MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product:

1.1. Name of the medicinal product:
Generic Name/INN Name: Tadalafil 20 mg and Dapoxetine 30mg Tablets
Trade Name: TADALIS 20 PLUS

1.2 Strength:
Each film coated tablet contains:
Tadalafil USP……..20 mg
Dapoxetine Hydrochloride eq. to
Dapoxetine ……..30 mg
Excipients……q.s.
Colour: Red oxide of iron USP & Titanium dioxide BP

1.3 Pharmaceutical form:
Solid Oral Dosage form (Tablet)

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2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Spec.	Label Claim (mg)	Qty. / Tab (mg)	% w/w	Function
1	Tadalafil *	USP	20.00	20.00	5.56 %	Active agent
2	Dapoxetine hydrochloride eq. to Dapoxetine*	In-House	33.57 Eq. to. 30.00	33.57	9.33 %	Active agent
3	Lactose monohydrate **	BP		246.43	68.45 %	Diluent
4	Hydroxypropyl Cellulose	BP		5.000	1.39 %	Binder
5	Croscarmellose sodium	BP		20.000	5.56 %	Super Disintegrant
Binding						
6	Sodium lauryl sulfate	BP		5.000	1.39 %	Surfactant
7	Hydroxypropyl Cellulose	BP		3.000	0.83 %	Binder
8	Purified water***	BP		40.000	--	Binding solvent
Lubrication						
9	Colloidal anhydrous silica	BP		2.000	0.56 %	Glidant
10	Croscarmellose sodium	BP		10.000	2.78 %	Super Disintegrant
11	Magnesium Stearate	BP		5.000	1.39 %	Lubricant
Weight of the uncoated tablet				350.00	--	--
Film Coating						
12.	Sheffcoat PVA Brown (Product code: 5Y01264)	IHS		10.000	2.78 %	Coating material
13.	Purified water***	BP		40.000	--	Solvent for coating
Weight of the film coated tablet				360.00	100 %	--

*The quantity of the Tadalafil & Dapoxetine hydrochloride has to be calculated as per the Assay & Loss on Drying.
** Quantity of Lactose monohydrate will vary as per the quantity of the APIs.
*** Not remain in final product.

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3. Pharmaceutical form:

Dosage Form:

Solid Oral Dosage form (Tablet)

Visual & Physical characteristics of the product:

A reddish brown colored capsule shaped film coated tablet debossed with "**Evans**" on one side and "**B**" and "**20**" on other side with breakline between "**B**" and "**20**"

4. Clinical particulars

4.1. Therapeutic indications:

TADALIS 20 PLUS Tablet is used in the treatment in the following conditions:

Treatment of erectile dysfunction in adult males.

In order for tadalafil to be effective for the treatment of erectile dysfunction, sexual stimulation is required.

Tadalis 20 Plus is indicated for the treatment of premature ejaculation (PE) in adult men aged 18 to 64 years.

Tadalis 20 Plus should only be prescribed to patients who meet all the following criteria:

An intravaginal ejaculatory latency time (IELT) of less than two minutes; and

Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the patient wishes; and

Marked personal distress or interpersonal difficulty as a consequence of PE; and

Poor control over ejaculation; and

A history of premature ejaculation in the majority of intercourse attempts over the prior 6 months.

Tadalis 20 Plus should be administered only as on-demand treatment before anticipated sexual activity. It should not be prescribed to delay ejaculation in men who have not been diagnosed with PE.

Tadalis 20 Plus is not indicated for use by women.

4.2. Posology and method of administration:

Method of administration

Tablets for oral use. Tablets should be swallowed whole to avoid the bitter taste. It is recommended that tablets be taken with at least one full glass of water. Dapoxetine may be taken with or without food.

Posology

Adult Men (aged 18 to 64 years)

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The recommended dose is Tadalafil 10 mg and Dapoxetine 30 mg is taken prior to anticipated sexual activity and with or without food.

In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity.

