

**Tadalafil 20 mg +
Dapoxetine 60 mg Tablets**

COMPOSITION:
Each film coated tablet contains:
Tadalafil 20mg
Dapoxetine Hydrochloride equivalent to Dapoxetine 60mg

DOSAGE FORM:
Tablets

DESCRIPTION:
Buff yellow to dark yellow colored, triangular shaped film coated tablets and plain on both sides.

EXCIPIENTS LIST:
Lactose BP, Croscarmillose Sodium USPNF, Sodium Lauryl Sulphate BP, Crospovidone BP, Povidone (P.V.P.K-30) BP, Isopropyl Alcohol BP, Magnesium Stearate BP, Instacoat Aqua-II A02D000050 (Yellow) IH, Purified water.

CLINICAL PARTICULARS:

Therapeutic Indications:

For the treatment of Erectile dysfunction and premature ejaculation in men 18 to 64 years of age.

Notorious Effect of Excipients:

Lactose: The T36 Plus (Tadalafil 20 mg and Dapoxetine 60 mg Tablets) contains Lactose. Adverse reactions to Lactose are largely attributed to Lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase. This results in Lactose being undigested and may lead to cramps, diarrhoea, distension, and flatulence. Therefore, Lactose intolerant people should not take this medicine.

Sodium lauryl sulfate: Sodium lauryl sulfate is widely used in cosmetics and oral and topical pharmaceutical formulations. It is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract, and stomach. Repeated, prolonged exposure to dilute solutions may cause drying and cracking of the skin; contact dermatitis may develop.

Isopropyl alcohol: Isopropyl alcohol is about twice as toxic as ethanol and should therefore not be administered orally; isopropyl alcohol also has an unpleasant taste. Symptoms of isopropyl alcohol toxicity are similar to those for ethanol except that isopropyl alcohol has no initial euphoric action and gastritis and vomiting are more prominent. Delta osmolality may be useful as rapid screen test to identify patients at risk of complications from ingestion of isopropyl alcohol. The lethal oral dose is estimated to be about 120–250 mL although toxic symptoms may be produced by 20 mL.

In the pharmaceutical industry, isopropyl alcohol may be used in small, safe quantities in capsule or tablet manufacturing.

Posology and Method of administration:
For oral use only.
The recommended dose is one tablet to be taken 1-3 hours before sexual activity. Take only when needed and do not take more than one tablet per day. It may be taken with or without food.

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.

The following groups of patients with cardiovascular disease were not included in clinical trials and the use of tadalafil is therefore contraindicated:
- patients with myocardial infarction within the last 90 days,
- patients with unstable angina or angina occurring during sexual intercourse,
- patients with New York Heart Association Class 2 or greater heart failure in the last 6 months,
- patients with uncontrolled arrhythmias, hypotension (<90/50 mm Hg), or uncontrolled hypertension,
- patients with a stroke within the last 6 months.
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

Dapoxetine hydrochloride

Significant pathological cardiac conditions such as;
• Heart failure (NYHA class II-IV)
• Conduction abnormalities such as AV block or sick sinus syndrome
• Significant ischemic heart disease
• Significant valvular disease
• A history of syncope.
A history of mania or severe depression.

Concomitant treatment with **monoamine oxidase inhibitors** (MAOIs), or within 14 days of discontinuing treatment with an MAOI. Similarly, an MAOI should not be administered within 7 days after dapoxetine has been discontinued.

Concomitant treatment with thioridazine, or within 14 days of discontinuing treatment with thioridazine. Similarly, thiondazine should not be administered within 7 days after dapoxetine has been discontinued.

Concomitant treatment with serotonin reuptake inhibitors [selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs)] or other medicinal/herbal products with serotonergic effects [e.g., L-tryptophan, triptans, tramadol, linezolid, lithium, St. John's Wort (Hypericum perforatum)] or within 14 days of discontinuing treatment with these medicinal/herbal products. Similarly, these medicinal/herbal products should not be administered within 7 days after dapoxetine has been discontinued.

