

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

## **ZYDALIS TADALAFIL TABLETS USP**

### **COMPOSITION:**

#### **Zydalis 10**

#### **Tadalafil Tablets USP 10MG**

Each film coated tablet contains:

Tadalafil USP 10mg

Colours : Iron oxide yellow, Titanium dioxide

#### **Zydalis 20**

#### **Tadalafil Tablets USP 20MG**

Each film coated tablet contains:

Tadalafil USP 20mg

Colours : Iron oxide yellow, Titanium dioxide

### **DESCRIPTION**

Tadalafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Tadalafil has the empirical formula  $C_{22}H_{19}N_3O_4$  representing a molecular weight of 389.41.

### **CLINICAL PHARMACOLOGY:**

#### **Pharmacodynamics Properties**

**Pharmacotherapeutic group:** Urologicals, Drugs used in erectile dysfunction

**ATC code:** G04BE08

#### **Mechanism of Action**

Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cGMP. Tadalafil inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by tadalafil has no effect in the absence of sexual stimulation.

The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum and pulmonary arteries is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The mechanism for reducing BPH symptoms has not been established.

Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in the smooth muscle of the corpus cavernosum, prostate, and bladder as well as in vascular and visceral smooth muscle, skeletal muscle, urethra, platelets, kidney, lung, cerebellum, heart, liver, testis, seminal vesicle, and pancreas.

*In vitro* studies have shown that the effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. These studies have shown that tadalafil is >10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes, which are found in

the heart, brain, blood vessels, liver, leukocytes, skeletal muscle, and other organs. Tadalafil is >10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. Additionally, tadalafil is 700-fold more potent for PDE5 than for PDE6, which is found in the retina and is responsible for phototransduction. Tadalafil is >9,000-fold more potent for PDE5 than for PDE8, PDE9, and PDE10. Tadalafil is 14-fold more potent for PDE5 than for PDE11A1 and 40-fold more potent for PDE5 than for PDE11A4, two of the four known forms of PDE11. PDE11 is an enzyme found in human prostate, testes, skeletal muscle and in other tissues (e.g., 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.

## Pharmacokinetics

### Absorption

Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration ( $C_{max}$ ) is achieved at a median time of 2 hours after dosing. 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. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

### Distribution

The mean volume of distribution is approximately 63 l, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function. Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

### Metabolism

Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13,000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

### Excretion

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

### Linearity/Non-Linearity

Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once daily dosing. Pharmacokinetics determined with a population approach in patients with erectile dysfunction are similar to pharmacokinetics in subjects without erectile dysfunction.

### Special Populations

#### Elderly

Healthy elderly subjects (65 years or over) had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. This effect of age is not clinically significant and does not warrant a dose adjustment.

#### Renal Insufficiency

In clinical pharmacology studies using single dose tadalafil (5 to 20mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients,  $C_{max}$  was 41% higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.

#### *Hepatic Insufficiency*

Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There is limited clinical data on the safety of TADALAFIL in patients with severe hepatic insufficiency (Child-Pugh class C). If Tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of once-a-day dosing of tadalafil to patients with hepatic impairment. If tadalafil is prescribed once-a-day, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.

#### *Patients with Diabetes*

Tadalafil exposure (AUC) in patients with diabetes was approximately 19% lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

### **THERAPEUTIC INDICATIONS:**

Tadalafil is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction (ED) and the signs and symptoms of benign prostatic hyperplasia(BPH)

### **RECOMMENDED DOSE AND METHOD OF ADMINISTRATION:**

#### *Erectile dysfunction in adult Men*

In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without food. In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity. The maximum dose frequency is once per day. Tadalafil 10 and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In patients who anticipate a frequent use of Tadalafil (i.e., at least twice weekly) a once daily regimen with the lowest doses of Tadalafil might be considered suitable, based on patient choice and the physician's judgement.

In these patients, the recommended dose is 5mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5mg once a day based on individual tolerability.

The appropriateness of continued use of the daily regimen should be reassessed periodically.

#### *Benign prostatic hyperplasia in adult men (tadalafil 5 mg only)*

The recommended dose is 5 mg, taken at approximately the same time every day with or without food. For adult men being treated for both benign prostatic hyperplasia and erectile dysfunction the recommended dose is also 5 mg taken at approximately the same time every day. Patients who are unable to tolerate tadalafil 5 mg for the treatment of benign prostatic hyperplasia should consider an alternative therapy as the efficacy of tadalafil 2.5 mg for the treatment of benign prostatic hyperplasia has not been demonstrated.

## **Special Populations**

### **Elderly Men**

Dose adjustments are not required in elderly patients.

### **Men with Renal Impairment**

Dose adjustments are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment, 10 mg is the maximum recommended dose.

