TADALAFIL

Indications

Below are the therapeutic indications for tadalafil:

1) Tadalafil is indicated for the treatment of erectile dysfunction.
2) Tadalafil is indicated in adult patients for the treatment of pulmonary arterial hypertension classified as functional class II and III, according to the World Health Organization (WHO) classification, to improve exercise capacity. The therapeutic efficacy of tadalafil has been demonstrated in idiopathic pulmonary arterial hypertension as well as in pulmonary arterial hypertension associated with collagen vascular disease.

Dosage

Monotherapy

Below is the dosage information for tadalafil across its various therapeutic indications.

Erectile Dysfunction

Oral administration.

Adults: The recommended dose is 10 mg, which may be taken with or without food, as needed. If necessary (in cases of insufficient response), the dose may be increased to 20 mg. Tadalafil can be administered within a time frame of 30 minutes to 12 hours prior to sexual activity. Its effectiveness may last for 24-36 hours; therefore, tadalafil should not be taken more than once per day. Tadalafil can also be administered daily. In this case, a lower dose than the "as-needed" option is recommended, specifically 5 mg/day, to be taken at approximately the same time each day.

Pulmonary Arterial Hypertension

Oral administration.

Adults: 40 mg/day taken as a single daily dose, with or without food.

Special populations

Patients with Renal Impairment

There is a lack of data in the literature on the safety and efficacy of tadalafil at doses above 10 mg in patients with renal impairment being treated for erectile dysfunction. Patients with moderate renal impairment should initiate treatment with tadalafil at a dose of 5 mg/day and should not exceed a maximum dose of 10 mg/day.

In patients with pulmonary arterial hypertension and mild to moderate renal impairment, the recommended starting dose is 20 mg once daily. This may be increased to 40 mg once daily, depending on patient response and individual tolerability.

The use of tadalafil in patients with severe renal impairment is not recommended.

Patients with Hepatic Impairment

For erectile dysfunction, there are no data in the literature regarding the efficacy and tolerability of tadalafil at doses above 10 mg in patients with hepatic impairment. Prescribing the drug requires careful consideration of the risk-benefit balance.

For the treatment of pulmonary arterial hypertension, data are available on patients with mild to moderate hepatic impairment. In this patient group, the recommended dose is 10 mg daily. For patients who tolerate this dose and may require a higher dose, 20 mg daily may be administered.

Since patients with severe hepatic impairment (Child-Pugh Class C) were not included in clinical studies, tadalafil is not recommended for this patient group.

Contraindications

Contraindications to the use of tadalafi:

1) Tadalafil is contraindicated in cases of hypersensitivity.
2) Tadalafil is contraindicated in patients undergoing therapy with nitrates or nitric oxide donors (such as amyl nitrite) due to inhibition of the NO-cGMP pathway, or in those receiving alpha-blocker therapy.
3) Tadalafil is contraindicated in patients with a history of myocardial infarction within the last three months and in cases of severe hypotension (blood pressure below 90/80 mmHg).
4) For the indication of erectile dysfunction, tadalafil is contraindicated in patients with pre-existing unstable angina or angina that occurs during sexual activity; in those with NYHA Class II or higher heart failure diagnosed in the past six months; in cases of uncontrolled arrhythmia; uncontrolled hypertension; or in patients who have experienced a cerebrovascular accident in the last six months.
5) Tadalafil is contraindicated in patients who have experienced vision loss in one eye due to non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this event was associated with previous use of a PDE5 inhibitor.

Warnings

Timing of Administration Before Sexual Activity: For erectile dysfunction treatment, tadalafil's pharmacological action typically begins around 45 minutes post-administration and may last up to 36 hours (long duration of action). The recommended dosage is a single daily dose, administered 30 minutes to 12 hours prior to sexual activity.

Cardiovascular Disease: Tadalafil is not recommended for the treatment of pulmonary arterial hypertension in patients with cardiovascular disease. Clinical studies excluded patients with the following conditions: clinically significant aortic and mitral valve disease, pericardial constriction, restrictive or congestive cardiomyopathy, severe left ventricular dysfunction, life-threatening arrhythmias, symptomatic coronary artery disease, and uncontrolled hypertension. Therefore, safety data for tadalafil in these patient groups is unavailable.