It is not intended for continuous daily use. It should be taken only when sexual activity is anticipated. It must not be taken more frequently than once every 24 hours.

The maximum dose frequency is once per day.

Tadalafil 10 mg and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

Special Populations

Elderly Men

Dose adjustments are not required in elderly patients.

Men with Renal Impairment

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

Once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment.

Men with Hepatic Impairment

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

Once-a-day dosing of tadalafil for the treatment of erectile dysfunction has not been evaluated in patients with hepatic impairment; therefore if prescribed, a careful individual benefit/risk evaluation must be undertaken by the prescribing physician.

Men with Diabetes

Dose adjustments are not required in diabetic patients.

Paediatric population

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

Dapoxetine is not intended for continuous daily use. Dapoxetine should be taken only when sexual activity is anticipated. Dapoxetine must not be taken more frequently than once every 24 hours.

If the individual response to 30 mg is insufficient and the patient has not experienced moderate or severe adverse reactions or prodromal symptoms suggestive of syncope, the dose may be increased to a maximum recommended dose of 60 mg taken as needed approximately 1 to 3 hours prior to sexual activity. The incidence and severity of adverse events is higher with the 60 mg dose.

If the patient experienced orthostatic reactions on the starting dose, no dose escalation to 60 mg should be performed.

A careful appraisal of individual benefit risk of Dapoxetine should be performed by the physician after the first four weeks of treatment (or at least after 6 doses of treatment) to determine whether continuing treatment with Dapoxetine is appropriate.

Data regarding the efficacy and safety of Dapoxetine beyond 24 weeks are limited. The clinical need of continuing and the benefit risk balance of treatment with Dapoxetine should be re-evaluated at least every six months.

Elderly (age 65 years and over)

The efficacy and safety of Dapoxetine have not been established in patient's age 65 years and over.

Paediatric population

There is no relevant use of Dapoxetine in this population in the indication of premature ejaculation.

Patients with renal impairment

Caution is advised in patients with mild or moderate renal impairment. Dapoxetine is not recommended for use in patients with severe renal impairment.

Patients with hepatic impairment

Dapoxetin is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh Class B and C).

Known CYP2D6 poor metabolizers or patients treated with potent CYP2D6 inhibitors

Caution is advised if increasing the dose to 60 mg in patients known to be of CYP2D6 poor metabolizer genotype or in patients concomitantly treated with potent CYP2D6 inhibitors.

Patients treated with moderate or potent inhibitors of CYP3A4

Concomitant use of potent CYP3A4 inhibitors is contraindicated. The dose should be restricted to 30 mg in patients concomitantly treated with moderate CYP3A4 inhibitors and caution is advised.

4.3. Contraindications

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

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, thioridazine should not be administered within 7 days after Tadalis 20 Plus 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.

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 (< 90/50mmHg), 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.

4.4. Special warnings and precautions for use:

General recommendations

Dapoxetine is only indicated in men with Premature Ejaculation who meet all the criteria above. 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.

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

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.

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.

The following groups of patients with cardiovascular disease were not included in PAH clinical studies:

- Patients with clinically significant aortic and mitral valve disease

- Patients with pericardial constriction

- Patients with restrictive or congestive cardiomyopathy

- Patients with significant left ventricular dysfunction

- Patients with life-threatening arrhythmias

- Patients with symptomatic coronary artery disease

- Patients with uncontrolled hypertension.

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Should signs of pulmonary oedema occur when tadalafil is administered, the possibility of associated PVOD should be considered.

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Tadalafil has systemic vasodilatory properties that may result in transient decreases in blood pressure. Physicians should carefully consider whether their patients with certain underlying conditions, such as severe left ventricular outflow obstruction, fluid depletion, autonomic hypotension or patients with resting hypotension, could be adversely affected by such vasodilatory effects.

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.

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.

Decreased or sudden hearing loss

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

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.

Renal and hepatic impairment

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

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.

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 and hepatic 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.

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). 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).

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.

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.

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.

