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PULMOPRES Tablets (Tadalafil)

Composition

Each film-coated tablet contains:
Tadalafil IP ..... 20 mg
Colours
Lake Indigo Carmine, Titanium Dioxide IP & Yellow Oxide of Iron

Dosage Form

Oral tablet

Pharmacology

Pharmacodynamics

Tadalafil is an inhibitor of phosphodiesterase type 5 (PDE-5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). Pulmonary arterial hypertension (PAH) is associated with the impaired release of nitric oxide (NO) by the vascular endothelium and the consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle. PDE-5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE-5 by tadalafil increases the concentrations of cGMP, resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.
Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE-5. PDE-5 is found in the pulmonary vascular smooth muscle, visceral smooth muscle, corpus cavernosum, skeletal muscle, platelets, kidneys, lungs, cerebellum, and pancreas.
In vitro studies have shown that the effect of tadalafil is more potent on PDE-5 than on other phosphodiesterases. These studies have shown that tadalafil is >10,000-fold more potent for PDE-5 than for PDE-1, PDE-2, PDE-4, and PDE-7 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 PDE-5 than for PDE-3, an enzyme found in the heart and blood vessels. Additionally, tadalafil is 700-fold more potent for PDE-5 than for PDE-6, which is found in the retina and is responsible for phototransduction. Tadalafil is >9,000-fold more potent for PDE-5 than for PDE-8, PDE-9, and PDE-10. Tadalafil is 14-fold more potent for PDE-5 than for PDE-11A1 and 40-fold more potent for PDE-5 than for PDE-11A4, two of the four known forms of PDE-11. PDE-11 is an enzyme found in the human prostate, testes, skeletal muscle and in other tissues. In vitro, tadalafil inhibits human recombinant PDE-11A1 and, to a lesser degree,PDE-11A4 activities at concentrations within the therapeutic range. The physiological role and clinical consequence of PDE-11 inhibition in humans have not been defined.
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. Do not

use tadalafil in patients taking any form of nitrates.

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) assessed the interaction between nitroglycerine and tadalafil. A significant interaction between tadalafil and nitroglycerine was observed at each time point, up to and including 24 hours. At 48 hours, by most haemodynamic measures, the interaction between tadalafil and nitroglycerine was not observed, although a few more tadalafil subjects compared to placebo experienced greater blood pressure-lowering effects at this time point. After 48 hours, the interaction was not detectable.

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 mm Hg, respectively) and in standing systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6 mm Hg, respectively). In addition, there was no significant effect on the heart rate.

Effects on Blood Pressure When Administered with Antihypertensives

Amlodipine: A study assessed the interaction between 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 because of tadalafil 10 mg in subjects taking amlodipine was 3/2 mm Hg, 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 assessed the interaction between 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 mm Hg in systolic/diastolic blood pressure.

Bendroflumethiazide: A study assessed the interaction between bendroflumethiazide (2.5 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure because of tadalafil 10 mg in subjects taking bendroflumethiazide was 6/4 mm Hg, compared to placebo.

Enalapril: A study assessed the interaction between enalapril (10 to 20 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure because of tadalafil 10 mg in subjects taking enalapril was 4/1 mm Hg, compared to placebo.

Metoprolol: A study assessed the interaction between sustained-release metoprolol (25 to 200 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/ diastolic blood pressure because of tadalafil 10 mg in subjects taking metoprolol was 5/3 mm Hg, compared to placebo.

Effects on Blood Pressure When Administered with Alcohol

Alcohol and PDE-5 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 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 with 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 4 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 Blood Pressure When Administered with Alpha-Blockers

Alpha-blockers and PDE-5 inhibitors, including tadalafil, are systemic vasodilators. In subjects receiving concomitant tadalafil (20 mg single dose) and doxazosin (8 mg daily), an alpha-1- adrenergic receptor blocker, there was an augmentation of the blood pressure-lowering effect of doxazosin. This effect was still present at 12 hours post-dose and had generally disappeared at 24 hours. The number of subjects with potentially clinically significant decreases in standing blood pressure was greater for the combination.

An additional study was performed with tadalafil (20 mg single dose) and doxazosin (4 and 8 mg daily) using ambulatory blood pressure monitoring. The augmentation appeared unrelated to dosing times and resulted in a greater number of outliers for the combination than had been observed in the previous study. Both of these studies had some symptomatology associated with these blood pressure changes.