Pulmonary Veno-Occlusive Disease: This is a rare subtype of pulmonary arterial hypertension with an unknown cause. Pulmonary vasodilator therapy may worsen this condition significantly. Due to a lack of clinical data, tadalafil is not recommended for patients with pulmonary veno-occlusive disease. Pulmonary edema occurring during tadalafil therapy may indicate this condition.

Hypotension: Tadalafil may cause hypotension due to systemic vasodilation. Caution is advised when administering tadalafil to patients with risk factors for hypotension (e.g., significant left ventricular outflow obstruction, dehydration, persistent hypotension).

Alpha-Blockers: Tadalafil administration in patients on alpha-blockers may lead to symptomatic hypotension. An increase in hypotensive effects has been observed with co-administration of tadalafil and doxazosin but not with tamsulosin (Guillaume et al., 2007; Kloner et al., 2004). Tadalafil’s manufacturer does not recommend co-administration with doxazosin (AIFA, 2013).

Ophthalmic Toxicity: PDE5 inhibitors may cause adverse ocular effects due to interactions with ocular PDE6, involved in retinal phototransduction. The WHO database reports 892 cases of ocular adverse events associated with PDE5 inhibitors, with causality established for some reactions (e.g., altered color and brightness perception, blurred vision, conjunctival hyperemia, eye pain, photophobia) and possible for others (e.g., non-arteritic anterior ischemic optic neuropathy, mydriasis, subconjunctival hemorrhage, retinal vascular events). In case of sudden vision issues during treatment, tadalafil should be discontinued.

Retinitis Pigmentosa: Although tadalafil-induced visual disturbances have not been reported, no safety data is available for patients with retinitis pigmentosa.

Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION): PDE5 inhibitors may rarely cause vision loss due to NAION, a sudden, painless, typically unilateral vision loss occurring more frequently in the morning, caused by restricted blood flow to the optic nerve. Most affected patients have risk factors for this condition, including

cardiovascular risk factors (e.g., hypertension, diabetes, hyperlipidemia) and a low optic cup-to-disc ratio. Tadalafil should be discontinued immediately if there is a sudden loss of vision or blindness.

Gastroesophageal Disorders: Caution is advised in cases of gastroesophageal reflux disease or hiatal hernia with associated esophagitis, as tadalafil may reduce esophageal sphincter tone and inhibit esophageal motility.

Cardiovascular Risk Factors: The presence of cardiovascular risk factors may increase the likelihood of events such as myocardial infarction, unstable angina, ventricular arrhythmias, cerebrovascular accidents, and transient ischemic attacks in patients receiving tadalafil.

Antihypertensive Therapy: Tadalafil should not be administered to patients on multiple antihypertensive drugs (it is contraindicated in cases of hypotension, blood pressure <90/50 mmHg).

Hepatic/Renal Impairment: In cases of severe renal (CLcr ≤30 mL/min) and hepatic impairment (Child-Pugh Class C), a careful risk-benefit assessment is advised prior to administering tadalafil, as comprehensive efficacy and safety data are lacking. The highest dose used in clinical trials for erectile dysfunction in patients with mild/moderate renal impairment (CLcr 31–80 mL/min) and those on dialysis was 10 mg.

Priapism: Although tadalafil is not typically associated with priapism (a prolonged, painful erection unrelated to sexual activity), patients should report erections lasting over four hours. Untreated priapism may lead to tissue damage and permanent erectile dysfunction. Tadalafil should be used cautiously in patients predisposed to priapism (e.g., sickle cell anemia, multiple myeloma, leukemia) or with anatomical penile deformities (e.g., angulation, cavernosal fibrosis, Peyronie's disease).

Spinal Cord Injury, Pelvic Surgery, or Radical Prostatectomy Without Nerve-Sparing: Tadalafil’s efficacy in these conditions is not established.

P-Glycoprotein: It is unknown whether variations in the activity of transport proteins, such as P-glycoprotein, may lead to pharmacological interactions affecting tadalafil.