Concomitant treatment of potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazadone, nelfinavir, atazanavir, etc.

Moderate and severe hepatic impairment

Contraindications:
Hypersensitivity to the active substance or to any of the excipients.

Special warning and precautions for use:
Tadalafil
Before treatment with Tadalafil
A medical history and physical examination should be undertaken to diagnose erectile dysfunction 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.

Cardiovascular
Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic 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.

In patients who are taking alpha1 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.

Hepatic 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). 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.

Dapoxetine hydrochloride

General recommendations
Dapoxetine should not be prescribed to men who have not been diagnosed with Premature Ejaculation. Safety has not been established and there are no data on the ejaculation-delaying effects in men without Premature Ejaculation.

Other forms of sexual dysfunction

Before treatment, subjects with other forms of sexual dysfunction, including erectile dysfunction, should be carefully investigated by physicians.

Orthostatic hypotension
Before treatment initiation, a careful medical examination including history of orthostatic events should be performed by the physician. An orthostatic test should be performed before initiating therapy (blood pressure and pulse rate, supine and standing). In case of a history of documented or suspected orthostatic reaction, treatment with Dapoxetine should be avoided.

Orthostatic hypotension has been reported in clinical trials. The prescriber should counsel the patient in advance that if he experiences possibly prodromal symptoms, such as lightheadedness soon after standing, he should immediately lie down so his head is lower than the rest of his body or sit down with his head between his knees until the symptoms pass. The prescriber should also inform the patient not to rise quickly after prolonged lying or sitting.

Suicide/suicidal thoughts
Antidepressants, including SSRIs, increased the risk compared to placebo of suicidal thinking and suicidality in short-term studies in children and adolescents with Major Depressive Disorder and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24. In clinical trials with Dapoxetine for the treatment of premature ejaculation, there was no clear indication of treatment-emergent suicidality in evaluation of possibly suicide-related adverse events evaluated by the Columbia Classification Algorithm of Suicide Assessment (C-CASA), Montgomery-Asberg Depression Rating Scale, or Beck Depression Inventory-II.

Syncope
Patients should be cautioned to avoid situations where injury could result, including driving or operating hazardous machinery, should syncope or its prodromal symptoms such as dizziness or lightheadedness occur.

Possibly prodromal symptoms such as nausea, dizziness/lightheadedness, and diaphoresis were reported more frequently among patients treated with Dapoxetine compared to placebo.
In the clinical trials, cases of syncope characterized as loss of consciousness, with bradycardia or sinus arrest observed in patients wearing Holter monitors, were considered vasovagal in etiology and the majority occurred during the first 3 hours after dosing, after the first dose, or associated with study-related procedures in the clinic setting (such as blood draw and orthostatic maneuvers and blood pressure measurements). Possibly prodromal symptoms, such as nausea, dizziness, lightheadedness, palpitations, asthenia, confusion and diaphoresis generally occurred within the first 3 hours following dosing, and often preceded the syncope.

Patients need to be made aware that they could experience syncope at any time with or without prodromal symptoms during their treatment with Dapoxetine. Prescribers should counsel patients about the importance of maintaining adequate hydration and about how to recognize prodromal signs and symptoms to decrease the likelihood of serious injury associated with falls due to loss of consciousness. If the patient experiences possibly prodromal symptoms, the patient should immediately lie down so his head is lower than the rest of his body or sit down with his head between his knees until the symptoms pass, and be cautioned to avoid situations where injury could result, including driving or operating hazardous machinery, should syncope or other CNS effects occur.

Patients with cardiovascular risk factors
Subjects with underlying cardiovascular disease were excluded from Phase 3 clinical trials. The risk of adverse cardiovascular outcomes from syncope (cardiac syncope and syncope from other causes) is increased in patients with underlying structural cardiovascular disease (e.g.,

documented outflow obstruction, valvular heart disease, carotid stenosis and coronary artery disease). There are insufficient data to determine whether this increased risk extends to vasovagal syncope in patients with underlying cardiovascular disease.