A further study was carried out with doxazosin (up to 4 mg daily) added to tadalafil (5 mg daily) and there was again an augmentation of response. In this clinical pharmacology study, there were symptoms associated with the decrease in blood pressure, including syncope. An interaction study with tadalafil (20 mg single dose) and alfuzosin, also an alpha---adrenergic receptor blocker, showed no clinically significant effect on blood pressure.

In two clinical pharmacology studies in healthy volunteers, tadalafil (5 mg daily, and 10 mg and 20 mg single dose) had no clinically significant effect on blood pressure changes because of tamsulosin, a selective alpha-1a-adrenergic receptor blocking agent.

Effects on Cardiac Electrophysiology

The effect of a single 100 mg dose of tadalafil (2.5 times the recommended dose) on the QT interval was evaluated at the time of peak tadalafil concentration in a randomized, double-blind, placebo- and active-controlled (intravenous ibutilide) crossover study in 90 healthy males, 18 to 53 years of age. The mean change in the 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 the QTc (Individual QT correction) for tadalafil, relative to placebo, was 2.8 milliseconds (two-sided 90% CI = 1.2, 4.4). 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.

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 blind 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 similar to placebo with respect to time to ischaemia. Of note, in this study, in some subjects who received tadalafil followed by sublingual nitroglycerine 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 PDE-6, which is involved in phototransduction in the retina. In a study to assess the effects of a single dose of tadalafi l 40 mg on vision (n = 59), no effects were observed on visual acuity, intraocular pressure, or pupillometry. 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 eff ect 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 eff ects 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.

Dose-Response Relationship

Dose-response relationships, between 20 mg and 40 mg, were not observed for the 6-minute walk distance (6MWD) or pulmonary vascular resistance (PVR) in subjects with PAH in the placebo-controlled study. Median change from baseline in the 6MWD was 32 metres and 35 metres at 16 weeks in subjects receiving 20 mg and 40 mg daily, respectively. Mean change from baseline PVR was -254 dynes*sec*cm-5 and -209 dynes*sec*cm-5 at 16 weeks in patients receiving 20 mg and 40 mg daily, respectively.

▶ Pharmacokinetics

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. In PAH patients administered between 20 and 40 mg of tadalafil, an approximately 1.5-fold greater AUC was observed, indicating a less than proportional increase in exposure over the entire dose range of 2.5 to 40 mg. During tadalafil 20 and 40 mg once daily dosing, steady-state plasma concentrations were attained within 5 days, and exposure was approximately 1.3-fold higher than after a single dose.

Absorption: After a single oral dose administration, the maximum observed plasma concentration (Cmax) of tadalafil is achieved between 2 and 8 hours (median time of 4 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 tablets may be taken with or without food.

Distribution: The mean apparent volume of distribution following oral administration is approximately 77 L, indicating that tadalafil is distributed into the tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins.

Metabolism: Tadalafil is predominantly metabolized by cytochrome (CY) P3A 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.

Elimination: Following a dose of 40 mg, the mean oral clearance for tadalafil is 3.4 L/hr and the mean terminal half-life is 15 hours in healthy subjects. In patients with pulmonary hypertension notreceiving concomitant bosentan, the mean oral clearance for tadalafil is 1.6 L/hr, and the mean terminal half-life is 35 hours. Tadalafil is excreted predominantly as metabolites, mainly in the faeces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Special Situations

Population Pharmacokinetics

In patients with pulmonary hypertension not receiving concomitant bosentan, the average tadalafil exposure at steady state following 40 mg was 26% higher when compared to those of healthy volunteers. The results suggest a lower clearance of tadalafil in patients with pulmonary hypertension compared to healthy volunteers.

Geriatric Patients

In healthy male elderly subjects (65 years of age or over) after a 10 mg dose, a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) with no effect on the Cmax was observed relative to that in healthy subjects, 19 to 45

years of age.

Renal Impairment

In clinical pharmacology studies using single-dose tadalafil (5 to 10 mg), tadalafil exposure (AUC) doubled in subjects with mild (creatinine clearance: 51 to 80 mL/min) or moderate (creatinine clearance: 31 to 50 mL/min) renal impairment. In subjects with end-stage renal disease on haemodialysis, there was a two-fold increase in Cmax and 2.7- to 4.1-fold increase in the AUC following single-dose administration of 10 or 20 mg tadalafil, respectively. 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.

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 subjectswith severe hepatic impairment (Child-Pugh Class C).

Patients with Diabetes Mellitus

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

Race

Pharmacokinetic studies have included subjects from different ethnic groups and no differences in the typical exposure to tadalafil have been identified. No dose adjustment is warranted.