Calcium Channel Blockers (Amlodipine), ACE Inhibitors (Enalapril), Beta Blockers (Metoprolol), and Thiazide Diuretics (Bendrofluazide): Tadalafil does not increase the antihypertensive effects of these drugs. When combined with angiotensin II receptor blockers, tadalafil may induce a mild blood pressure reduction, with the impact on hypertension management depending on the individual patient profile.

Cytochrome Isoenzymes CYP1A2, 2C9, and 2D6: Tadalafil does not affect the metabolic activity of these cytochrome enzymes, as shown by the lack of interaction with theophylline, warfarin, and metoprolol. The slight increase in heart rate seen with tadalafil-theophylline co-administration results from theophylline’s weak non-selective PDE inhibition. This combination requires caution.

Cytochrome Isoenzyme CYP3A4: Co-administration of tadalafil with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) or inducers (e.g., rifampicin) is not recommended, as tadalafil is a CYP3A4 substrate.

Prostacyclin and Analogs: There is no literature data regarding the combined use of tadalafil and prostacyclin or its analogs, so caution is advised.

Pregnancy: Limited data is available on tadalafil use in pregnancy. Although embryofetal or postnatal toxicity has not been observed, tadalafil is not recommended in pregnancy as a precaution. The FDA classifies tadalafil as Category B, indicating no fetal risk in animal studies without controlled studies in pregnant women or that adverse animal findings were not confirmed in controlled studies in early and later pregnancy.

Lactation: In vivo studies (rats) have shown that tadalafil and its metabolites are excreted in breast milk, with concentrations reaching 2.4 times that of plasma. Tadalafil administration is not recommended in breastfeeding women.

Interactions

Alcohol: According to available literature, there is no pharmacokinetic interaction between alcohol and tadalafil. Tadalafil does not affect the plasma concentration of alcohol (mean peak concentration: 0.08%) or its effects on cognitive function and blood pressure. Alcohol also does not impact the absorption of tadalafil.

CYP2C9-Metabolized Drugs (e.g., warfarin): Tadalafil (10–20 mg) does not alter the area under the concentration-time curve (AUC), an indicator of systemic exposure, of warfarin, a CYP2C9 substrate. Tadalafil also does not affect warfarin-induced changes in prothrombin time.

Acetylsalicylic Acid (ASA): Co-administration of tadalafil and acetylsalicylic acid has shown no pharmacological interaction.

P-Glycoprotein Substrates (e.g., digoxin): Co-administration of tadalafil (40 mg/day) with digoxin has shown no pharmacological interaction.

Doxazosin: Combining tadalafil with doxazosin may result in an additive hypotensive effect (orthostatic hypotension). Co-administration of tadalafil (20 mg/day) and doxazosin (8 mg/day) for one week resulted in a significantly greater reduction in systolic blood pressure compared to doxazosin monotherapy (mean difference: 9.8 mmHg). This interaction has not been observed with tamsulosin (patients receiving tadalafil 10 and 20 mg/day plus tamsulosin 0.4 mg/day for one week showed no differences) (Kloner et al., 2004), nor with alfuzosin (in healthy volunteers). Co-administration of tadalafil and doxazosin is contraindicated.

Ethinylestradiol, Terbutaline: Tadalafil may increase their oral bioavailability. At steady state, tadalafil (40 mg/day) increases the systemic exposure (AUC) and peak plasma levels of ethinylestradiol by 26% and 70%, respectively. A similar effect is expected for terbutaline. This interaction is likely due to tadalafil's inhibitory effect on the sulfation process of ethinylestradiol and terbutaline. The clinical significance of this interaction is currently unknown.

CYP3A4 Inducers (rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, dexamethasone, nevirapine, troglitazone): These may reduce plasma levels of tadalafil due to pharmacometabolic induction. Rifampin, in particular, has been shown to reduce tadalafil's AUC by 88%.

CYP3A4 Inhibitors (ketoconazole, fluconazole, itraconazole, voriconazole, ritonavir, saquinavir, delavirdine, efavirenz, imatinib, amiodarone, cimetidine, diltiazem, fluoxetine, fluvoxamine, isoniazid, loratadine, nefazodone, niacin, omeprazole, propoxyphene, quinidine, quinine, sparfloxacin, testosterone, verapamil, zafirlukast, zileuton, erythromycin, clarithromycin, grapefruit juice): These may increase plasma levels of tadalafil by inhibiting its metabolism, potentially leading to a higher incidence of adverse effects. Specifically, ketoconazole has been shown to increase tadalafil's AUC by 107%.

