochloride/Tadalafil 0.2/5mg → 0.4/5mg group, 138 subjects in the Tamsulosin hydrochloride/Tadalafil 0.4/5mg).

Table 2. Adverse events collected during the 12-week extension period in ≥1% of overall 440 subjects

	Tadalafil/tamsulosin hydrochloride group		Tadalafil 5mg group	Total
System organ class	**5/0.4mg (N=138) N(%)**	**5/0.2mg → 5/0.4mg (N=152) N(%)**	**5mg → 5/0.4mg (N=150) N(%)**	**(N=440) N(%)**
Infections and infestations				
nasopharyngitis	1 (0.72%)	2 (1.32%)	2 (1.33%)	5 (1.14%)
Nervous system disorders				
headache	0 (0%)	3 (1.97%)	0 (0%)	3 (0.68%)
Respiratory, thoracic and mediastinal disorders				
allergic rhinitis	2 (1.45%)	0 (0%)	1 (0.67%)	3 (0.68%)
nasal congestion	2 (1.45%)	0 (0%)	0 (0%)	2 (0.45%)
dry nasal mucous membrane	0 (0%)	0 (0%)	2 (1.33%)	2 (0.45%)
Gastrointestinal disorders				
gastritis	0 (0%)	0 (0%)	2 (1.33%)	2 (0.45%)
colonic polyp	2 (1.45%)	0 (0%)	0 (0%)	2 (0.45%)
Test value abnormalities				
Decreased volume of ejaculate	0 (0%)	2 (1.32%)	0 (0%)	2 (0.45%)

3) In 163 subjects in the Tamsulosin hydrochloride/Tadalafil 0.4/5mg group, adverse events possibly related to hypotension were 3 events of dizziness (1.84%) and 9 events of headache (5.52%).

In an interaction study with a limited number of healthy volunteers, orthostatic hypotension with or without symptoms was more commonly reported in those treated with the Tamsulosin 0.4 mg plus Tadalafil 5 mg fixed dose combination therapy compared with those treated with the respectively monotherapy.

TADALAFIL

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Tadalafil was administered to over 9000 men during clinical trials worldwide. In trials of Tadalafil for once daily use, a total of 1434, 905, and 115 were treated for at least 6 months, 1year, and 2 years, respectively.

Tadalafil for Once Daily Use for ED

In three placebo-controlled clinical trials of 12 or 24 weeks duration, mean age was 58 years (range 21 to 82) and the discontinuation rate due to adverse events in patients treated with tadalafil was 4.1%, compared to 2.8% in placebo-treated patients. The following adverse reactions were reported in clinical trials of 12 weeks duration [see Table 3].

Table 3. Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with Tadalafil for Once Daily Use (5 mg) and More Frequent on Drug than Placebo in the Three Primary Placebo-Controlled Phase 3 Studies of 12 weeks Treatment Duration (Including a Study in Patients with Diabetes) for Tadalafil for Once Daily Use for ED.

Adverse Reaction	Placebo (N=248)	Tadalafil 5 mg (N=304)
Headache	5%	6%
Dyspepsia	2%	5%
Nasopharyngitis	4%	3%
Back pain	1%	3%
Upper respiratory tract infection	1%	3%
Flushing	1%	3%
Myalgia	1%	2%
Cough	0%	2%
Diarrhea	0%	2%
Nasal congestion	0%	2%
Pain in extremity	0%	2%
Urinary tract infection	0%	0%
Gastroesophageal reflux disease	0%	1%
Abdominal pain	0%	1%

The following adverse reactions were reported over 24 weeks treatment duration in one placebo-controlled clinical study [see Table 4].

Table 4. Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with Tadalafil for Once Daily Use 5 mg and More Frequent on Drug than Placebo in One Placebo-Controlled Clinical Study of 24 Weeks Treatment Duration for Tadalafil for Once Daily Use for ED.

Adverse Reaction	Placebo (N=94)	Tadalafil 5 mg (N=97)
Nasopharyngitis	5%	6%
Gastroenteritis	2%	5%
Back pain	3%	2%
Upper respiratory tract infection	0%	4%
Dyspepsia	1%	1%
Gastroesophageal reflux disease	0%	2%
Myalgia	2%	1%
Hypertension	0%	3%
Nasal congestion	0%	4%

Tadalafil for Once Daily Use for BPH and for ED and BPH

In three placebo-controlled clinical trials of 12 weeks duration, two in patients with BPH and one in patients with ED and BPH, the mean age was 63 years (range 44 to 93) and the discontinuation rate due to adverse events in patients treated with tadalafil was 3.6% compared to 1.6% in placebo-treated patients. Adverse reactions leading to discontinuation reported by at least 2 patients treated with tadalafil included headache, upper abdominal pain, and myalgia. The following adverse reactions were reported [see Table 5].

