75 (L) x 18 (W) x 58 (H) mm

1. Name of the medicinal product:

SENGRA FORTE

1.1 Name of the medicinal product:

Tadalafil & Dapoxetine Tablets

1.2 Strength:

Each film coated tablet contains:

Tadalafil USP 10 mg

Dapoxetine Hydrochloride

Eq to Dapoxetine 30 mg

Excipients …… q.s.

Colour: Red Oxide of Iron

1.3 Pharmaceutical form:

Film Coated Tablets for Oral use

2. Qualitative and quantitative composition

Qualitative declaration:

Each film coated tablet contains:

Tadalafil USP 10 mg

Dapoxetine Hydrochloride

Eq to Dapoxetine 30 mg

Quantitative declaration:

Each film coated tablet contains:

Tadalafil USP 10 mg

Dapoxetine Hydrochloride

Eq to Dapoxetine 30 mg

Colour: Red Oxide of Iron

For Excipients see section 6.1

3. Pharmaceutical form

Film Coated Tablets for Oral use

4. Clinical particulars:

4.1 Therapeutic indications:

SENGRA FORTE is indicated for the treatment of premature ejaculation (PE) & Treatment of erectile dysfunction in adult male aged 18 to 64 years.

SENGRA FORTE 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.

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

SENGRA FORTE is not indicated for use by women.

4.2 Posology and method of administration

SENGRA FORTE is not indicated for use by women.

Adult men (aged 18 to 64 years)

The recommended starting dose for all patients is Tadalafil 10 mg & Dapoxetine Hydrochloride 30 mg, taken as needed approximately 1 to 3 hours prior to sexual activity. Treatment should not be initiated with the Tadalafil 20 mg & Dapoxetine Hydrochloride 60 mg dose.

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

If the individual response to Tadalafil 10 mg & Dapoxetine Hydrochloride 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 Tadalafil 20 mg & Dapoxetine Hydrochloride 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 Tadalafil 20 mg & Dapoxetine Hydrochloride 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 SENGRA FORTE 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 SENGRA FORTE is appropriate.

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

Elderly (age 65 years and over)

The efficacy and safety of SENGRA FORTE have not been established in patients age 65 years and over

Paediatric population

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

Patients with renal impairment

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

Patients with hepatic impairment

SENGRA FORTE 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

Patients with diabetes

Dose adjustments are not required in diabetic patients.

Method of administration

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.

SENGRA FORTE may be taken with or without food

Precautions to be taken before handling or administering the medicinal product

Before treatment is initiated, regarding orthostatic hypotension.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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.

In clinical studies, SENGRA FORTE 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 SENGRA FORTE to patients who are using any form of organic nitrate is contraindicated

SENGRA FORTE, 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 SENGRA FORTE 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.

SENGRA FORTE 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.

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 SENGRA FORTE 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 SENGRA FORTE 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 SENGRA FORTE 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.

4.4 Special warnings and precautions for use

General recommendations

SENGRA FORTE is only indicated in men with Premature Ejaculation who meet all the criteria listed in sections 4.1 and 5.1. SENGRA FORTE 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. SENGRA FORTE should not be used in men with erectile dysfunction (ED) who are using PDE5 inhibitors.

Orthostatic hypotension

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 SENGRA FORTE should be avoided.

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.

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.

Patients with cardiovascular risk factors

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. In patients who are taking alpha1 blockers, concomitant administration of SENGRA FORTE may lead to symptomatic hypotension in some patients. The combination of SENGRA FORTE and doxazosin is not recommended.

Use with recreational drugs

Patients should be advised not to use SENGRA FORTE in combination with recreational drugs. Use of SENGRA FORTE 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 SENGRA FORTE in combination with alcohol.
Combining alcohol with SENGRA FORTE 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 SENGRA FORTE

Medicinal products with vasodilatation properties

SENGRA FORTE 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 Tadalafil 10 mg & Dapoxetine Hydrochloride 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

SENGRA FORTE 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

SENGRA FORTE 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

SENGRA FORTE should not be used in individuals below 18 years of age.

Depression and/or psychiatric disorders

SENGRA FORTE 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, Priligy should be discontinued.

Haemorrhage

Caution is advised in patients taking Priligy, 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

SENGRA FORTE 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

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 SENGRA FORTE showed mild withdrawal symptoms with a slightly higher incidence of insomnia and dizziness in subjects switched to placebo after daily dosing

Eye disorders

SENGRA FORTE should be used with caution in patients with raised intraocular pressure or those at risk of angle closure glaucoma.

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

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).

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 inhibitors

A selective inhibitor of CYP3A4, increased Tadalafil exposure (AUC) and Cmax.

A protease inhibitor increased Tadalafil exposure (AUC) with no change in Cmax. Other protease inhibitors, such as and grapefruit juice should be co-administered with caution as they would be expected to increase plasma concentrations of Tadalafil

Cytochrome P450 inducers

A CYP3A4 inducer, reduced tadalafil AUC relative to the AUC values for tadalafil alone. Other inducers of CYP3A4 may also decrease plasma concentrations of tadalafil.

Nitrates

In a patient prescribed any dose of tadalafil (2.5 mg-20 mg), where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Anti-hypertensives (including calcium channel blockers)

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

Riociguat

Concomitant use of riociguat with PDE5 inhibitors, including tadalafil, is contraindicated

5- alpha reductase inhibitors

Caution should be exercised when tadalafil is co- administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)

Although small increase in heart rate 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 increase the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

Alcohol

Alcohol concentrations (mean maximum blood concentration 0.08 %) were not affected by co-administration with tadalafil (10 mg or 20 mg). 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).