Use with recreational drugs
Patients should be advised not to use Dapoxetine in combination with recreational drugs.
Recreational drugs with serotonergic activity such as ketamine, methylenedioxymethamphetamine (MDMA) and lysergic acid diethylamide (LSD) may lead to potentially serious reactions if combined with Dapoxetine. These reactions include, but are not limited to, arrhythmia, hyperthermia, and serotonin syndrome. Use of Dapoxetine with recreational drugs with sedative properties such as narcotics and benzodiazepines may further increase somnolence and dizziness.

Ethanol
Patients should be advised not to use Dapoxetine in combination with alcohol.
Combining alcohol with dapoxetine may increase alcohol-related neurocognitive effects and may also enhance neurocardiogenic adverse events such as syncope, thereby increasing the risk of accidental injury; therefore, patients should be advised to avoid alcohol while taking Dapoxetine

Medicinal products with vasodilatation properties
Dapoxetine should be prescribed with caution in patients taking medicinal products with vasodilatation properties (such as alpha adrenergic receptor antagonists and nitrates) due to possible reduced orthostatic tolerance.

Moderate CYP3A4 inhibitors
Caution is advised in patients taking moderate CYP3A4 inhibitors and the dose is restricted to 30 mg.

Potent CYP2D6 inhibitors
Caution is advised if increasing the dose to 60 mg in patients taking potent CYP2D6 inhibitors or if increasing the dose to 60 mg in patients known to be of CYP2D6 poor metabolizer genotype, as this may increase exposure levels, which may result in a higher incidence and severity of dose dependent adverse events.

Mania
Dapoxetine should not be used in patients with a history of mania/hypomania or bipolar disorder and should be discontinued in any patient who develops symptoms of these disorders.

Seizure
Due to the potential of SSRIs to lower the seizure threshold, Dapoxetine should be discontinued in any patient who develops seizures and avoided in patients with unstable epilepsy. Patients with controlled epilepsy should be carefully monitored.

Paediatric population
Dapoxetine should not be used in individuals below 18 years of age.

Depression and/or psychiatric disorders
Men with underlying signs and symptoms of depression should be evaluated prior to treatment with Dapoxetine to rule out undiagnosed depressive disorders. Concomitant treatment of Dapoxetine with antidepressants, including SSRIs and SNRIs, is contraindicated. Discontinuation of treatment for ongoing depression or anxiety in order to initiate Dapoxetine for the treatment of PE is not recommended. Dapoxetine is not indicated for psychiatric disorders and should not be used in men with these disorders, such as schizophrenia, or in those suffering with co-morbid depression, as worsening of symptoms associated with depression cannot be excluded. This could be the result of underlying psychiatric disorder or might be a result of medicinal product therapy. Physicians should encourage patients to report any distressing thoughts

or feelings at any time and if signs and symptoms of depression develop during treatment, Dapoxetine should be discontinued.

Haemorrhage
There have been reports of bleeding abnormalities with SSRIs. Caution is advised in patients taking Dapoxetine, particularly in concomitant use with medicinal products known to affect platelet function (e.g., atypical antipsychotics and phenothiazines, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs [NSAIDs], anti-platelet agents) or anticoagulants (e.g., warfarin), as well as in patients with a history of bleeding or coagulation disorders.

Renal impairment
Dapoxetine is not recommended for use in patients with severe renal impairment and caution is advised in patients with mild or moderate renal impairment

Withdrawal effects
Abrupt discontinuation of chronically administered SSRIs used to treat chronic depressive disorders has been reported to result in the following symptoms: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia and hypomania.