Once-a-day dosing of 2.5 or 5 mg tadalafil both for the treatment of erectile dysfunction or benign prostatic hyperplasia is not recommended in patients with severe renal impairment.

### **Men with Hepatic Impairment**

For the treatment of erectile dysfunction using on-demand Tadalafil the recommended dose of Tadalafil is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of Tadalafil in patients with severe hepatic impairment (Child-Pugh class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10mg of tadalafil to patients with hepatic impairment.

Once-a-day dosing both for the treatment of erectile dysfunction and benign prostatic hyperplasia has not been evaluated in patients with hepatic impairment; therefore, if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician (see sections 4.4 and 5.2).

### **Men with Diabetes**

Dose adjustments are not required in diabetic patients.

### **Paediatric population**

There is no relevant use of Tadalafil in the paediatric population with regard to the treatment of erectile dysfunction.

### **Method of administration**

Tadalafil is available as 2.5, 5, 10, and 20 mg film-coated tablets for oral use.

## **CONTRAINDICATIONS:**

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

In clinical studies, tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway. Therefore, administration of Tadalafil to patients who are using any form of organic nitrate is contraindicated.

Tadalafil must not be used in men with cardiac disease for whom sexual activity is inadvisable. Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease.

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.

The co-administration of PDE5 inhibitors, including tadalafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.

## **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:**

### **Before treatment with Tadalafil**

A medical history and physical examination should be undertaken to diagnose erectile dysfunction or benign prostatic hyperplasia and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure and as such potentiates the hypotensive effect of nitrates. The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following an appropriate medical assessment. It is not known if Tadalafil is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

**Tadalafil 5 mg** - Prior to initiating treatment with tadalafil for benign prostatic hyperplasia patients should be examined to rule out the presence of carcinoma of the prostate and carefully assessed for cardiovascular conditions.

### Cardiovascular

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischaemic attacks, chest pain, palpitations and tachycardia, have been reported either post marketing and/or in clinical trials. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to Tadalafil, to sexual activity, or to a combination of these or other factors.

**Tadalafil 2.5 mg and 5 mg** - In patients receiving concomitant antihypertensive medicinal products, tadalafil may induce a blood pressure decrease. When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy.

In patients who are taking  $\alpha_1$  blockers, concomitant administration of Tadalafil may lead to symptomatic hypotension in some patients. The combination of tadalafil and doxazosin is not recommended.

### Vision

Visual defects and cases of NAION have been reported in connection with the intake of Tadalafil and other PDE5 inhibitors. Analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to tadalafil or other PDE5 inhibitors. As this may be relevant for all patients exposed to tadalafil, the patient should be advised that in case of sudden visual defect, he should stop taking Tadalafil and consult a physician immediately.

### Decreased or sudden hearing loss

Cases of sudden hearing loss have been reported after the use of tadalafil. Although other risk factors were present in some cases (such as age, diabetes, hypertension and previous hearing loss history) patients should be advised to stop taking tadalafil and seek prompt medical attention in the event of sudden decrease or loss of hearing.

### Renal and hepatic impairment (tadalafil 2.5 mg and 5 mg)

Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of Tadalafil is not recommended in patients with severe renal impairment.

There is limited clinical data on the safety of single-dose administration of Tadalafil in patients with severe hepatic insufficiency (Child-Pugh Class C). Once-a-day administration has not been evaluated in patients with hepatic insufficiency. If Tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

### Hepatic impairment (tadalafil 10 mg and 20 mg)

There is limited clinical data on the safety of single-dose administration of Tadalafil in patients with severe hepatic insufficiency (Child-Pugh Class C). If Tadalafil is

prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

#### Priapism and anatomical deformation of the penis

Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

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

#### Use with CYP3A4 inhibitors

Caution should be exercised when prescribing Tadalafil to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin), as increased tadalafil exposure (AUC) has been observed if the medicinal products are combined (see section 4.5).

#### Tadalafil and other treatments for erectile dysfunction

The safety and efficacy of combinations of Tadalafil and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. The patients should be informed not to take Tadalafil in such combinations.

#### Lactose

Tadalafil contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

### **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:**

Interaction studies were conducted with 10 mg and/or 20 mg tadalafil, as indicated below. With regard to those interaction studies where only the 10 mg tadalafil dose was used, clinically relevant interactions at higher doses cannot be completely ruled out.

