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# TADAFLO 5 Tablets (Tadalafil)

## Composition

TADAFLO 5 Tablets
Each tablet contains:
Tadalafil.....5 mg

## Dosage Form

Tablet

## Pharmacology

▶ Pharmacodynamics

*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 NO, 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 benign prostatic hyperplasia (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, kidneys, lungs, cerebellum, heart, liver, testes, seminal vesicles, and pancreas.
*In vitro* studies have shown that the effect of tadalafil is more potent on PDE5 than on other PDEs. 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, leucocytes, 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. adrenal cortex). 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.

*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.

A study was conducted to assess the degree of interaction between nitroglycerin (NTG) and tadalafil, should NTG 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 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 haemodynamic 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 haemodynamic monitoring.

*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. 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 two-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 7 days of doxazosin dosing.

Table 1: Doxazosin (8 mg/day) Study 1: Mean Maximal Decrease (95%CI) in Systolic Blood Pressure

| Placebo-subtracted mean maximal decrease in systolic blood pressure (mmHg) | Tadalafil 20 mg |
|---|---|
| Supine | 3.6 (–1.5, 8.8) |
| Standing | 9.8 (4.1, 15.5) |

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 9 and 3 outliers following administration of tadalafil 20 mg and placebo, respectively. While 5 and 2 subjects were outliers due to a decrease from baseline in standing systolic BP of >30 mmHg, 5 and 1 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 1 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 three-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.

The placebo-subtracted mean maximal decreases in systolic blood pressure over a 12-hour period after dosing in the placebo-controlled portion of the study (part C) are shown in Table 2.

Table 2: Doxazosin (8 mg/day) Study 2 (Part C): Mean Maximal Decrease in Systolic Blood Pressure

| Placebo-subtracted mean maximal decrease in systolic blood pressure (mmHg) | Tadalafil 20 mg at 8 a.m. | Tadalafil 20 mg at 8 p.m. |
|---|---|---|
| Ambulatory blood pressure monitoring (ABPM) | 7 | 8 |

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), two such events were reported following administration of tadalafil (symptomatic hypotension in 1 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-pe--day dosing of tadalafil 5 mg or placebo in a two-period crossover design. After 7 days, 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). The results are shown in Table 3.

Table 3: Doxazosin Study 3: Mean Maximal Decrease (95%CI) in Systolic Blood Pressure

| Placebo-subtracted mean maximal decrease in systolic blood pressure | | Tadalafil 5 mg |
|---|---|---|
| Day 1 of 4 mg Doxazosin | Supine | 2.4 (–0.4, 5.2) |
| | Standing | –0.5 (–4.0, 3.1) |
| Day 7 of 4 mg Doxazosin | Supine | 2.8 (–0.1, 5.7) |
| | Standing | 1.1 (–2.9, 5.0) |

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 1 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 2 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 3 on placebo following the first dose of doxazosin 4 mg due to standing systolic BP <85 mmHg. Following the seventh day of doxazosin 4 mg, there were no outliers on tadalafil 5 mg, 1 subject on placebo had a decrease >30 mmHg in standing systolic blood pressure, and 1 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: 1 subject following a dose of tadalafil 5 mg alone, and another subject following co-administration of tadalafil 5 mg and doxazosin 4 mg.

*Tamsulosin:* In the first tamsulosin study, a single oral dose of tadalafil 10, 20 mg, or placebo was administered in a three-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 7 days of tamsulosin dosing.

Table 4: Tamsulosin (0.4 mg/day) Study 1: Mean Maximal Decrease (95%CI) in Systolic Blood Pressure

| Placebo-subtracted mean maximal decrease in systolic blood pressure (mmHg) | Tadalafil 10 mg | Tadalafil 20 mg |
|---|---|---|

| | | |
|---|---|---|
| Supine | 3.2 (–2.3, 8.6) | 3.2 (–2.3, 8.7) |
| Standing | 1.7 (–4.7, 8.1) | 2.3 (–4.1, 8.7) |

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 mm Hg. No severe adverse events potentially related to blood pressure effects were reported. No syncope was reported.
In the second tamsulosin study, 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 7 days of each period.