A double-blind clinical trial in subjects with PE designed to assess the withdrawal effects of 62 days of daily or as needed dosing with 60 mg Dapoxetine showed mild withdrawal symptoms with a slightly higher incidence of insomnia and dizziness in subjects switched to placebo after daily dosing

Eye disorders
The use of Dapoxetine has been associated with ocular effects such as mydriasis and eye pain. Dapoxetine should be used with caution in patients with raised intraocular pressure or those at risk of angle closure glaucoma

Interactions with other medicinal products and other forms of interactions:
Tadalafil
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 Cmax by 15 %, relative to the AUC and Cmax values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20 mg) exposure (AUC) 4-fold and Cmax 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 Cmax. 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
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. Based on the results of a clinical study in which 150 subjects received 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.

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

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 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
Concomitant use of riociguat with PDES 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 coadministered 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 coadministration 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).

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 acetyl salicylic acid.

Antidiabetic medicinal products
Specific interaction studies with antidiabetic medicinal products were not conducted.

Dapoxetine hydrochloride

Potential for interaction with monoamine oxidase inhibitors
In patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Animal data on the effects of combined use of an SSRI and MAOIs suggest that these medicinal products may act synergistically to elevate blood pressure and evoke behavioural excitation. Therefore, Dapoxetine should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, an MAOI should not be administered within 7 days after Dapoxetine has been discontinued.

Potential for interaction with thiondazine
Thiondazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias. Medicinal products such as Dapoxetine that inhibit the CYP2D6 isoenzyme appear to inhibit the metabolism of thiondazine and the resulting elevated levels of thiondazine are expected to augment the prolongation of the QTc interval. Dapoxetine should not be used in combination with thiondazine or within 14 days of discontinuing treatment with thiondazine. Similarly, thiondazine should not be administered within 7 days after Dapoxetine has been discontinued.

Medicinal/herbal products with serotonergic effects
As with other SSRIs, co-administration with serotonergic medicinal/herbal products (including MAOIs, L-tryptophan, triptans, tramadol, linezolid, SSRIs, SNRIs, lithium and St. John's Wort (Hypericum perforatum) preparations) may lead to an incidence of serotonin associated effects. Dapoxetine should not be used in combination with other SSRIs, MAOIs or other serotonergic medicinal/herbal products or within 14 days

of discontinuing treatment with these medicinal/herbal products. Similarly, these medicinal/herbal products should not be administered within 7 days after Dapoxetine has been discontinued.

CNS active medicinal products

The use of Dapoxetine in combination with CNS active medicinal products (e.g., antiepileptics, antidepressants, antipsychotics, anxiolytics, sedative hypnotics) has not been systematically evaluated in patients with premature ejaculation. Consequently, caution is advised if the concomitant administration of Dapoxetine and such medicinal products is required.

Pharmacokinetic interactions

Effects of co-administered medicinal products on the pharmacokinetics of dapoxetine
In vitro studies in human liver, kidney, and intestinal microsomes indicate dapoxetine is metabolized primarily by CYP2D6, CYP3A4 and flavin monooxygenase 1 (FMO1). Therefore, inhibitors of these enzymes may reduce dapoxetine clearance.

CYP3A4 inhibitors

Potent CYP3A4 inhibitors. Administration of ketoconazole (200 mg twice daily for 7 days) increased the Cmax and AUCinf of dapoxetine (60 mg single dose) by 35% and 99%, respectively. Considering the contribution of both unbound dapoxetine and desmethyldapoxetine, the Cmax of the active fraction may be increased by approximately 25% and the AUC of the active fraction may be doubled if taken with potent CYP3A4 inhibitors.

The increases in the Cmax and AUC of the active fraction may be markedly increased in a part of the population which lack a functional CYP2D6 enzyme, i.e., CYP2D6 poor metabolizers, or in combination with potent inhibitors of CYP2D6. Therefore, concomitant use of Dapoxetine and potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazodone, nelfinavir and atazanavir, is contraindicated.