Table 5. Treatment-Emergent Adverse Reactions Reported by ≥1% of Patients Treated with Tadalafil for Once Daily Use (5 mg) and More Frequent on Drug than Placebo in Three Placebo-Controlled Clinical Studies of 12 Weeks Treatment Duration, including Two Studies for Tadalafil for Once Daily Use for BPH and One Study for ED and BPH.

Adverse Reaction	Placebo (N=576)	Tadalafil 5 mg (N=581)
Headache	2.3%	4.1%
Dyspepsia	0.2%	2.4%
Back pain	1.4%	2.4%
Nasopharyngitis	1.6%	2.1%
Diarrhea	1.0%	1.4%
Pain in extremity	0.0%	1.4%
Myalgia	0.3%	1.2%
Dizziness	0.5%	1.0%

Additional, less frequent adverse reactions (<1%) reported in the controlled clinical trials of Tadalafil for BPH or ED and BPH included: gastroesophageal reflux disease, upper abdominal pain, nausea, vomiting, arthralgia, and muscle spasm.

Back pain or myalgia was reported at incidence rates described in Tables 3 through 5. In tadalafil clinical pharmacology trials, back pain or myalgia generally occurred 12 to 24 hours after dosing and typically resolved within 48 hours. The back pain/myalgia associated with tadalafil treatment was characterized by diffuse bilateral lower lumbar, gluteal, thigh, or thoracolumbar muscular discomfort and was exacerbated by recumbency. In general, pain was reported as mild or moderate in severity and resolved without medical treatment, but severe back pain was reported with a low frequency (<5% of all reports). When medical treatment was necessary, acetaminophen or non-steroidal anti-inflammatory drugs were generally effective; however, in a small percentage of subjects who required treatment, a mild narcotic (e.g. codeine) was used. In the 1-year open label extension study, back pain and myalgia were reported in 5.5% and 1.3% of patients, respectively. Diagnostic testing, including measures for inflammation, muscle injury, or renal damage revealed no evidence of medically significant underlying pathology. Incidence rates for Tadalafil for once daily use for ED, BPH and BPH/ED are described in Table 3-5. In studies of Tadalafil for once daily use, adverse reactions of back pain and myalgia were generally mild or moderate with a discontinuation rate of <1% across all indications.

Across all studies with any Tadalafil dose, reports of changes in color vision were rare (<0.1% of patients).

The following section identifies additional, less frequent events (<2%) reported in controlled clinical trials of Tadalafil for once daily use. A causal relationship of these events to Tadalafil is uncertain. Excluded from this list are those events that were minor, those with no plausible relation to drug use, and reports too imprecise to be meaningful:

Body as a Whole: asthenia, face edema, fatigue, pain, peripheral edema.

Cardiovascular: angina pectoris, chest pain, hypotension, myocardial infarction, postural hypotension, palpitations, syncope, tachycardia.

Digestive: abnormal liver function tests, dry mouth, dysphagia, esophagitis, gastritis, GGTP increased, loose stools, nausea, upper abdominal pain, vomiting, gastroesophageal reflux disease, hemorrhoidal hemorrhage, rectal hemorrhage.

Musculoskeletal: arthralgia, neck pain.

Nervous: dizziness, hypesthesia, insomnia, paresthesia, somnolence, vertigo.

Renal and Urinary: renal impairment.

Respiratory: dyspnea, epistaxis, pharyngitis.

Skin and Appendages: pruritus, rash, sweating.

Ophthalmologic: blurred vision, changes in color vision, conjunctivitis (including conjunctival hyperemia), eye pain, lacrimation increase, swelling of eyelids.

Otologic: sudden decrease or loss of hearing, tinnitus.

Urogenital: erection increased, spontaneous penile erection.

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of Tadalafil. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors.

Cardiovascular and Cerebrovascular: Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported post-marketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of Tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of Tadalafil and sexual activity. It is not possible to determine whether these events are related directly to Tadalafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors [see Precautions].

Body as a Whole: hypersensitivity reactions including urticaria, Stevens-Johnson syndrome, and exfoliative dermatitis.

Nervous: migraine, seizure and seizure recurrence, transient global amnesia.

Ophthalmologic: visual field defect, retinal vein occlusion, retinal artery occlusion. Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of PDE5 inhibitors, including Tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking [see Precautions].

Otologic: Cases of sudden decrease or loss of hearing have been reported post-marketing in temporal association with the use of PDE5 inhibitors, including Tadalafil. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of Tadalafil, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors [see Precautions].

Urogenital: priapism [see Precautions].