Visual defects and cases of NAION have been reported in connection with the intake of tadalafil and other PDE5 inhibitors. Tadalafil and consult a physician immediately.

4.5. Interaction with other medicinal products and other forms of interaction:

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. 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 thioridazine

Thioridazine 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 thioridazine and the resulting elevated levels of thioridazine are expected to augment the prolongation of the QTc interval. Dapoxetine should not be used in combination with thioridazine or within 14 days of discontinuing treatment with thioridazine. Similarly, thioridazine 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.

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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.

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. Concomitant use of Dapoxetine and potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazodone, nelfinavir and atazanavir, is contraindicated. Grapefruit juice is also a potent CYP3A4 inhibitor and should be avoided within 24 hours prior to taking Dapoxetine.

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.

Potent CYP2D6 inhibitors

The C_{max} and AUC_{inf} 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 C_{max} 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 C_{max} 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. 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

Dapoxetine may give rise to a similar increase in the plasma concentrations of other drugs metabolized by CYP2D6.

Medicinal products metabolized by CYP3A4

Multiple dosing of dapoxetine (60 mg/day for 6 days) decreased the AUC_{inf} of midazolam (8 mg single dose) by approximately 20% (range -60 to +18%).

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 glibenclamide. 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

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 of warfarin following a single 25 mg dose.

There have been reports of bleeding abnormalities with SSRIs.

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.

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.

Alcohol concentrations (mean maximum blood concentration 0.08 %) were not affected by co-administration with tadalafil (10 mg or 20 mg). In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol. Alcohol was administered in a manner to maximise the rate of alcohol absorption (overnight fast with no food until 2 hours after alcohol).

Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 mL of 40 % alcohol [vodka] in an 80 kg male) but, in some subjects, postural dizziness and orthostatic hypotension were observed. When tadalafil was administered with lower doses of alcohol (0.6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).

Effects of other substances on tadalafil

Cytochrome P450 inhibitors

Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased tadalafil (10 mg) exposure (AUC) 2-fold and C_{max} by 15 %, relative to the AUC and C_{max} values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20 mg) exposure (AUC) 4-fold and C_{max} by 22 %. Ritonavir, a protease inhibitor (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20 mg) exposure (AUC) 2-fold with no change in C_{max}. Ritonavir (500 mg or 600 mg twice daily) increased tadalafil (20 mg) single-dose exposure (AUC) by 32 % and decreased Cmax by 30 %. 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.

Consequently, the incidence of the adverse reactions might be increased.

Transporters

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

P-glycoprotein substrates (e.g. digoxin)

Tadalafil (40 mg once per day) had no clinically significant effect on the pharmacokinetics of digoxin.

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.

Endothelin-1 receptor antagonists (e.g. bosentan)

Bosentan (125 mg twice daily), a substrate of CYP2C9 and CYP3A4 and a moderate inducer of CYP3A4, CYP2C9 and possibly CYP2C19, reduced tadalafil (40 mg once per day) systemic exposure by 42 % and Cmax by 27 % following multiple dose co-administration. The efficacy of tadalafil in patients already on bosentan therapy has not been conclusively demonstrated. Tadalafil did not affect the exposure (AUC and Cmax) of bosentan or its metabolites.

The safety and efficacy of combinations of tadalafil and other endothelin-1 receptor antagonists have not been studied.

Effects of tadalafil on other medicinal products

Nitrates

In clinical studies, tadalafil (5 mg, 10 mg 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 to 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 mg 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 12 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 -doxazosin see above) is, in general, minor and not likely to be clinically relevant. Analysis of Phase 3 clinical trial data showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medicinal products. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicinal products.

Riociguat

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

5-alpha reductase inhibitors

In a clinical trial that compared tadalafil 5 mg co-administered with finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal drug-drug interaction study evaluating the effects of

tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)

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

Oral contraceptive pill

At steady-state, tadalafil (40 mg once per day) increased ethinylestradiol exposure (AUC) by 26 % and Cmax by 70 % relative to oral contraceptive administered with placebo. There was no statistically significant effect of tadalafil on levonorgestrel which suggests the effect of ethinylestradiol is due to inhibition of gut sulphation by tadalafil. The clinical relevance of this finding is uncertain.