Gender

In healthy female and male subjects following single and multiple doses of tadalafil, no clinically relevant differences in exposure (AUC and Cmax) were observed. No dose adjustment is warranted.

Indications

PULMOPRES tablets is indicated for the treatment of PAH (WHO Group I) to improve the exercise capacity.

Dosage And Administration

The recommended dose of PULMOPRES tablets is 40 mg (two 20 mg tablets) taken once daily with or without food. Dividing the dose (40 mg) over the course of the day is not recommended.

▶ Use in Special Populations

Renal Impairment

● Mild (creatinine clearance: 51 to 80 mL/min) or moderate (creatinine clearance: 31 to 50 mL/min): Start dosing at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability.

● Severe (creatinine clearance <30 mL/min and on haemodialysis): Avoid the use of tadalafil because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.

Hepatic Impairment

● Mild or moderate (Child Pugh Class A or B): Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis, consider a starting dose of 20 mg once per day.

● Severe (Child Pugh Class C): Patients with severe hepatic cirrhosis have not been studied. Avoid the use of PULMOPRES tablets.

Geriatric Patients

No dose adjustment is required in patients >65 years of age without renal or hepatic impairment.
Use with Ritonavir
Co-administration of Tadalafil in Patients on Ritonavir: In patients receiving ritonavir for at least 1 week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.
Co-administration of Ritonavir in Patients on Tadalafil: Avoid the use of tadalafil during the initiation of ritonavir. Stop tadalafil at least 24 hours prior to starting ritonavir. After at least 1 week following the initiation of ritonavir, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.

Contraindications

▶ Concomitant Organic Nitrates

Do not use tadalafil in patients who are using any form of organic nitrate, either regularly or intermittently. Tadalafil potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and tadalafil on the NO/cGMP pathway.

▶ Concomitant Guanylate Cyclase (GC) Stimulators

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

▶ Loss of vision in one eye

Tadalafil is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure.

▶ Hypersensitivity Reactions

Tadalafil is contraindicated in patients with a known serious hypersensitivity to tadalafil. Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis.

Warnings And Precautions

▶ Cardiovascular Effects

Discuss with patients the appropriate action to take in the event that they experience angina chest pain requiring nitroglycerine following an intake of tadalafil. At least 48 hours should elapse after the last dose of tadalafil before taking nitrates. If a patient has taken tadalafil within 48 hours, administer nitrates under close medical supervision with appropriate haemodynamic monitoring. Patients who experience anginal chest pain after taking tadalafil should seek immediate medical attention. PDE-5 inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing tadalafil, carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure or with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaorticstenosis) may be particularly sensitive to the actions of vasodilators, including PDE-5 inhibitors. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on the administration of tadalafil to patients with veno-occlusive disease, administration of tadalafil to such patients is not recommended. Should signs of pulmonary oedema occur when tadalafil is administered, the possibility of associated PVOD should be considered. There is a lack of data on

safety and efficacy in the following groups who were specifically excluded from the PAH clinical trials:

- Patients with clinically significant aortic and mitral valve disease
- Patients with pericardial constriction
- Patients with restrictive or congestive cardiomyopathy
- Patients with significant left ventricular dysfunction
- Patients with life-threatening arrhythmias
- Patients with symptomatic coronary artery disease
- Patients with hypotension (<90/50 mm Hg) or uncontrolled hypertension

▶ Use with Alpha-Blockers and Antihypertensives

PDE-5 inhibitors, including tadalafil, and alpha-adrenergic blocking agents, are vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on the 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). Safety of combined use of PDE-5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and use of other antihypertensive drugs.

▶ Use with Alcohol

Both alcohol and tadalafil are mild vasodilators. When mild vasodilators are taken in combination, the blood pressure-lowering effects are increased.

▶ Effects on the Eye

Physicians should advise patients to seek immediate 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 cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE-5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors or other factors.

Physicians should also discuss with patients about the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE-5 inhibitors.

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.

▶ Hearing Impairment

Physicians should advise patients to seek immediate 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 PDE-5 inhibitors, including tadalafil. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors or to other factors.

▶ Combination with Other PDE-5 Inhibitors

Tadalafil is also marketed for erectile dysfunction. The safety and efficacy of taking tadalafil together with tadalafil for erectile dysfunction or other PDE-5 inhibitors have not been studied. Inform patients taking tadalafil not to take other PDE-5 inhibitors.

▶ 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.
Tadalafil should be used with caution in patients who have conditions that might predisposethem 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 Bleeding

PDE-5 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.

