SIAFIL

Tablets

Composition

Each tablet contains Tadalafil 5, 10 or20 mg.

Action

Tadalafil is a potent, selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by Tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation.

Tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of Tadalafil is more potent on PDE5 than on other phosphodiesterase. 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.

This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, Tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also >9,000-fold more potent for PDE5 than for PDE8, 9 and 10 and 14-fold more potent for PDE5 than for PDE11. The tissue distribution and physiological effects of the inhibition of PDE8 through PDE11 have not been elucidated.

Tadalafil produced no significant difference in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mm Hg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mm Hg, respectively), and no significant change in heart rate. Larger effects were recorded among subjects receiving concomitant nitrates.

No impairment of colour discrimination (blue/green) was detected. This finding is consistent with the low affinity of Tadalafil for PDE6 compared to PDE5. In addition, no effects were observed on visual acuity, electroretinograms, intraocular pressure, or pupillometry. There were no clinically relevant effects on sperm concentration, sperm count, and motility.

Pharmacokinetics

Absorption

Tadalafil is rapidly absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. The rate and extent of absorption of Tadalafil are not influenced by food, thus Siafil 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 liters, 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.

Biotransformation

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.

Elimination
The mean oral clearance for Tadalafil is 2.5 l/hour 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).

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 Impairment
In subjects with renal insufficiency, including those on haemodialysis, Tadalafil exposure (AUC) was higher than in healthy subjects. Therefore, the recommended starting dose of Tadalafil in patients with mild or moderate renal impairment is 10 mg. For patients with severe renal impairment 10 mg is the maximum recommended dose.

Hepatic Impairment
Tadalafil exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects. No controlled data are available in patients with severe hepatic impairment (Child-Pugh Class C).

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.

Indications

Erectile Dysfunction
Siafil is indicated for the treatment of erectile dysfunction (ED).

Benign Prostatic Hyperplasia
Siafil is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

Erectile Dysfunction And Benign Prostatic Hyperplasia
Siafil is indicated for the treatment of ED and the signs and symptoms of BPH (ED/BPH).

Pulmonary Arterial Hypertension
SIAFIL 20MG is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

Contraindications

- Hypersensitivity to Tadalafil.
- Abnormal heart beats (arrhythmias) not controlled by treatment
- Angina not well controlled by medical treatment (unstable angina)
- Children and adolescents under 18 years of age
- Conditions in which sexual activity is not advisable, for example severe heart disorders
- Hereditary galactose intolerance
- Hereditary Lapp lactase deficiency
- Inherited inability to absorb the sugars glucose and galactose (glucose-galactose malabsorption)
- Low blood pressure (hypotension)
- People taking any form of nitrate medications, eg glyceryl trinitrate
- People who have had a heart attack in the last three months
- People who have had a stroke in the last six months
- People with angina that occurs during sex
- People with mild to severe heart failure in the last six months

- Uncontrolled high blood pressure (hypertension)
- Women

Warnings & Precautions

Tadalafil is not indicated for use by women.

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 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. The patient should be advised that in case of sudden visual defect, he should stop taking Tadalafil and consult a physician immediately.

Renal and hepatic impairment (Tadalafil 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.

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.

Pregnancy

There are limited data from the use of Tadalafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy**,** embryonal/foetal development, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use of Tadalafil during pregnancy.

Breastfeeding

Available pharmacodynamic/toxicological data in animals have shown excretion of Tadalafil in milk. A risk to the suckling child cannot be excluded. Tadalafil should not be used during breast feeding.

Fertility

Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men.

Effects on ability to drive and use machines

Tadalafil has negligible influence on the ability to drive or use machines. Although the frequency of reports of dizziness in placebo and Tadalafil arms in clinical trials was similar, patients should be aware of how they react to Tadalafil before driving or using machines.

Adverse Reactions

Summary of the safety profile

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

Frequency convention: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥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**
Immune system disorders			
		Hypersensitivity reactions	Angioedema[2]
Nervous system disorders			
	Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures[2], Transient amnesia
Eye disorders			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischaemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss
Cardiac disorders[1]			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular arrhythmia[2]
Vascular disorders			
	Flushing	Hypotension[3], Hypertension	
Respiratory, thoracic and mediastinal disorders			
	Nasal congestion	Dyspnoea, Epistaxis	
Gastrointestinal disorders			
	Dyspepsia	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux	
Skin and subcutaneous tissue disorders			
		Rash	Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2], Hyperhydrosis (sweating)
Musculoskeletal, connective tissue and bone disorders			
	Back pain, Myalgia, Pain in extremity		
Renal and urinary disorders			
		Haematuria	
Reproductive system and breast disorders			
		Prolonged erections	Priapism, Penile haemorrhage, Haematospermia
General disorders and administration site conditions			
		Chest pain[1], Peripheral	Facial oedema[2], Sudden

		oedema, Fatigue	cardiac death[1,2]

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

Drug Interactions

Effects of Other Substances on Tadalafil

Cytochrome P450 inhibitors

Tadalafil is principally metabolized 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 .

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

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. 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 (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.

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 (bendrofluazide), 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.

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 .

5- alpha reductase inhibitors
In a clinical trial that compared Tadalafil 5 mg coadministered 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 maximize 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 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.

Dosage and Administration

Do not split SIAFIL tablets; entire dose should be taken.

SIAFIL For Use As Needed For Erectile Dysfunction

- The recommended starting dose of SIAFIL for use as needed in most patients is 10 mg, taken prior to anticipated sexual activity.
- The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients.
- SIAFIL for use as needed was shown to improve erectile function compared to placebo up to 36 hours following dosing. Therefore, when advising patients on optimal use of Siafil, this should be taken into consideration.

SIAFIL For Once Daily Use For Erectile Dysfunction

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

SIAFIL For Once Daily Use For Benign Prostatic Hyperplasia

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

SIAFIL For Once Daily Use For Erectile Dysfunction And Benign Prostatic Hyperplasia
The recommended dose of SIAFIL for once daily use is 5 mg, taken at approximately the same time every day, without regard to timing of sexual activity.

Use With Food
SIAFIL may be taken without regard to food.

Pulmonary Arterial Hypertension
The recommended dose of SIAFIL 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.

Over Dosage

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.

Symptoms of overdose may include headache, indigestion or heartburn, flushing, pain in the back, muscles, or any limb, stuffy or runny nose, erection that lasts longer than 4 hours.

Presentation

Siafil 5 mg tab
Box of 14 tablets

Siafil 10 mg tab
Box of 4 tablets

Siafil 20 mg tab
Box of one tablet.