Terbutaline

A similar increase in AUC and Cmax seen with ethinylestradiol may be expected with oral administration of terbutaline, probably due to inhibition of gut sulphation by tadalafil. The clinical relevance of this finding is uncertain.

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.

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.

4.6. Pregnancy and lactation

Pregnancy

Tadalis 20 plus is not indicated for use by women.

Breast-feeding

Tadalafil should not be used during breast-feeding. It is not known if either dapoxetine or its metabolites are excreted in human milk.

Fertility

Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men.

4.7. Effects on ability to drive and use machines

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 neurocardiogenic adverse events such as syncope, thereby increasing the risk of accidental injury; therefore, patients should be advised to avoid alcohol while taking Dapoxetine.

Tadalafil has negligible influence on the ability to drive or use machines.

4.8. Undesirable effects:

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 prn 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 Reactions (MedDRA)

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System Organ Class	**Very common (> 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10000 to < 1/1000)**
Psychiatric disorders		Anxiety, Agitation, Restlessness, Insomnia, Abnormal dreams, Libido decreased	Depression, Depressed mood, Euphoric mood, Mood altered, Nervousness, Indifference, Apathy, Confusional state, Disorientation, Thinking abnormal, Hypervigilance, Sleep disorder, Initial insomnia, Middle insomnia, Nightmare, Bruxism, Loss of libido, Anorgasmia	
Immune system disorders			Hypersensitivity reactions	Angioedema
Nervous system disorders	Dizziness, Headache	Somnolence, Disturbance in attention, Tremor, Paraesthesia, Headache	Syncope, Syncope vasovagal, Dizziness postural, Akathisia, Dysgeusia, Hypersomnia, Lethargy, Sedation, Depressed level of consciousness	Dizziness exertional, Sudden onset of sleep, Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures[2], Transient amnesia
Eye disorders		Vision blurred	Mydriasis, Eye pain, Visual disturbance Blurred vision,	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischaemic optic neuropathy

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				(NAION)[2], Retinal vascular occlusion
Ear and labyrinth disorders		Tinnitus	Vertigo	Sudden hearing loss
Cardiac disorders			Sinus arrest, Sinus bradycardia, Tachycardia	Myocardial infarction, Unstable angina pectoris, Ventricular arrhythmia
Vascular disorders		Flushing	Hypotension, Systolic hypertension, Hot flush	
Respiratory, thoracic and mediastinal disorders		Sinus congestion, Yawning	Dyspnoea, Epistaxis	
Gastrointestinal disorders	Nausea, Dyspepsia	Diarrhoea, Vomiting, Constipation, Abdominal pain, Abdominal pain upper, Dyspepsia, Flatulence, Stomach discomfort, Abdominal distension, Dry mouth	Abdominal discomfort, Epigastric discomfort	Defaecation urgency
Skin and subcutaneous tissue disorders		Hyperhidrosis	Pruritis, Cold sweat, Rash	Urticaria, Stevens-Johnson syndrome, Exfoliative dermatitis, Hyperhydrosis (sweating)
Reproductive system and		Erectile dysfunction	Ejaculation failure, Male orgasmic disorder,	

MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

breast disorders			Paraesthesia of genital male	
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	

Adverse drug reactions reported in the 9-month long-term open-label extension trial were consistent with those reported in the double-blind studies and no additional adverse drug reactions were reported.

Description of selected adverse reactions

Syncope characterized as loss of consciousness, with bradycardia or sinus arrest observed in patients wearing Holter monitors, has been reported in clinical trials and is considered medicinal product-related. The majority of cases occurred during the first 3 hours after dosing, after the first dose or associated with study-related procedures in the clinical setting (such as blood draw and orthostatic maneuvers and blood pressure measurements). Prodromal symptoms often preceded the syncope.