Mifepristone: This drug may increase serum levels of tadalafil by inhibiting CYP3A4. Due to mifepristone's slow elimination, interaction may persist for a considerable time after administration.

Nicorandil: Nicorandil may enhance the vasodilatory effect of tadalafil due to its nitrate-like activity. The combination is not recommended.

Nitrates: Tadalafil potentiates the hypotensive effects of nitrates by acting on the nitric oxide/cGMP pathway. Concomitant administration of tadalafil and nitrate-containing medications is contraindicated.

Simvastatin: Co-administration with tadalafil has been associated with myopathy, requiring hospitalization. The interaction is likely due to competition for the same metabolic pathway (CYP3A4) (Gargante et al., 2009).

Grapefruit Juice: May increase tadalafil blood levels by inhibiting intestinal CYP3A4 isoenzyme.

Theophylline: Co-administration of theophylline, a non-selective phosphodiesterase inhibitor, with tadalafil has been shown to cause a slight increase in heart rate (3.5 bpm).

Side effects

The incidence of side effects in patients treated with tadalafil for erectile dysfunction was 66.7% and 54.3% for patients receiving 20 mg and 10 mg doses, respectively, and 47.8% in the placebo group.

The most common adverse effects associated with tadalafil for erectile dysfunction, in decreasing order of frequency, were headache, dyspepsia, back pain, myalgia, facial flushing, nasal congestion, and diarrhea. These side effects led to treatment discontinuation in approximately 1.7% of patients (vs. 1.1% with placebo) (Kuan, Brock, 2002). Headache, flushing, and dyspepsia are linked to tadalafil's mechanism of action as a phosphodiesterase 5 (PDE5) inhibitor.

In patients with pulmonary arterial hypertension treated with tadalafil (40 mg), the most frequent adverse effects (incidence ≥10%) were headache, nausea, back pain, dyspepsia, flushing, myalgia, nasopharyngitis, and limb pain. These effects were generally mild and transient. The percentage of patients who discontinued tadalafil (2.5-40 mg) due to adverse reactions was 11% (16% in the placebo group).

Respiratory System: (very common: >10%) nasopharyngitis; (common: 1-10%) nasal congestion, (common to uncommon depending on clinical study and therapeutic indication) epistaxis; (uncommon: 0.1-1%) dyspnea.

Cardiovascular: (ranging from very common, >10%, to common, 1-10%, depending on clinical study and therapeutic indication) flushing; (common) palpitations; (uncommon) hypotension, hypertension, sudden cardiac death, tachycardia; (rare: 0.01-0.1%) myocardial infarction; (post-marketing) unstable angina pectoris, ventricular arrhythmia.

Most patients reporting these events, excluding flushing, had pre-existing cardiovascular risk factors. Hypotension risk increases when tadalafil is co-administered with antihypertensive drugs. In clinical studies on pulmonary arterial hypertension, hypotension was a common adverse event (incidence between 1% and 10%) (Agenzia Italiana del Farmaco – AIFA, 2013).

Central Nervous System: (very common: >10%) headache; (common: 1-10%) dizziness, syncope; (uncommon: 0.1-1%) lightheadedness; (rare: 0.01-0.1%) stroke, syncope, transient ischemic attacks, seizures, transient amnesia; (post-marketing) migraine.

Both the frequency of headache and the incidence of initial headache episodes tend to decrease with repeated drug use, with headache episodes lasting between 3 and 8 hours. Syncope was classified as a common side effect in clinical studies on pulmonary arterial hypertension but was classified as rare in clinical trials for erectile dysfunction (Agenzia Italiana del Farmaco – AIFA, 2013 and 2014). Cardiovascular adverse events were generally observed in patients with cardiovascular risk factors.