Table 5: Tamsulosin Study 2: Mean Maximal Decrease (95%CI) in Systolic Blood Pressure

| Placebo-subtracted mean maximal decrease in systolic blood pressure | | Tadalafil 5 mg |
|---|---|---|
| Day 1 of 0.4 mg Tamsulosin | Supine | –0.1 (–2.2, 1.9) |
| | Standing | 0.9 (–1.4, 3.2) |
| Day 7 of 0.4 mg Tamsulosin | Supine | 1.2 (–1.2, 3.6) |
| | Standing | 1.2 (–1.0, 3.5) |

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). In 1 subject on placebo plus tamsulosin (Day 7) and 1 subject on tadalafil plus tamsulosin (Day 6), had standing systolic blood pressure <85 mmHg was present. 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 two-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 7 days of alfuzosin dosing.

Table 6: Alfuzosin (10 mg/day) Study: Mean Maximal Decrease (95%CI) in Systolic Blood Pressure

| Placebo-subtracted mean maximal decrease in systolic blood pressure (mmHg) | Tadalafil 20 mg |
|---|---|
| Supine | 2.2 (–0.9,–5.2) |
| Standing | 4.4 (–0.2, 8.9) |

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 <85 mmHg) 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 5/3 mmHg, 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 three clinical pharmacology studies. In two of these, alcohol was administered at a dose of 0.7 g/kg, which is equivalent to approximately six 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 four ounces 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, haemodynamics, 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 ischaemia were enrolled. The primary endpoint was time to cardiac ischaemia. 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 NTG 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 PDE inhibitors have demonstrated transient dose-related impairment of colour 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 colour 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 QTc (Fridericia QT correction) for tadalafil, relative to placebo, was 3.5 milliseconds (two-sided 90%CI=1.9, 5.1). The mean change in QTc (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 co-administration 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.

▶ Pharmacokinetics

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 a 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 cytochrome (CY) P450 3A4 (CYP3A4) 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).

*Pharmacokinetics in Special Populations*

*Geriatric*

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.

*Paediatric*

Tadalafil has not been evaluated in individuals less than 18 years old.

*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 doses 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.

*Hepatic Impairment*

In clinical pharmacology studies, tadalafil exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a dose of 10 mg was administered. There are no available data for doses higher than 10 mg of tadalafil in patients with hepatic impairment. Insufficient data are available for subjects with severe hepatic impairment (Child-Pugh Class C).

*Renal Impairment*

In clinical pharmacology studies using single-dose tadalafil (5 to 10 mg), tadalafil exposure (AUC) doubled in subjects with creatinine clearance 30 to 80 mL/min. In subjects with end-stage renal disease on haemodialysis, there was a two-fold increase in $C_{max}$ and 2.7-to 4.8-fold increase in AUC following single-dose administration of 10 or 20 mg tadalafil. Exposure to total methylcatechol (unconjugated plus glucuronide) was 2-to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. Haemodialysis (performed between 24 and 30 hours post-dose) contributed negligibly to tadalafil or metabolite elimination.

## Indications

▶ Erectile Dysfunction and BPH

TADAFLO is indicated for the treatment of erectile dysfunction (ED) and the signs and symptoms of BPH (ED/BPH).

▶ Limitation of Use

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.

## Dosage And Administration

▶ TADAFLO for ED and BPH

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

▶ Use with Food

TADAFLO tablets may be taken without regard to food.

▶ Special Populations

*Renal Impairment*

*Creatinine clearance of 30 to 50 mL/min:* A starting dose of 2.5 mg is recommended. An increase to 5 mg may be considered based on individual response.

*Creatinine clearance <30 mL/min or on haemodialysis:* TADAFLO tablets 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 TADAFLO tablets for once-daily use is prescribed to these patients.

*Severe (Child Pugh Class C):* The use of TADAFLO tablets is not recommended.

Concomitant Medications

*Nitrates*

Concomitant use of nitrates in any form is contraindicated.

*Alpha-Blockers*

TADAFLO tablets are 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, the maximum recommended dose is 2.5 mg.

## Contraindications

▶ Nitrates

Administration of TADAFLO tablets 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.

▶ Hypersensitivity Reactions

TADAFLO tablets are contraindicated in patients with a known serious hypersensitivity to tadalafil.

Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis.

▶ Concomitant Guanylate Cyclase (GC) Stimulators

Do not use TADAFLO tablets in patients who are using a GC stimulator, such as riociguat. PDE5 inhibitors, including tadalafil, may potentiate the hypotensive effects of GC stimulators.