Aspirin

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

Potential for interaction with thioridazine

SENGRA FORTE 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 SENGRA FORTE has been discontinued

Medicinal/herbal products with serotonergic effects

SENGRA FORTE 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 SENGRA FORTE has been discontinued

4.6 Pregnancy and lactation

SENGRA FORTE is not indicated for use by women.

Pregnancy

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

Breastfeeding

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

Fertility

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

4.7 Effects on ability to drive and use machines:

SENGRA FORTE has negligible influence on the ability to drive or use machines. Although the frequency of reports of Dizziness, disturbance in attention, syncope, blurred vision and somnolence and SENGRA FORTE arms in clinical trials was similar. Therefore, patients should be warned to avoid situations where injury could result, including driving or operating hazardous machinery.

Combining alcohol with SENGRA FORTE 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 SENGRA FORTE.

4.8 Undesirable effects:

Very common	**Common**	**Uncommon**	**Rare**
Immune system disorders			
	-----	Hypersensitivity reactions	Angioedema

Nervous system disorders			
-----	Headache	Dizziness	Stroke (including haemorrhagic events), Syncope, Transient ischaemic attacks, Migraine, Seizures, Transient amnesia
Eye disorders			
-----	-----	Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischemic optic neuropathy (NAION[2], Retinal vascular occlusion
Ear and labyrinth disorders			
-----	-----	Tinnitus	Sudden hearing loss
Cardiac disorders[1]			
-----	-----	Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris, Ventricular arrhythmia
Vascular disorders			
-----	Flushing	Hypotension, Hypertension	-----

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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, Exfoliative dermatitis, Hyperhydrosis (sweating)
Musculoskeletal, connective tissue and bone disorders			
-----	Back pain, Myalgia, Pain in extremity	-----	-----
Renal and urinary disorders			
-----	-----	Haematuria	-----
Reproductive system and breast disorders			
-----	-----	Prolonged erections	Priapism, Penile haemorrhage, Haematospermia
General disorders and administration site conditions			
-----	-----	Chest pain[1], Peripheral oedema, Fatigue	Facial oedema, Sudden cardiac death

4.9 Overdose:

No case of overdose has been reported.

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There were no unexpected adverse events in a clinical pharmacology study of SENGRA FORTE with 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. Dapoxetine Hydrochloride daily doses up to 240 mg (two 120 mg doses given 3 hours apart).

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.

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 Hydrochloride are known.

5. Pharmacological properties:

5.1 Pharmacodynamics properties:

Mechanism of action

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

Dapoxetine is a potent selective serotonin reuptake inhibitor (SSRI). 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.

5.2 Pharmacokinetic 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 2 hours after dosing. Absolute bioavailability of Tadalafil following oral dosing has not been determined.

The rate and extent of absorption of Tadalafil are not influenced by food, thus Tadalafil may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Distribution

The mean volume of distribution is approximately 63 l, indicating that Tadalafil is distributed into tissues. At therapeutic concentrations, 94 % of Tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.

Less than 0.0005 % of the administered dose appeared in the semen of healthy subjects.

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

Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-daily dosing.

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

Special populations

Elderly

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

Renal insufficiency

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

Hepatic insufficiency

Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There is limited clinical data on the safety of tadalafil in patients with severe hepatic insufficiency (Child- Pugh Class C). If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.

Patients with diabetes

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

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 aninitial (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, 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 (Cmax, AUCinf, Tmax) 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 Cmax of Dapoxetine is decreased by 28% and unbound AUC is unchanged. The unbound Cmax 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 Cmax of Dapoxetine is essentially unchanged (decrease of 3%) and unbound AUC is increased by 66%. The unbound Cmax and AUC of the active fraction were essentially unchanged and doubled, respectively. In patients with severe hepatic impairment, the unbound Cmax of Dapoxetine was decreased by 42% but the unbound AUC was increased by approximately 223%. The Cmax 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 Cmax and 36% higher for AUCinf of Dapoxetine and 98% higher for Cmax and 161% higher for AUCinf of desmethyldapoxetine). The active fraction may be increased by approximately 46% at Cmax and by approximately 90% at AUC. This increase may result in a higher incidence and severity of dose dependent adverse events. The safety 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

5.3 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 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.

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.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose BP

Microcrystalline Cellulose BP

Croscarmellose Sodium BP

Purified Water BP

Hydrophobic Colloidal Anhydrous Silica BP

Magnesium Stearate BP

Hypromellose BP (15 CPS)

Titanium Dioxide BP

Purified Talc BP

Red Iron Oxide In house

Isopropyl Alcohol BP

Dichloromethane BP

6.2 Incompatibilities

None

6.3 Shelf life

36 months (3 Years) from date of manufacturing

6.4 Special precautions for storage

Store below 30°C in a dry place.

Keep medicines out of reach of children.

6.5 Nature and contents of container

4 Tablets to be packed in Alu-PVC blister. Such 1 blister to be packed in a carton along with pack insert.

6.6 Special precautions for disposal:

None

7. Registrant :

MARKETING AUTHORISATION HOLDER

SEAL HEALTHCARE LIMITED

1, Ashimolowo Street, Off 5th Avenue, Abesan Estate, Ipaja, Lagos State, Nigeria**.**

8. MANUFACTURER

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9. Date of revision of the text: NA

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