The occurrence of syncope and possibly prodromal symptoms appears dose dependent as demonstrated by higher incidence among patients treated with higher than recommended doses in Phase 3 clinical trials.

Orthostatic hypotension has been reported in clinical trials.The frequency of syncope characterized as loss of consciousness in the Dapoxetine clinical development program varied depending on the population studied and ranged from 0.06% (30 mg) to 0.23% (60 mg) for subjects enrolled in the Phase 3 placebo-controlled clinical trials to 0.64% (all doses combined) for Phase 1 non-PE healthy volunteer studies.

Other special populations

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.

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.

Results of a safety study showed a slightly higher incidence of withdrawal symptoms of mild or moderate insomnia and dizziness in subjects switched to placebo after 62 days of daily dosing.

4.9. Overdose

Single doses of Tadalafil 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.

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.

5. Pharmacological properties:

5.1. Pharmacodynamics properties:

Dapoxetine

Pharmacotherapeutic group: Other Urologicals, ATC code: G04BX14

Mechanism of action

Dapoxetine is a potent selective serotonin reuptake inhibitor (SSRI) with an IC_{50} of 1.12 nM, while its major human metabolites, desmethyldapoxetine and didesmethyldapoxetine are equivalent or less potent (dapoxetine-N-oxide (IC_{50} = 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.

Tadalafil
Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction, ATC Code: G04BE08.

Mechanism of action

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

Erectile dysfunction

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 treatment of erectile dysfunction in the absence of sexual stimulation.

Pulmonary arterial hypertension

Pulmonary arterial hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed.

5.2. Pharmacokinetic properties:

Dapoxetine

Absorption

Dapoxetine is rapidly absorbed with maximum plasma concentrations (C_{max}) occurring approximately 1-2 hours after tablet intake. The absolute bioavailability is 42% (range 15-76%), and dose proportional increases in exposure (AUC and C_{max}) 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 C_{max} (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.

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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 ^{14}C-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 dapoxetin. The unbound exposures (AUC and C_{max}) 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.

Pharmacokinetics in special populations

The metabolite DED contributes to the pharmacological effect of Dapoxetine, particularly when the exposure of DED is increased. Below, in some populations, the increase in active fraction parameters is presented. This is the sum of the unbound exposure of dapoxetine and DED. DED is equipotent to dapoxetine. The estimation assumes equal distribution of DED to the CNS but it is unknown whether this is the case.

Race

Analyses of single dose clinical pharmacology studies using 60 mg dapoxetine indicated no statistically significant differences between Caucasians, Blacks, Hispanics and Asians. A clinical study conducted to compare the pharmacokinetics of dapoxetine in Japanese and Caucasian subjects showed 10% to 20% higher plasma levels (AUC and peak concentration)

of dapoxetine in Japanese subjects due to lower body weight. The slightly higher exposure is not expected to have a meaningful clinical effect.

Elderly (age 65 years and over)

Analyses of a single dose clinical pharmacology study using 60 mg dapoxetine showed no significant differences in pharmacokinetic parameters (C_{max}, AUC_{inf}, T_{max}) between healthy elderly males and healthy young adult males. The efficacy and safety has not been established in this population.

Renal impairment

A single-dose clinical pharmacology study using a 60 mg dapoxetine dose was conducted in subjects with mild (CrCL 50 to 80 mL/min), moderate (CrCL 30 to < 50 mL/min), and severe renal impairment (CrCL < 30 mL/min) and in subjects with normal renal function (CrCL > 80 mL/min). No clear trend for an increase in dapoxetine AUC with decreasing renal function was observed. AUC in subjects with severe renal impairment was approximately 2-fold that of subjects with normal renal function, although there are limited data in patients with severe renal impairment. Dapoxetine pharmacokinetics have not been evaluated in patients requiring renal dialysis.