Moderate CYP3A4 inhibitors. Concomitant treatment with moderate CYP3A4 inhibitors (e.g., erythromycin, clarithromycin, fluconazole, amprenavir, fosamprenavir, aprepitant, verapamil, diltiazem) may also give rise to significantly increased exposure of dapoxetine and desmethyldapoxetine, especially in CYP2D6 poor metabolizers. The maximum dose of dapoxetine should be 30 mg if dapoxetine is combined with any of these drugs

These two measures apply to all patients unless the patient has been verified to be a CYP2D6 extensive metabolizer by geno- or phenotyping. In patients verified to be CYP2D6 extensive metabolizers, a maximum dose of 30 mg is advised if dapoxetine is combined with a potent CYP3A4 inhibitor and caution is advised if dapoxetine in 60 mg doses is taken concomitantly with a moderate CYP3A4 inhibitor.

Potent CYP2D6 inhibitors

The Cmax and AUCinf of dapoxetine (60 mg single dose) increased by 50% and 88%, respectively, in the presence of fluoxetine (60 mg/day for 7 days). Considering the contribution of both unbound dapoxetine and desmethyldapoxetine, the Cmax of the active fraction may be increased by approximately 50% and the AUC of the active fraction may be doubled if taken with potent CYP2D6 inhibitors. These increases in the Cmax and AUC of the active fraction are similar to those expected for CYP2D6 poor metabolizers and may result in a higher incidence and severity of dose dependent adverse events.

Effects of dapoxetine on the pharmacokinetics of co-administered medicinal products

Tamsulosin
Concomitant administration of single or multiple doses of 30 mg or 60 mg dapoxetine to patients receiving daily doses of tamsulosin did not result in changes in the pharmacokinetics of tamsulosin. The addition of dapoxetine to tamsulosin did not result in a change in the orthostatic profile and there were no differences in orthostatic effects between tamsulosin

combined with either 30 or 60 mg dapoxetine and tamsulosin alone; however, Dapoxetine should be prescribed with caution in patients who use alpha adrenergic receptor antagonists due to possible reduced orthostatic tolerance.

Medicinal products metabolized by CYP2D6

Multiple doses of dapoxetine (60 mg/day for 6 days) followed by a single 50 mg dose of desipramine increased the mean Cmax and AUCinf of desipramine by approximately 11% and 19%, respectively, compared to desipramine administered alone. Dapoxetine may give rise to a similar increase in the plasma concentrations of other drugs metabolized by CYP2D6. The clinical relevance is likely to be small.

Medicinal products metabolized by CYP3A4

Multiple dosing of dapoxetine (60 mg/day for 6 days) decreased the AUCinf of midazolam (8 mg single dose) by approximately 20% (range -60 to +18%). The clinical relevance of the effect on midazolam is likely to be small in most patients. The increase in CYP3A activity may be of clinical relevance in some individuals concomitantly treated with a medicinal product mainly metabolized by CYP3A and with a narrow therapeutic window.

Medicinal products metabolized by CYP2C19

Multiple dosing of dapoxetine (60 mg/day for 6 days) did not inhibit the metabolism of a single 40 mg dose of omeprazole. Dapoxetine is unlikely to affect the pharmacokinetics of other CYP2C19 substrates.

Medicinal products metabolized by CYP2C9

Multiple dosing of dapoxetine (60 mg/day for 6 days) did not affect the pharmacokinetics or pharmacodynamics of a single 5 mg dose of glyburide. Dapoxetine is unlikely to affect the pharmacokinetics of other CYP2C9 substrates.

Warfarin and medicinal products that are known to affect coagulation and/or platelet function

There are no data evaluating the effect of chronic use of warfarin with dapoxetine; therefore, caution is advised when dapoxetine is used in patients taking warfarin chronically. In a pharmacokinetic study, dapoxetine (60 mg/day for 6 days) did not affect the pharmacokinetics or pharmacodynamics (PT or INR) of warfarin following a single 25 mg dose. There have been reports of bleeding abnormalities with SSRIs.