TAMSULOSIN HYDROCHLORIDE

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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 capsules were used. These studies evaluated safety in 1783 patients treated with tamsulosin capsules and 798 patients administered placebo. Table 6 summarizes the treatment-emergent adverse events that occurred in ≥2% of patients receiving either tamsulosin capsules 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 6. Treatment-Emergent* Adverse Events Occuring in ≥2% of Tamsulosin Capsules or Placebo Patients in Two U.S. Short-Term Placebo-Controlled Clinical Studies

BODY SYSTEM/ ADVERSE EVENT	TAMSULOSIN CAPSULES GROUPS		PLACEBO
	0.4 mg n=502	0.8 mg n=492	n=493
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			
Blurred vision	1 (0.2%)	10 (2.0%)	2 (0.4%)

*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.

†Coding preferred terms also include cold, common cold, head cold, flu, and flu-like symptoms.

‡Coding preferred terms also include nasal congestion, stuffy nose, runny nose, sinus congestion, and hay fever.

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 ≥20 mmHg upon standing from the supine position during the orthostatic tests; (2) a decrease in diastolic blood pressure ≥10 mmHg upon standing, with the standing diastolic blood pressure <65 mmHg during the orthostatic test; (3) an increase in pulse rate of ≥20 bpm upon standing with a standing pulse rate ≥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 in Study 1, a positive orthostatic test result at 4 hours post dose was observed in 7% of patients (37 of 498) who received Tamsulosin capsules 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 capsules 0.4 mg once daily and 4% (9 of 250) who received placebo (Note: patients in the 0.8 mg group received 0.4 mg once daily for the first week of Study 1).

In Studies 1 and 2, at least one positive orthostatic test result was observed during the course of these studies for 81 of the 502 patients (16%) in the Tamsulosin capsules 0.4 mg once-daily group, 92 of the 491 patients (19%) in the Tamsulosin capsules 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 capsule-treated patients than in placebo recipients, there is a potential risk of syncope [see Precautions].

Abnormal Ejaculation: Abnormal ejaculation includes ejaculation failure, ejaculation disorder, retrograde ejaculation, and ejaculation decrease. As shown in Table 6, abnormal ejaculation was associated with Tamsulosin capsules administration and was dose-related in the U.S. studies. Withdrawal from these clinical studies of Tamsulosin capsules 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.

Laboratory Tests: No laboratory test interactions with Tamsulosin capsules are known. Treatment with Tamsulosin capsules for up to 12 months had no significant effect on prostate-specific antigen (PSA).

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Tamsulosin capsules. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to Tamsulosin capsules.

Allergic-type reactions such as skin rash, urticaria, pruritus, angioedema, and respiratory symptoms have been reported with positive rechallenge in some cases. Priapism has been reported rarely. Infrequent reports of dyspnea, palpitations, hypotension, atrial fibrillation, arrhythmia, tachycardia, skin desquamation including reports of Stevens-Johnson syndrome, erythema multiforme, dermatitis exfoliative, constipation, vomiting, dry mouth, visual impairment, and epistaxis have been received during the postmarketing period.

During cataract and glaucoma surgery, a variant of small pupil syndrome known as Intraoperative Floppy Iris Syndrome (IFIS) has been reported in association with alpha$_1$ blocker therapy [see Precautions].

【Overdosage】

TADALAFIL

A single Tadalafil dose of up to 500 mg has been administered to healthy subjects, and multiple Tadalafil doses of up to 100 mg/day have been administered to patients. Adverse events were similar to those identified at lower doses.

In the event of overdose, standard supportive measures should be taken as required. Hemodialysis hardly affects Tadalafil excretion.

TAMSULOSIN HYDROCHLORIDE

Should overdosage of Tamsulosin capsules lead to hypotension [see Precautions; 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.

【Storage conditions】 Store at temperatures not exceeding 30°C.

【Availability】 30 capsules (10 capsules/PTP X 3)/carton

【Instructions and Special Precautions for Storage and Handling】
- Keep out of reach of children.
- Caution should be exercised for proper storage as placing the drug in another container instead of its original one is undesirable for quality maintenance and can result in an accident.

【Caution Statement】
- Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
- The patient should be reminded that the pellets in the capsule should not be chewed and that the capsule should not be opened (which may alter the pharmacokinetics of the drug because it is a capsule filled with sustained release pellets of Tamsulosin hydrochloride).

【ADR Reporting Statement】For adverse drug reaction, report to the FDA: www.fda.gov.ph

【Manufactured by:】
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※ Precautions
1. Keep out of reach of children.
2. Comply with the specified dosage and administration.
3. Do not place the drug in another container instead of its original one to prevent misuse and maintain quality.
4. Take the drug with sufficient water.

Be careful for possible damage caused by packages (container, package) during product opening or handling.

※ Carefully read the package insert before using the drug and keep this package insert with the drug.

Customer information center of Hanmi Pharmaceutical Co., Ltd.: 080-916-9000 (toll-free)

※ Any amendments made to the package insert after the date of preparation (revision) can be found in the product information at the website of Hanmi Pharmaceutical Co., Ltd. or by telephone to the product information center.