Hepatic impairment

In patients with mild hepatic impairment, unbound C_{max} of dapoxetine is decreased by 28% and unbound AUC is unchanged. The unbound C_{max} and AUC of the active fraction (the sum of the unbound exposure of dapoxetine and desmethyldapoxetine) were decreased by 30% and 5%, repectively. In patients with moderate hepatic impairment, unbound C_{max} of dapoxetine is essentially unchanged (decrease of 3%) and unbound AUC is increased by 66%. The unbound C_{max} and AUC of the active fraction were essentially unchanged and doubled, respectively.

In patients with severe hepatic impairment, the unbound C_{max} of dapoxetine was decreased by 42% but the unbound AUC was increased by approximately 223%. The C_{max} and AUC of the active fraction had similar changes.

CYP2D6 Polymorphism

In a single dose clinical pharmacology study using 60 mg dapoxetine, plasma concentrations in poor metabolizers of CYP2D6 were higher than in extensive metabolizers of CYP2D6 (approximately 31% higher for C_{max} and 36% higher for AUC_{inf} of dapoxetine and 98% higher for C_{max} and 161% higher for AUC_{inf} of desmethyldapoxetine). The active fraction of Dapoxetine may be increased by approximately 46% at C_{max} and by approximately 90% at AUC. This increase may result in a higher incidence and severity of dose dependent adverse events. The safety of Dapoxetine in poor metabolizers of CYP2D6 is of particular concern

with concomitant administration of other medicinal products that may inhibit the metabolism of dapoxetine such as moderate and potent CYP3A4 inhibitors.

Tadalafil

Absorption

Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food, thus Tadalafil may be taken with or without food. The time of dosing (morning versus evening 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 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.

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

Linearity/Non-Linearity

Over a dose range of 2.5 mg to 20 mg, exposure (AUC) increases proportionally with dose in healthy subjects. Between 20 mg to 40 mg, a less than proportional increase in exposure is observed.

During tadalafil 20 mg and 40 mg once daily dosing, steady-state plasma concentrations are attained within 5 days, and exposure is approximately 1.5 fold of that after a single dose.

Population Pharmacokinetics

Pharmacokinetics determined with a population approach in patients with erectile dysfunction is similar to pharmacokinetics in subjects without erectile dysfunction.

In patients with pulmonary hypertension not receiving concomitant bosentan, the average tadalafil exposure at steady-state following 40 mg was 26 % higher when compared to those of healthy volunteers. There were no clinically relevant differences in Cmax compared to healthy volunteers. The results suggest a lower clearance of tadalafil in patients with pulmonary hypertension compared to healthy volunteers.

Special Populations

Elderly

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

Renal Insufficiency

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

Hepatic Insufficiency

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

Patients with diabetes

Tadalafil exposure (AUC) in patients with diabetes was approximately 19 % lower than the AUC value for healthy subjects after a 10 mg dose. This difference in exposure does not warrant a dose adjustment.

Race

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

Gender

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

5.3. Preclinical safety data

Dapoxetine

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 (C_{max} and $AUC_{0\text{-}24\ hr}$) 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.

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 foetotoxicity 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.

6. Pharmaceutical particulars:

6. 1. List of Excipients:

The excipients used are
Lactose Monohydrate,
Cross Carmellose Sodium,
Hydroxypropyl Cellulose,
Colloidal anhydrous silica
Sodium Lauryl Sulfate,
Magnesium Stearate
Sheffcoat PVA Brown (Product code: 5Y01264)

6. 2. Incompatibilities:

Not applicable

6.3. Shelf life:

36 months

6.4. Special precautions for storage:

Store below 30°C in dry place.

6.5. Nature and contents of container:

1) In ALU-PVC Blister

Primary Packing:

4 Tablets pack in ALU-PVC Blister pack.

Secondary Packing:

Such one ALU-PVC blister each contain 4 tablets was packed in printed mono carton with patient information leaflet.

2) 1000 Tablets in white colour HDPE Jar.

6.6. Special precautions for disposal:

Any unused medicinal product or waste material should be disposed of in accordance with local requirement.

MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

7. Applicant:

Name and Address of Applicant

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