Ethanol

Coadministration of a single dose of ethanol, 0.5 g/kg (approximately 2 drinks), did not affect the pharmacokinetics of dapoxetine (60 mg single dose); however, dapoxetine in combination with ethanol increased somnolence and significantly decreased self-rated alertness. Pharmacodynamic measures of cognitive impairment (Digit Vigilance Speed, Digit Symbol Substitution Test) also showed an additive effect when dapoxetine was coadministered with ethanol. Concomitant use of alcohol and dapoxetine increases the chance or severity of adverse reactions such as dizziness, drowsiness, slow reflexes, or altered judgment. Combining alcohol with dapoxetine may increase these alcohol-related effects and may also enhance neurocardiogenic adverse events such as syncope, thereby increasing the risk of accidental injury; therefore, patients should be advised to avoid alcohol while taking Dapoxetine.

Pregnancy and Lactation:

Tadalafil – Dapoxetine is not indicated for use by women.

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/fetal 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

Effects on ability to drive and use machine:

Tadalafil

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.

Dapoxetine hydrochloride

Dapoxetine has minor or moderate influence on the ability to drive and use machines. Dizziness, disturbance in attention, syncope, blurred vision and somnolence have been reported in subjects receiving dapoxetine in clinical trials. Therefore, patients should be warned to avoid situations where injury could result, including driving or operating hazardous machinery.

Combining alcohol with dapoxetine may increase alcohol-related neurocognitive effects and may also enhance neuro-cardiogenic adverse events such as syncope, thereby increasing the risk of accidental injury; therefore, patients should be advised to avoid alcohol while taking Dapoxetine

Undesirable Effects:

Tadalafil

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

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 (≥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). b. Tabulated summary of adverse reactions

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), Retinal vascular occlusion ¹
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss
Cardiac disorders¹			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris ¹ , Ventricular arrhythmia ¹

Vascular disorders			
	Flushing	Hypotension ¹ , 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 ¹ , Exfoliative dermatitis ¹ , Hyperhidrosis (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

- (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.

Dapoxetine hydrochloride

Summary of the safety profile

Syncope and orthostatic hypotension have been reported in clinical trials.

The following adverse drug reactions were reported during Phase 3 clinical trials most commonly and were dose related: nausea (11.0% and 22.2% in 30 mg and 60 mg pm dapoxetine groups, respectively), dizziness (5.8% and 10.9%), headache (5.6% and 8.8%), diarrhoea (3.5% and 6.9%), insomnia (2.1% and 3.9%) and fatigue (2.0% and 4.1%). The most common adverse events leading to discontinuation were nausea (2.2% of Dapoxetine-treated subjects) and dizziness (1.2% of Dapoxetine-treated subjects).

Tabulated list of adverse reactions

The safety of Dapoxetine was evaluated in 4224 subjects with premature ejaculation who participated in five double-blind, placebo-controlled clinical trials. Of the 4224 subjects, 1616 received Dapoxetine 30 mg as needed and 2608 received 60

mg, either as needed or once daily.