Dermatological: (ranging from very common, >10%, to common, 1-10%, depending on clinical study and therapeutic indication) rash; (uncommon: 0.1-1%)

sweating (hyperhidrosis); (rare: 0.01-0.1%) urticaria; (post-marketing) Stevens-Johnson syndrome, exfoliative dermatitis.

Hematological: thrombocytopenia.

A case of thrombocytopenia has been reported in a patient on tadalafil therapy (GIF Database, 2008). The patient (age: 50 years) developed petechiae and severe thrombocytopenia after one month of tadalafil therapy; symptoms resolved upon discontinuation. The same database reports another case of spontaneously resolving thrombocytopenia in a 73-year-old patient after one day of vardenafil therapy. A case report describes sildenafil-induced thrombocytopenia, but the authors exclude a class-effect causality (Philip et al., 2008).

Gastrointestinal: (very common: >10%) nausea, dyspepsia, abdominal pain; (common) vomiting, gastroesophageal reflux; (uncommon: 0.1-1%) abdominal pain. Dyspepsia is likely due to relaxation of the smooth muscle in the lower esophageal tract.

Renal: (uncommon) hematuria.

Musculoskeletal: back pain, myalgia, limb pain.

Musculoskeletal side effects were reported with an incidence greater than 10% in clinical studies for pulmonary arterial hypertension, and slightly lower (1-10%) in studies for erectile dysfunction. In clinical trials for erectile dysfunction, back pain and myalgia typically appeared within 12–24 hours of administration and resolved within 48 hours. Pain extended from the lumbar area to the thigh but could also affect thoracolumbar muscles, with exacerbation in the supine position. In patients with moderate renal impairment, back pain was reported by four out of six patients, though it generally remained mild to moderate in severity and resolved spontaneously without pharmacological treatment.

Ophthalmological: (common, 1-10%, to uncommon, 0.1-1%, depending on clinical studies) blurred vision; (uncommon: 0.1-1%) eye pain; (rare: 0.01-0.1%) visual field changes, eyelid swelling, conjunctival hyperemia; (post-marketing) non-arteritic anterior ischemic optic neuropathy with potential permanent vision loss, retinal vascular occlusion (Peter et al., 2005; Escaravage et al., 2005; Bollinger, Lee, 2005).

Tadalafil's higher selectivity for PDE5 over PDE6, which is concentrated in the retina, is thought to result in lower ocular toxicity compared to sildenafil (0.1% vs. 3-11%).

Auditory: (uncommon: 0.1-1%) tinnitus; (rare) sudden hearing loss, potentially accompanied by tinnitus and vertigo. These effects are common to all three PDE5 inhibitors, though no causal relationship has been established.

Reproductive Organs: (common: 1-10%) abnormal menstrual bleeding; (uncommon: 0.1-1%) penile bleeding, hemospermia; (rare: 0.01-0.1%) prolonged erection; (post-marketing) priapism.

Systemic: malaise; (uncommon: 0.1-1%) chest pain, hypersensitivity reactions; (post-marketing) facial edema, angioedema.

The adverse event of chest pain has primarily been reported in patients with pre-existing cardiovascular risk factors.

Toxicity

Single doses of tadalafil up to 500 mg in healthy volunteers and multiple doses up to 100 mg in patients produced side effects comparable to those observed at therapeutic dosages.

In cases of overdose, renal dialysis should not be performed, as tadalafil binds extensively to plasma proteins and thus would not be significantly eliminated via urine.

In vivo, administration of tadalafil at doses (25 mg/kg/day for 6–12 months) resulting in an exposure three times higher than the clinically used dose induced seminiferous tubule epithelial regression, leading to decreased spermatogenesis.

Daily administration of therapeutic doses to healthy volunteers over 6 months did not impact spermatogenesis (Hellstrom et al., 2003). There were no significant differences compared to placebo in the percentage of patients with a 50% or greater reduction in sperm concentration, nor in sperm count, morphology, motility, or mean testosterone, LH, and FSH levels.

The mild decreases in sperm concentration reported in clinical trials fall within normal intra-individual variability.

In vivo, tadalafil has not been associated with teratogenicity, embryonic or fetal toxicity (doses up to 1000 mg/kg/day), or adverse effects on fertility, mutagenicity, or teratogenicity.