## Warnings And Precautions

▶ General

Evaluation of ED and BPH should include an appropriate medical assessment 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 ED, 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 haemodynamic monitoring. Therefore, patients who experience anginal chest pain after taking tadalafil should seek immediate medical attention.

Patients with left ventricular outflow obstruction, (e.g. aortic stenosis and idiopathic hypertrophic sub-aortic 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, TADAFLO tablets are 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 TADAFLO tablets, 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.

*Potential for Drug Interactions When Taking Tadalafil for Once-Daily Use*

Physicians should be aware that tadalafil for once-daily use provides continuous plasma tadalafil levels and

should consider this when evaluating the potential for interactions with medications (e.g. nitrates, alpha-blockers, antihypertensives and potent inhibitors of CYP3A4) and with substantial consumption of alcohol.

*Prolonged Erection*

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

TADAFLO tablets should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anaemia, multiple myeloma, or leukaemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

*Effects on the Eye*

Physicians should advise patients to stop use of all phosphodiesterase type 5 (PDE5) inhibitors, including TADAFLO tablets, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischaemic optic neuropathy (NAION), a rare condition and a cause of decreased vision, including permanent loss of vision, that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. Based on published literature, the annual incidence of NAION is 2.5 to 11.8 cases per 100,000 in males aged ≥50 years. An observational study evaluated whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION. The results suggest an approximate 2-fold increase in the risk of NAION within five half-lives of PDE5 inhibitor use. From this information, it is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors.

Physicians should consider whether their patients with underlying NAION risk factors could be adversely affected by use of PDE5 inhibitors. Individuals who have already experienced NAION are at increased risk of NAION recurrence. Therefore, PDE5 inhibitors, including TADAFLO tablets, should be used with caution in these patients and only when the anticipated benefits outweigh the risks. Individuals with 'crowded' optic disc are also considered at greater risk for NAION compared to the general population; however, evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including tadalafil, for this uncommon condition.

Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials and use in these patients is not recommended.

*Sudden Hearing Loss*

Physicians should advise patients to stop taking PDE5 inhibitors, including TADAFLO tablets, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including tadalafil. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

*Alpha-Blockers and Antihypertensives*

Physicians should discuss with patients the potential for tadalafil to augment the blood pressure-lowering effect of alpha-blockers and antihypertensive medications.

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. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, which may lead to symptomatic hypotension (e.g. fainting). Consideration should be given to the following:

The efficacy of the co-administration of an alpha-blocker and tadalafil for the treatment of BPH has

not been adequately studied, and due to the potential vasodilatory effects of combined use resulting in blood pressure-lowering, the combination of tadalafil and alpha-blockers is not recommended for the treatment of BPH.

Patients on alpha-blocker therapy for BPH should discontinue their alpha-blocker at least one day prior to starting tadalafil for once-daily use for the treatment of BPH.

*Alcohol*

Patients should be made aware that 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. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with TADAFLO can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

*Concomitant Use of Potent Inhibitors of CYP3A4*

Tadalafil is metabolized predominantly by CYP3A4 in the liver. The dose of TADAFLO tablets for use as needed should be limited to 10 mg no more than once every 72 hours in patients taking potent inhibitors of CYP3A4 such as ritonavir, ketoconazole, and itraconazole. In patients taking potent inhibitors of CYP3A4 and tadalafil for once-daily use, the maximum recommended dose is 2.5 mg.

*Combination with Other PDE5 Inhibitors or ED Therapies*

The safety and efficacy of combinations of tadalafil and other PDE5 inhibitors or treatments for ED have not been studied. Inform patients not to take TADAFLO tablets with other PDE5 inhibitors.

*Effects on Bleeding*

Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. Tadalafil has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although tadalafil has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk–benefit assessment and caution.

*Counselling Patients about Sexually Transmitted Diseases*

The use of tadalafil offers no protection against sexually transmitted diseases. Counselling patients about the protective measures necessary to guard against sexually transmitted diseases, including human immunodeficiency virus (HIV), should be considered.

*Consideration of Other Urological Conditions Prior to Initiating Treatment for BPH*

Prior to initiating treatment with TADAFLO tablets for BPH, consideration should be given to other urological conditions that may cause similar symptoms. In addition, prostate cancer and BPH may coexist.