▶ Use with Potent CYP3A Inhibitors or Inducers

Co-administration of Tadalafil in Patients on Ritonavir: In patients receiving ritonavir for at least 1 week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.
Co-administration of Ritonavir in Patients on Tadalafil: Avoid the use of tadalafil during the initiation of ritonavir. Stop tadalafil at least 24 hours prior to starting ritonavir. After at least 1 week following the initiation of ritonavir, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.
Other Potent Inhibitors of CYP3A: Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole and itraconazole, avoid use of tadalafil.
Potent Inducers of CYP3A: For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of Tadalafil.
Use in Renal Impairment: In patients with mild or moderate renal impairment start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. In patients with severe renal impairment: Avoid use of tadalafil because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.
Use in Hepatic Impairment: In patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B). Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis, consider a starting dose of 20 mg once daily Tadalafil. In patients with severe hepatic cirrhosis (Child-Pugh Class C). Patients with severe hepatic cirrhosis have not been studied. Avoid use of tadalafil.

▶ Drug Interactions

Potential for Pharmacodynamic Interactions with Tadalafil
Nitrates
Do not use tadalafil in patients who are using any form of organic nitrate. In clinical pharmacology studies, tadalafil potentiated 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
PDE-5 inhibitors, including tadalafil, and alpha-adrenergic blocking agents, are both vasodilators with blood-pressur--lowering effects. When vasodilators are used in combination, an additive effect on the blood pressure may be anticipated. Clinical pharmacology studies have been conducted with co-administration of tadalafil with doxazosin, alfuzosin or tamsulosin.

Antihypertensives

PDE-5 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, bendroflumethiazide, 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 PDE-5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, the 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 the heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

Potential for Other Drugs to Affect Tadalafil

Ritonavir

Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At the steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir.

Other Potent Inhibitors of CYP3A

Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and itraconazole, avoid the use of tadalafil.

Potent Inducers of CYP3A

For patients chronically taking potent inducers of CYP3A such as rifampin, avoid the use of tadalafil.

Potential for Tadalafil to Affect Other Drugs

CYP450 Substrates

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by CYP450 isoforms (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan).

Aspirin

Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin.

P-glycoprotein (e.g. digoxin)

Co-administration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects.

▶ Pregnancy

Pregnancy Category B

Animal reproduction studies in rats and mice revealed no evidence of foetal harm. There are, however, no adequate and well-controlled studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed.

Non-teratogenic effects

Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to unbound tadalafil concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.

▶ Lactation

It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excreted into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when tadalafil is administered to a nursing mother.

▶ Paediatric Use

Safety and effectiveness of tadalafil in paediatric patients have not been established.

▶ Geriatric Use

Of the total number of subjects in the clinical study of tadalafil for PAH, 28% were 65 years of age and over, while 8% were 75 years of age and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some elderly individuals should be considered.

▶ Renal Impairment

For patients with mild or moderate renal impairment, start tadalafil at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. In patients with severe renal impairment, avoid the use of tadalafil because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.

▶ Hepatic Impairment

Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A or B), consider a starting dose of tadalafil 20 mg once daily. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied; thus, avoid the use of tadalafil in such patients.

Undesirable Effects

The most common adverse events seen with tadalafil were generally transient and mild to moderate in intensity. Treatment-emergent adverse events reported by ≥9% of patients in the tadalafil 40 mg group and occurring more frequently than with placebo were headache, myalgia, nasopharyngitis, flushing, respiratory tract infection (upper and lower), pain in the extremities, nausea, back pain, dyspepsia, and nasal congestion (including sinus congestion).

▶ 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, and transient global amnesia.

▶ Ophthalmologic

Visual field defect, retinal vein occlusion, and 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 PDE-5 inhibitors, including tadalafil.

▶ Otologic

Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE-5 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.

▶ Urogenital

Priapism.

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via national pharmacovigilance program of India by calling on 1800 180 3024.

By reporting side effects, you can help provide more information on the safety of this product.

Overdosage

Single doses up to 500 mg have been given to healthy male subjects, and multiple daily doses up to 100 mg have been given to male patients with erectile dysfunction. Adverse reactions were similar to those seen at lower doses. Doses greater than 40 mg have not been studied in patients with PAH. In cases of overdose, standard supportive measures should be adopted as needed. Haemodialysis contributes negligibly to tadalafil elimination.

Storage & Handling Instructions

Store below 25°C. Protect from moisture.

Packaging Information

PULMOPRES: Blister pack of 10 tablets

Last updated: *November 2017*

Last reviewed: *June 2018*

PULMOPRES Tablets