Pharmacology

Tadalafil is an orally administered medication indicated for the treatment of male erectile dysfunction and World Health Organization (WHO) Class II–III pulmonary arterial hypertension.

Mechanism of Action and Selectivity

Tadalafil is a potent, selective inhibitor of phosphodiesterase type 5 (PDE5), part of a family of ubiquitous enzymes. PDE5 is highly concentrated in the smooth muscle cells of the corpus cavernosum and, in lower amounts, in visceral and vascular smooth tissues, skeletal muscle, platelets, kidneys, lungs, and cerebellum. Other phosphodiesterases, like PDE3, located in the heart and blood vessels, are involved in myocardial contractility, while PDE6, located in the retina, plays a role in phototransduction.

Tadalafil exhibits a high selectivity for PDE5, with potency approximately 10,000 times greater than for other phosphodiesterases (PDE1, PDE2, PDE3, PDE4, PDE7) and 780 times greater than for PDE6 (Porst, 2002). This selectivity minimizes side effects in tissues where other PDEs are active. Its low affinity for PDE6, concentrated in the retina, results in a lower incidence of ocular side effects compared to sildenafil (0.1% vs. 3-11%). Unlike sildenafil, tadalafil has a higher affinity for PDE11, found in skeletal muscle, testes, heart, prostate, kidneys, liver, and pituitary gland, though PDE11's function remains unclear.

Chemical Characteristics

Tadalafil is water-insoluble and has no ionizable groups at pH 1–11. It is soluble in organic solvents such as dimethyl sulfoxide and dimethylformamide and contains two chiral centers, resulting in four stereoisomers. The clinically used form is the RR stereoisomer. Tadalafil does not exhibit polymorphism in crystallization.

Erectile Dysfunction

Erectile dysfunction (ED) is defined as the inability to attain or maintain an erection sufficient for satisfactory sexual performance. Given the multiple factors involved (psychological, neurological, vascular, hormonal, and anatomical), ED has a multifactorial etiology. Conditions commonly associated with ED include cardiovascular disease, diabetes, hypertension, neuropathy, stroke, endocrine disorders (e.g., hyperprolactinemia), Peyronie's disease, penile deformities, and certain medications (antidepressants, thiazides, anabolic steroids, cimetidine, digoxin, metoclopramide). Risk behaviors, notably smoking and alcohol abuse, also significantly contribute.

ED, strongly linked to cardiovascular risk factors, is considered a predictor of cardiovascular morbidity. The prevalence of ED is highest between ages 50–69, with an incidence of 19% at ages 50–59 and 51% at ages 60–69 (1999 Italian data).

The physiological mechanism of erection involves nitric oxide (NO) release from non-adrenergic, non-cholinergic nerve endings in the corpus cavernosum and endothelial cells lining vascular structures. NO release, triggered by sexual stimulation or reflexive nerve activation, activates guanylate cyclase, converting GMP to cGMP, which acts as a second messenger to promote calcium ion efflux from smooth muscle cells, resulting in smooth muscle relaxation in the corpus cavernosum. This relaxation allows for increased blood flow, initiating erection. PDE5, which converts cGMP to GMP, supports penile flaccidity. Tadalafil inhibits PDE5, prolonging cGMP's muscle-relaxing effect.

Tadalafil requires sexual stimulation to be effective, as it merely extends the action initiated by central or reflexive stimuli.

Tadalafil's effects begin approximately 16 minutes post-administration and last up to 24 hours, with 60% of patients experiencing efficacy up to 36 hours (20 mg dose) (Kuan, Brock, 2002). In trials, tadalafil increased the number of satisfactory sexual encounters within 24 hours compared to placebo.

In a study of 1,112 patients with mild to severe ED, aged 22–82 (mean age 59), tadalafil (20 mg) improved erections in 81% of patients vs. 35% with placebo, with efficacy rates of 86% for mild, 83% for moderate, and 72% for severe ED cases compared to placebo (Brock et al., 2002). Higher efficacy (up to 93%) was seen in mild/moderate ED cases with tadalafil doses of 50 mg, and 88% with doses of 2–25 mg. Most common side effects included headache (23% vs. 17% with placebo), dyspepsia (11% vs. 7%), back pain (4.7% vs. 0%), and myalgia (4.1% vs. 2.4%) (Porst, 2002).