▶ Drug Interactions

*Potential for Pharmacodynamic Interactions with Tadalafil*

*Nitrates:* Administration of TADAFLO tablets to patients who are using any form of organic nitrate, is contraindicated. In clinical pharmacology studies, tadalafil was shown to potentiate the 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 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 haemodynamic monitoring.

*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 co-administration of tadalafil with doxazosin, tamsulosin or alfuzosin.

*Antihypertensives:* 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, bendrofluazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following co-administration of tadalafil with these agents compared with placebo.

*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.

*Potential for Other Drugs to Affect Tadalafil*

*Antacids:* Simultaneous administration of an antacid (magnesium hydroxide/aluminium 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.

*CYP450 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.

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.

*CYP450 Inducers:* Studies have shown that drugs that induce CYP3A4 can decrease tadalafil exposure.

*CYP3A4 (e.g. Rifampin):* Rifampin (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 co-administration of rifampin 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.

*CYP450 Substrates:* Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by CYP450 (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):* Co-administration 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.

▶ Information for Patients

*Nitrates*
Physicians should discuss with patients the contraindication of tadalafil with regular and/or intermittent use of organic nitrates. Patients should be counselled that concomitant use of tadalafil with nitrates could cause blood pressure to suddenly drop to an unsafe level, resulting in dizziness, syncope, or even heart attack or stroke.
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 haemodynamic monitoring. Therefore, patients who experience anginal chest pain after taking TADAFLO tablets should seek immediate medical attention.
*Guanylate Cyclase (GC) Stimulators*
Physicians should discuss with patients the contraindication of tadalafil with any use of a GC stimulator, such as riociguat, for pulmonary arterial hypertension. Patients should be counselled that the concomitant use of TADAFLO tablets with GC stimulators may cause blood pressure to drop to an unsafe level.
*Cardiovascular Considerations*
Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. Physicians should advise patients who experience symptoms upon initiation of sexual activity to refrain from further sexual activity and seek immediate medical attention.
*Concomitant Use with Drugs That Lower Blood Pressure*
Physicians should discuss with patients the potential for tadalafil to augment the blood-pressure-lowering effect of alpha-blockers and antihypertensive medications.
*Potential for Drug Interactions When Taking Tadalafil for Once-Daily Use*
Physicians should discuss with patients the clinical implications of continuous exposure to tadalafil when prescribing TADAFLO tablets for once daily use, especially the potential for interactions with medications (e.g. nitrates, alpha-blockers, antihypertensives and potent inhibitors of CYP450 3A4) and with substantial consumption of alcohol.
*Priapism*
There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Physicians should advise patients who have an erection lasting greater than 4 hours, whether painful or not, to seek emergency medical attention.
*Sudden Loss of Vision*

Physicians should advise patients to stop use of all PDE5 inhibitors, including TADAFLO tablets, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of NAION, a cause of decreased vision, including possible permanent loss of vision, that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye. Physicians should also discuss with patients the increased risk of NAION among the general population in patients with a 'crowded' optic disc, although evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including tadalafil, for this uncommon condition.

*Sudden Hearing Loss*

Physicians should advise patients to stop taking PDE5 inhibitors, including TADAFLO tablets, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including tadalafil. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

*Alcohol*

Patients should be made aware that 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. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g. 5 units or greater) in combination with TADAFLO tablets can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

*Sexually Transmitted Diseases*

The use of tadalafil offers no protection against sexually transmitted diseases. Counselling of patients about the protective measures necessary to guard against sexually transmitted diseases, including HIV should be considered.

*Recommended Administration*

In case of TADAFLO tablets for once-daily use in men with ED/BPH, patients should be instructed to take one tablet at approximately the same time every day without regard for the timing of sexual activity. TADAFLO tablets are effective at improving erectile function over the course of therapy.

▶ Renal Impairment

Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis, TADAFLO tablets for once-daily use is not recommended in patients with creatinine clearance <30 mL/min. In patients with creatinine clearance of 30 to 50 mL/min, start dosing at 2.5 mg once daily, and increase the dose to 5 mg once daily based upon individual response.