Table 1 presents the adverse reactions that have been reported

Table 1: Frequency of Adverse Drug Reactions				
System Organ Class	Adverse Drug Reactions			
	Very Common (1/10)	Common (1/100 to 1/10)	Uncommon (1/1000 to 1/100)	Rare (1/10000 to 1/1000)
Psychiatric disorders		Insomnia, Anxiety, Agitation, Restlessness, Libido decreased, Abnormal dreams	Depression, Depressed mood, Nervousness, Nightmare, Sleep disorder, Bruxism, Euphoric mood, Indifference, Apathy, Mood altered, Initial insomnia, Middle insomnia, Anorgasmia, Confusional state, Hypervigilance, Thinking abnormal, Disorientation, Loss of libido	
Nervous system disorders	Dizziness, Headache	Somnolence, Disturbance in attention, Tremor, Paraesthesia	Dysgeusia, Hypersomnia, Lethargy, Sedation, Depressed level of consciousness, Syncope, Syncope vasovagal, Dizziness postural, Akathisia	Dizziness exertional, Sudden onset of sleep
Eye disorders		Vision blurred	Mydriasis, Visual disturbance	
Ear and labyrinth disorders		Tinnitus	Vertigo	
Cardiac disorders			Sinus arrest, Sinus bradycardia, Tachycardia	
Vascular disorders	Flushing		Hot flush, Hypotension, Systolic hypertension	
Respiratory, thoracic and mediastinal disorders		Sinus congestion, Yawning		
Gastrointestinal disorders	Nausea	Diarrhoea, Dry mouth, Vomiting, Constipation, Abdominal pain, Abdominal pain upper, Dyspepsia, Flatulence, Stomach discomfort, Abdominal distention	Abdominal discomfort, Epigastric discomfort	Defaecation urgency
Skin and subcutaneous tissue disorders		Hyperhidrosis	Pruritis, Cold sweat	
Reproductive system and breast disorders		Erectile dysfunction	Ejaculation failure, Paraesthesia of genital male, Male orgasmic disorder	
General disorders and Administration site conditions		Fatigue, Irritability	Asthenia, Feeling hot, Feeling jittery, Feeling abnormal, Feeling drunk	
Investigations		Blood pressure increased	Heart rate increased, Blood Pressure diastolic increased, Blood pressure orthostatic increased	

Overdose:

Tadalafil

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 with erectile dysfunction. 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.

Dapoxetine hydrochloride

No case of overdose has been reported. There were no unexpected adverse events in a clinical pharmacology study of dapoxetine with daily doses up to 240 mg (two 120 mg doses given 3 hours apart). In general, symptoms of overdose with SSRIs include serotonin-mediated adverse reactions such as somnolence, gastrointestinal disturbances such as nausea and vomiting, tachycardia, tremor, agitation and dizziness. In cases of overdose, standard supportive measures should be adopted as required. Due to high protein binding and large volume of distribution of dapoxetine hydrochloride, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for dapoxetine are known.

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic Properties:

Tadalafil

Mechanism of action

Tadalafil is a potent and selective inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP).
Pharmacodynamic effects
Studies in vitro have shown that 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 phosphodiesterases. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE1, PDE2, and PDE4, enzymes which are found in the heart, brain, blood vessels, liver, 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 > 10,000-fold more potent for PDE5 than for PDE7 through PDE10.

Dapoxetine hydrochloride

Mechanism of action

Dapoxetine is a potent selective serotonin reuptake inhibitor (SSRI) with an IC50 of 1.12 nM, while its major human metabolites, desmethyldapoxetine (IC50 = 1.0 nM) and didesmethyldapoxetine (IC50 = 2.0 nM) are equivalent or less potent (dapoxetine-N-oxide (IC50 = 282 nM)). Human ejaculation is primarily mediated by the sympathetic nervous system. The ejaculatory pathway originates from a spinal reflex centre, mediated by the brain stem, which is influenced initially by a number of nuclei in the brain (medial preoptic and paraventricular nuclei). The mechanism of action of dapoxetine in premature ejaculation is presumed to be linked to the inhibition of neuronal reuptake of serotonin and the subsequent potentiation of the neurotransmitter's action at pre- and postsynaptic receptors.

Pharmacokinetics Properties:

Tadalafil

Absorption

Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (Cmax) is achieved at a median time of 4 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 after a single 10 mg administration) had no clinically relevant effects on the rate and extent of absorption.

Distribution

The mean volume of distribution is approximately 77 l at steady state, 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.

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 3.4 l/h at steady state and the mean terminal half-life is 16 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).

Dapoxetine hydrochloride

Absorption

Dapoxetine is rapidly absorbed with maximum plasma concentrations (Cmax) occurring approximately 1-2 hours after tablet intake. The absolute bioavailability is 42% (range 15–76%), and dose proportional increases in exposure (AUC and Cmax) are observed between the 30 and 60 mg dose strengths. Following multiple doses, AUC values for both dapoxetine and the active metabolite desmethyldapoxetine (DED) increase by approximately 50% when compared to single dose AUC values.