In the SURE study, tadalafil (20 mg three times a week or "as needed") was administered for 5-6 weeks to patients, average age 55, with erectile dysfunction of varying severity. Based on patient responses, the preferred treatment regimen was identified. Despite similar therapeutic efficacy (75%), 42.2% of patients chose scheduled weekly therapy over "as needed" treatment. In the same study, tadalafil treatment, regardless of the regimen (chronic or as needed), allowed 60% of patients to achieve a normal functional score, leading to discontinuation of pharmacological treatment (psychological and organic rehabilitation, the latter due to tadalafil's positive effect on testosterone production and hypothalamic action) (Mirone et al., 2005).

Tadalafil proved effective with an acceptable tolerability profile even with daily use. In this case, the dosage is lower, 5 mg/day, compared to the "as needed" regimen of 10 mg. Comparison between "as needed" and daily administration showed comparable therapeutic efficacy (Porst et al., 2006).

Tadalafil also demonstrated effectiveness in diabetic patients, both type I and II, with no impact on baseline HbA1c levels (Saenz et al., 2002). Tadalafil improved erection in 56% and 64% of diabetic patients (10 and 20 mg, respectively) vs. 25% with placebo (Porst, 2002).

The administration of the drug to healthy volunteers did not alter blood pressure either in the supine position (mean maximum reduction: 1.6/0.8 mmHg) or in the

erect position (mean maximum reduction: 0.2/4.6 mmHg), nor did it cause significant changes in heart rate.

In a clinical trial assessing potential interactions of tadalafil with PDE6, no alterations in color perception (blue/green) were detected according to the Farnsworth-Munsell 100 Hue test. The incidence of drug-related chromatic disturbances in all clinical trials was 0.1%.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is linked to insufficient endothelial nitric oxide release and reduced pulmonary vascular smooth muscle cGMP levels. PDE5 predominates in pulmonary vessels, and tadalafil's inhibition of PDE5 increases cGMP levels, promoting pulmonary vasodilation.

Tadalafil has demonstrated therapeutic efficacy in improving exercise capacity in patients with pulmonary hypertension. In a randomized clinical trial, tadalafil (40 mg/day) significantly improved the 6-minute walk distance (primary endpoint) after 16 weeks ($p=0.0004$). Improvement was already evident after 8 weeks of therapy, with a statistically significant difference after 12 weeks ($p<0.01$). Patients in the study (405) had an age range from 14 to 90 years (mean age: 54 years) and a diagnosis of predominantly idiopathic pulmonary arterial hypertension (61%) or associated with collagen vascular diseases (23.5%) (other causes included anorexigenic substance use, HIV infection, cardiocirculatory defects). About two-thirds of patients were in WHO functional class III, and about one-third were in class II (Galié et al., 2009).

At the end of the study, the percentage of patients who showed improvement in WHO functional class did not differ between the tadalafil and placebo groups; however, the percentage of patients experiencing clinical deterioration was higher in the placebo group (16% vs. 4%). With tadalafil, improvement in the physical activity domain of the SF-36 score was observed. The SF-36 is a questionnaire assessing patient health, divided into 8 domains, one of which evaluates physical health.

Some of the patients from the previous study (357 patients) participated in the extension phase of the clinical trial (311 patients received tadalafil for at least 6 months, and 293 for 12 months). The effects of the drug on physical activity were maintained over time.

Combination therapy of tadalafil (40 mg) with ambrisentan (10 mg) for pulmonary arterial hypertension halved clinical failure risk compared to monotherapy (HR=0.502; 95% CI: 0.348–0.724; $p=0.0002$) (Galiè et al., 2015).

Pharmacokinetics

After oral administration, tadalafil is absorbed in the gastrointestinal tract. The presence of food does not alter the rate or extent of drug absorption.

The pharmacokinetic profile is linear over time and with dose; for doses ranging from 2.5 to 20 mg, the AUC (area under the curve, or drug exposure) increases proportionally to the dose.

No significant variations in pharmacokinetics have been reported between patients with or without erectile dysfunction.