In a clinical pharmacology study (N=28) at a dose of 10 mg, back pain was reported as a limiting adverse event in male patients with creatinine clearance of 30 to 50 mL/min. At a dose of 5 mg, the incidence and severity of back pain was not significantly different than in the general population. In patients on haemodialysis taking 10 or 20 mg tadalafil, there were no reported cases of back pain.

▶ Hepatic Impairment

Tadalafil use has not been extensively evaluated in patients with mild or moderate hepatic impairment. Therefore, caution is advised if tadalafil for once-daily use is prescribed to these patients. Because of insufficient information in patients with severe hepatic impairment, use of TADAFLO tablets in this group is not recommended.

▶ Pregnancy

*Pregnancy Category B*
TADAFLO tablets are not indicated for use in women. There are no adequate and well-controlled studies of tadalafil use in pregnant women.
*Risk Summary:* Based on animal data, tadalafil is not predicted to increase the risk of adverse developmental abnormalities in humans.

▶ Lactation

TADAFLO tablets are not indicated for use in women. Tadalafil and/or its metabolites were secreted into the milk in lactating rats at concentrations approximately 2.4-fold greater than found in the plasma.

▶ Paediatric Use

TADAFLO tablets are not indicated for use in paediatric patients. Safety and efficacy in patients below the age of 18 years has not been established.

▶ Geriatric Use

Of the total number of subjects in ED clinical studies of tadalafil, approximately 25% were aged 65 years and over, while approximately 3% were aged 75 years and over. Of the total number of subjects in BPH clinical studies of tadalafil (including the ED/BPH study), approximately 40% were aged >65 years, while approximately 10% were aged ≥75 years. In these clinical trials, no overall differences in efficacy or safety were observed between older (>65 and ≥75 years of age) and younger subjects (≤65 years of age). Therefore no dose adjustment is warranted based on age alone. However, a greater sensitivity to medications in some older individuals should be considered.

## Undesirable Effects

▶ 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 9,000 men during clinical trials worldwide. In trials of tadalafil for once daily use, a total of 1,434, 905 and 115 men were treated for at least 6 months, 1 year and 2 years, respectively. For tadalafil for use as needed, over 1,300 and 1,000 subjects were treated for at least 6 months and 1 year, respectively.
*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.

Table 7: 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% |
| Diarrhoea | 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 the following: gastro-oesophageal reflux disease, upper abdominal pain, nausea, vomiting, arthralgia, and muscle spasm.

Back pain or myalgia was reported at incidence rates described in Table 7. 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. Overall, approximately 0.5% of all subjects treated with tadalafil for on-demand use discontinued treatment as a consequence of back pain/myalgia. 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. 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 colour 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 or use as needed. 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 oedema, fatigue, pain.

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

*Digestive:* abnormal liver function tests, dry mouth, dysphagia, oesophagitis, gastritis, GGTP increased, loose stools, nausea, upper abdominal pain, vomiting, gastro-oesophageal reflux disease, haemorrhoidal haemorrhage, rectal haemorrhage.

*Musculoskeletal:* arthralgia, neck pain.

*Nervous:* dizziness, hypoesthesia, insomnia, paraesthesia, somnolence, vertigo.

*Renal and Urinary:* renal impairment.

*Respiratory:* dyspnoea, epistaxis, pharyngitis.
*Skin and Appendages:* pruritus, rash, sweating.
*Ophthalmologic:* blurred vision, changes in colour vision, conjunctivitis (including conjunctival hyperaemia), eye pain, lacrimation increase, swelling of eyelids.
*Otologic:* sudden decrease or loss of hearing, tinnitus.
*Urogenital:* erection increased, spontaneous penile erection.

▶ Postmarketing 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 postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had pre-existing 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.
*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
NAION, a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing 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 years, diabetes, hypertension, coronary artery disease, hyperlipidaemia, and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.
*Otologic:* Cases of sudden decrease or loss of hearing have been reported postmarketing 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.
*Urogenital:* priapism.

## Overdosage

Single doses up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses. In cases of overdose, standard supportive measures should be adopted as required. Haemodialysis contributes negligibly to tadalafil elimination.

## Storage And Handling Instructions

Store below 30°C

## Packaging Information

TADAFLO 5 Tablets ..... Blister Pack of 15 tablets

Last Updated: *Mar 2016*

Last Reviewed: *Mar 2016*

# TADAFLO 5 Tablets

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