#### Effects of Other Substances on Tadalafil

##### *Cytochrome P450 inhibitors*

Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased tadalafil (10 mg) exposure (AUC) 2-fold and  $C_{max}$  by 15%, relative to the AUC and  $C_{max}$  values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20 mg) exposure (AUC) 4-fold and  $C_{max}$  by 22%. Ritonavir, a protease inhibitor (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20 mg) exposure (AUC) 2-fold with no change in  $C_{max}$ . Although specific interactions have not been studied, other protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole, and grapefruit juice, should be co-administered with caution, as they would be expected to increase plasma concentrations of tadalafil (see section 4.4). Consequently, the incidence of the adverse reactions listed in section 4.8 might be increased.

##### *Transporters*

The role of transporters (for example, p-glycoprotein) in the disposition of tadalafil is not known. Therefore, there is the potential of drug interactions mediated by inhibition of transporters.

##### *Cytochrome P450 inducers*

A CYP3A4 inducer, rifampicin, reduced tadalafil AUC by 88%, relative to the AUC values for tadalafil alone (10 mg). This reduced exposure can be anticipated to decrease the efficacy of tadalafil; the magnitude of decreased efficacy is unknown. Other inducers of CYP3A4, such as phenobarbital, phenytoin, and carbamazepine, may also decrease plasma concentrations of tadalafil.

#### Effects of Tadalafil on Other Medicinal Products

##### *Nitrates*

In clinical studies, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of Tadalafil to patients who are using any form of organic nitrate is contraindicated (see section 4.3). Based on the results of a clinical study in which 150 subjects receiving daily doses of tadalafil 20 mg for 7 days and 0.4 mg sublingual nitroglycerin at various times, this interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Thus, in a patient prescribed any dose of Tadalafil (2.5 mg- 20 mg), where nitrate administration is deemed medically necessary in 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 only be administered under close medical supervision with appropriate haemodynamic monitoring.

##### *Anti-hypertensives (including calcium channel blockers)*

The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore, this combination is not recommended (see section 4.4).

In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin. However, caution should be exercised when using tadalafil in patients treated with any alpha-blockers, and notably in the elderly. Treatments should be initiated at minimal dosage and progressively adjusted.

In clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied, including calcium-channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendrofluzide), and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium-channel blockers, beta-blockers, and/or alpha-blockers). Tadalafil (10 mg, except for studies with angiotensin II receptor blockers and amlodipine in which a 20 mg dose was applied) had no clinically significant interaction with any of these classes. In another clinical pharmacology study, tadalafil (20 mg) was studied in combination with up to 4 classes of antihypertensives. In subjects taking multiple antihypertensives, the ambulatory-blood-pressure changes appeared to relate to the degree of blood pressure control. In this regard, study subjects whose blood pressure was well controlled, the reduction was minimal and similar to that seen in healthy subjects. In study subjects whose blood pressure was not controlled, the reduction was greater, although this reduction was not associated with hypotensive symptoms in the majority of subjects. In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha-blockers - see above) is, in general, minor and not likely to be clinically relevant. Analysis of Phase 3 clinical trial data showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medicinal products. However, appropriate clinical advice should be given to patients regarding a possible

decrease in blood pressure when they are treated with antihypertensive medicinal products.

#### *Riociguat*

Preclinical studies showed an additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including tadalafil, is contraindicated (see section 4.3).

#### *5- $\alpha$ reductase inhibitors*

In a clinical trial that compared tadalafil 5 mg co administered with finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal drug-drug interaction study evaluating the effects of tadalafil and 5- $\alpha$  reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

#### *CYP1A2 substrates (e.g. theophylline)*

When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate. Although this effect is minor and was of no clinical significance in this study, it should be considered when co-administering these medicinal products.

#### *Ethinylestradiol and terbutaline*

Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

#### *Alcohol*

Alcohol concentrations (mean maximum blood concentration 0.08%) were not affected by co-administration with tadalafil (10 mg or 20 mg). In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol. Alcohol was administered in a manner to maximise the rate of alcohol absorption (overnight fast with no food until 2 hours after alcohol). Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 ml of 40% alcohol [vodka] in an 80 kg male) but, in some subjects, postural dizziness and orthostatic hypotension were observed. When tadalafil was administered with lower doses of alcohol (0.6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).

#### *Cytochrome P450 metabolised medicinal products*

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicinal products metabolised by CYP450 isoforms. Studies have confirmed that tadalafil does not inhibit or induce CYP450 isoforms, including CYP3A4, CYP1A2, CYP2D6, CYP2E1, CYP2C9 and CYP2C19.

#### *CYP2C9 substrates (e.g. R-warfarin)*

Tadalafil (10 mg and 20 mg) had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did tadalafil affect changes in prothrombin time induced by warfarin.

#### *Aspirin*

Tadalafil (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetylsalicylic acid.

#### *Antidiabetic medicinal products*

Specific interaction studies with antidiabetic medicinal products were not conducted.