Ingestion of a high fat meal modestly reduced the Cmax (by 10%) and modestly increased the AUC (by 12%) of dapoxetine and slightly delayed the time for dapoxetine to reach peak concentrations. These changes are not clinically significant. Dapoxetine can be taken with or without food.

Distribution

More than 99% of dapoxetine is bound in vitro to human serum proteins. The active metabolite desmethyldapoxetine (DED) is 98.5% protein bound. Dapoxetine has a mean steady state volume of distribution of 162 L.

Biotransformation

In vitro studies suggest that dapoxetine is cleared by multiple enzyme systems in the liver and kidneys, primarily CYP2D6, CYP3A4, and flavin monooxygenase (FMO1). Following oral dosing of 14C-dapoxetine, dapoxetine was extensively metabolized to multiple metabolites primarily through the following biotransformational pathways: N-oxidation, N-demethylation, naphthyl hydroxylation, glucuronidation and sulfation. There was evidence of presystemic first-pass metabolism after oral administration.

Intact dapoxetine and dapoxetine-N-oxide were the major circulating moieties in the plasma. In vitro binding and transporter studies show that dapoxetine-N-oxide is inactive. Additional metabolites including desmethyldapoxetine and didesmethyldapoxetine account for less than 3% of the total circulating drug-related materials in plasma. In vitro binding studies indicate that DED is equipotent to dapoxetine and didesmethyldapoxetine has approximately 50% of the potency of dapoxetine. The unbound exposures (AUC and Cmax) of DED are approximately 50% and 23%, respectively, of the unbound exposure of dapoxetine.

Elimination

The metabolites of dapoxetine were primarily eliminated in the urine as conjugates. Unchanged active substance was not detected in the urine. Following oral administration, dapoxetine has an initial (disposition) half-life of approximately 1.5 hours, with plasma levels less than 5% of peak concentrations by 24 hours post-dose, and a terminal half-life of approximately 19 hours. The terminal half-life of DED is approximately 19 hours.

Preclinical Safety data:

Tadalafil

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

There was no evidence of teratogenicity, embryotoxicity, or fetotoxicity in rats or mice that received up to 1000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free drug at this dose was approximately 18-times the human AUC at a 20 mg dose.

There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7-18.6] than seen in humans given a single 20 mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs.

Dapoxetine hydrochloride

A full assessment of the safety pharmacology, repeat dose toxicology, genetic toxicology, carcinogenicity, dependence/withdrawal liability, phototoxicity and developmental reproductive toxicology of dapoxetine was conducted in preclinical species (mouse, rat, rabbit, dog and monkey) up to the maximum tolerated doses in each species. Due to the more rapid bioconversion in the preclinical species than in man, pharmacokinetic exposure indices (Cmax and AUC0-24 hr) at the maximum tolerated doses in some studies approached those observed in man. However, the body weight normalized dose multiples were greater than 100-fold. There were no clinically relevant safety hazards identified in any of these studies.

In studies with oral administration, dapoxetine was not carcinogenic to rats when administered daily for approximately two years at doses up to 225 mg/kg/day, yielding approximately twice the exposures (AUC) seen in human males given the Maximum Recommended Human Dose (MRHD) of 60 mg. Dapoxetine also did not cause tumors in Tg rasH2 mice when administered at the maximum possible doses of 100 mg/kg for 6 months and 200 mg/kg for 4 months. The steady state exposures of dapoxetine in mice following 6-months oral administration at 100 mg/kg/day were less than the single dose exposures observed clinically at 60 mg.

There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats and no adverse signs of embryotoxicity or fetotoxicity in the rat or rabbit. Reproductive toxicity studies did not include studies to assess the risk of adverse effects after exposure during the peri-post-natal period.

PHARMACEUTICAL PARTICULARS:

Incompatibilities: Not applicable.

Shelf life: 24 Months.

Special Precautions for storage: Store below 30°C.

Nature and contents of container: Carton containing Blister packs of 4 tablets along with pack insert.

VERSION NO.: 00

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