In patients with pulmonary arterial hypertension, exposure to tadalafil (40 mg) at steady-state was on average 26% higher than in healthy volunteers. No clinically relevant differences in peak plasma concentration (Cmax) were observed compared to healthy volunteers.

Peak Plasma Time: 30 minutes to 6 hours.

Serum Protein Binding: 94%. This does not vary with altered renal function.

Steady-state is achieved within 5 days with daily dosing.

Volume of Distribution (Vd): 63 L.

Tadalafil distributes throughout the body tissues. Less than 0.0005% of the administered dose is found in semen.

Tadalafil is metabolized by the cytochrome enzyme CYP3A4. It does not alter the enzymatic activity of CYP3A4, 1A2, 2D6, 2E1, or 2C9. The primary metabolite is methylcatecholglucuronide, which has about 13,000 times lower activity on PDE5 than tadalafil itself.

Clearance (mean value): 2.5 L/hour.

Data suggest a lower clearance of tadalafil in patients with pulmonary arterial hypertension compared to healthy volunteers.

Half-life: 17.5 hours.

Approximately 61% and 36% of the administered dose are excreted via feces and urine, respectively.

Special populations

Elderly Patients

In elderly patients (65-78 years), tadalafil excretion decreases (due to the physiological decline in renal function with age), resulting in a 25% higher drug exposure (AUC) compared to patients aged 19-45 years. This increase does not necessitate a dosage adjustment.

Smokers

In smoking patients, pharmacokinetic parameters such as peak plasma concentration, AUC, and half-life are significantly lower than in non-smoking patients.

Diabetic Patients

The AUC is approximately 19% lower in diabetic patients; this variation in pharmacokinetics does not require dose adjustment.

Patients with Renal Impairment

Available pharmacokinetic data in the literature are inconsistent. In some trials, tadalafil AUC (10 mg) was lower in patients with mild to moderate renal impairment (CLcr: 50-80 ml/min). In others, in dialysis patients, AUC was similar to that observed in patients with normal renal function.

Patients with Hepatic Impairment

The AUC of tadalafil (10 mg) in patients with mild to moderate hepatic impairment (Child-Pugh classes A and B) was comparable to that observed in patients with normal hepatic function.

Classification

Chemical formula

C22H19N3O4

Molecular weight

269.08

Atc code

G04BE08

Bibliography

Agenzia Italiana del Farmaco – AIFA, Adcirca – Summary of Product Characteristics, 2013, November 12, available online at www.agenziafarmaco.gov.it/bancadatifarmaci/

Agenzia Italiana del Farmaco – AIFA, Cialis – Summary of Product Characteristics, 2014, January 9, available online athttp://www.agenziafarmaco.gov.it/bancadatifarmaci/

GIF Database, Interregional Pharmacovigilance Group, 2008, available online at www.gruppogif.org

Bollinger K., Lee M.S., Arch. Ophthalmol., 2005, 123, 400.

Brock G.B. et al., J. Urol., 2002, 168 (4Pt 1), 1332.

Escaravage G.K. Jr. et al., Arch. Ophthalmol., 2005, 123, 399.

Gargante M.P. et al., Case Report Med., 2009, vol 2009, 378287.

Galiè N. et al., Circulation, 2009, 119, 2894

Galiè N. et al., NEJM, 2015, 373 (9), 834

Guillame M. et al., J. Clin. Pharmacol., 2007, 47 (10), 1303.

Hellstrom W.J.G. et al., J. Urol., 2003, 170, 887.

Kloner R.A. et al., J. Urol., 2004, 172, 1935.

Kuan J., Brock G., Expert. Opin. Investig. Drugs, 2002, 11 (11), 1605.

Mirone V. et al., Eur. Urol., 2005, 47 (6), 846.

Peter N.M. et al., Eye, 2005, 19, 715.

Philip A. et al., Ann. Intern. Med., 2008, 149 (6), 437.

Porst H., Int. J. Import. Res., 2002, 14 (Suppl. 1), S57.

Porst H. et al., Eur. Urol., 2006, 50, 351.

Saenz De Tejada et al., Diabetes care, 2002, 25 (12), 2159.