## USE IN SPECIFIC POPULATIONS:

### Pregnancy

**Pregnancy Category B** — Tadalafil is not indicated for use in women. There are no adequate and well controlled studies of Tadalafil use in pregnant women. Animal reproduction studies in rats and mice revealed no evidence of fetal harm.

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

### Nursing Mothers

Tadalafil is not indicated for use in women. 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.

### Pediatric Use

Tadalafil is not indicated for use in pediatric 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 clinical studies of tadalafil, approximately 25 percent were 65 and over, while approximately 3 percent were 75 and over. No overall differences in efficacy or safety were observed between subjects over 65 years of age compared to younger subjects, therefore no dose adjustment is warranted based on age alone. However, a greater sensitivity to medications in some older individuals should be considered.

### 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 Insufficiency

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 insufficiency. In subjects with end-stage renal disease on hemodialysis, there was a two-fold increase in C<sub>max</sub> and 2.7- to 4.1-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. Hemodialysis (performed between 24 and 30 hours post-dose) contributed negligibly to tadalafil or metabolite elimination. 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 moderate renal impairment. 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 hemodialysis taking 10- or 20-mg tadalafil, there were no reported cases of back pain.

## UNDESIRABLE EFFECTS:

The most commonly reported adverse reactions in patients taking Tadalafil for the treatment of erectile dysfunction or benign prostatic hyperplasia were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of Tadalafil. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with Tadalafil once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

#### Tabulated summary of adverse reactions

The table below lists the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 8022 patients on Tadalafil and 4422 patients on placebo) for on-demand and once-a-day treatment of erectile dysfunction and the once-a-day treatment of benign prostatic hyperplasia.

Frequency convention: Very common ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $< 1/10$ ), Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), Very Rare ( $< 1/10,000$ ) and Not known (cannot be estimated from the available data).

Very common	Common	Uncommon	Rare
<i>Immune system disorders</i>			
		Hypersensitivity reactions	Angioedema <sup>2</sup>
<i>Nervous system disorders</i>			
	Headache	Dizziness	Stroke <sup>1</sup> (including haemorrhagic events), Syncope, Transient ischaemic attacks <sup>1</sup> , Migraine <sup>2</sup> , Seizures <sup>2</sup> , Transient amnesia
<i>Eye disorders</i>			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischaemic optic neuropathy (NAION) <sup>2</sup> , Retinal vascular occlusion <sup>2</sup>
<i>Ear and labyrinth disorders</i>			
		Tinnitus	Sudden hearing loss
<i>Cardiac disorders<sup>1</sup></i>			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris <sup>2</sup> , Ventricular arrhythmia <sup>2</sup>
<i>Vascular disorders</i>			
	Flushing	Hypotension <sup>3</sup> , Hypertension	
<i>Respiratory, thoracic and mediastinal disorders</i>			

	Nasal congestion	Dyspnoea, Epistaxis	
<i>Gastrointestinal disorders</i>			
	Dyspepsia	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux	
<i>Skin and subcutaneous tissue disorders</i>			
		Rash	Urticaria, Stevens- Johnson syndrome <sup>2</sup> , Exfoliative dermatitis <sup>2</sup> , Hyperhydrosis (sweating)
<i>Musculoskeletal, connective tissue and bone disorders</i>			
	Back pain, Myalgia, Pain in extremity		
<i>Renal and urinary disorders</i>			
		Haematuria	
<i>Reproductive system and breast disorders</i>			
		Prolonged erections	Priapism, Penile haemorrhage, Haemospermia
<i>General disorders and administration site conditions</i>			
		Chest pain <sup>1</sup> , Peripheral oedema, Fatigue	Facial oedema <sup>2</sup> , Sudden cardiac death <sup>1,2</sup>

(1) Most of the patients had pre-existing cardiovascular risk factors (see section 4.4).

(2) Postmarketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.

(3) More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.

#### Description of selected adverse reactions

A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with tadalafil once a day as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

#### Other special populations

Data in patients over 65 years of age receiving tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. In clinical trials with tadalafil taken on demand for the treatment of erectile dysfunction, diarrhoea was reported more frequently in patients over 65 years of age. In clinical trials with tadalafil 5 mg taken once a day for the treatment of benign prostatic hyperplasia, dizziness and diarrhoea were reported more frequently in patients over 75 years of age.

#### OVERDOSAGE:

Single doses of 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.

### **PRESENTATION**

Alu-Alu Blister pack of 4's

Alu-PVC/PVDC Blister pack of 4's

### **STORAGE:**

Store up to 30°C.

Keep out of reach of children.

**Zydus**  
**Cadila**

Manufactured by:

Cadila Healthcare Limited,  
Kundaim Industrial Estate,  
Plot No. 203-213, Kundaim,  
Goa - 403 115, INDIA.