



McW HEALTHCARE PRIVATE LIMITED

286, 287A, 287B, SECTOR E, INDUSTRIAL AREA, SANWER ROAD, INDORE (M.P.), INDIA

KIXTAT TABLETS

(SILDENAFIL 100 MG AND DAPOXETINE 60 MG)

COMMON TECHNICAL DOCUMENT

MODULE 1.3.1: SUMMARY OF PRODUCT CHARACTERISTICS

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTIC:

1.3 SUMMARY OF PRODUCT CHARACTERISTICS:

1. NAME OF THE MEDICINAL PRODUCT:

KIXTAT TABLETS (Sildenafil 100mg and Dapoxetine 60 mg)

2. Qualitative and Quantitative Composition

Composition:

Each Film Coated Tablet Contains:

Sildenafil Citrate BP Equivalent to

Sildenafil 100 mg

Dapoxetine Hydrochloride Equivalent to

Dapoxetine..... 60 mg

Excipients..... Q.S.

Colour: Permitted Colour

For the full list of excipients, see section 6.1

3. Pharmaceutical Form

Solid Dosage form (Film Coated tablets)

Red Coloured, diamond shaped, film coated tablets, plain on both sides.

4. Clinical Particulars

4.1 Therapeutic indications

Sildenafil is indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for Sildenafil to be effective, sexual stimulation is required.

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

Dapoxetine Hydrochloride 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.

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

4.2 Posology and method of administration

Posology

Use in adults

The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based on efficacy and tolerability, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If Sildenafil is taken with food, the onset of activity may be delayed compared to the fasted state.

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

Special populations

Elderly

Dosage adjustments of Sildenafil citrate are not required in elderly patients (≥ 65 years old).

The efficacy and safety of Dapoxetine Hydrochloride have not been established in patients age 65 years and over

Renal impairment

The dosing recommendations described in “Use in adults” apply to patients with mild to moderate renal impairment (creatinine clearance = 30-80 mL/min).

Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance < 30 mL/min) a 25 mg dose should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 50 mg up to 100 mg as necessary.

Hepatic impairment

Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25 mg dose should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 50 mg up to 100 mg as necessary.

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

Paediatric population

Sildenafil is not indicated for individuals below 18 years of age.

Use in patients taking other medicinal products

With the exception of ritonavir for which co-administration with sildenafil is not a starting dose of 25 mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors.

In order to minimise the potential of developing postural hypotension in patients receiving alpha-blocker treatment patients should be stabilised on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered.

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

Method of administration

For oral use.

4.3 Contraindications

Sildenafil

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

Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated.

The co-administration of PDE5 inhibitors, including sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.

Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure).

Sildenafil 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 safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated: severe hepatic impairment, hypotension (blood pressure < 90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

Dapoxetine Hydrochloride

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 hydrochloride 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 Dapoxetine hydrochloride 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 hydrochloride 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

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Cardiovascular risk factors

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. Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure. Prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, especially in combination with sexual activity. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.

Sildenafil potentiates the hypotensive effect of nitrates.

Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of Sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of Sildenafil without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.

Priapism

Agents for the treatment of erectile dysfunction, including sildenafil, 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).

Prolonged erections and priapism have been reported with sildenafil in post-marketing experience. In the event of an erection that persists for longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

Concomitant use with other PDE5 inhibitors or other treatments for erectile dysfunction

The safety and efficacy of combinations of sildenafil with other PDE5 inhibitors, or other pulmonary arterial hypertension (PAH) treatments containing sildenafil (REVATIO), or other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

Effects on vision

Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil and other PDE5 inhibitors. Cases of non-arteritic anterior ischaemic optic neuropathy, a rare condition, have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other PDE5 inhibitors. Patients should be advised that in the event of any sudden visual defect, they should stop taking sildenafil and consult a physician immediately.

Concomitant use with ritonavir

Co-administration of sildenafil with ritonavir is not advised.

Concomitant use with alpha-blockers

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the co-administration may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing. In order to minimise the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered. In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms.

Effect on bleeding

Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside in vitro. There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore, sildenafil should be administered to these patients only after careful benefit-risk assessment.

Excipients

The film coating of the tablet contains lactose. Sildenafil should not be administered to men with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

Women

Sildenafil is not indicated for use by women.

DAPOXETINE HYDROCHLORIDE

Dapoxetine Hydrochloride 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. Dapoxetine Hydrochloride should not be used in men with erectile dysfunction (ED) who are using PDE5 inhibitors.

Orthostatic hypotension

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

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

Suicide/suicidal thoughts

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

Syncope

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

Possibly prodromal symptoms such as nausea, dizziness/lightheadedness, and diaphoresis were reported more frequently among patients treated with Dapoxetine Hydrochloride compared to placebo.

In the clinical trials, cases of syncope characterized as loss of consciousness, with bradycardia or sinus arrest observed in patients wearing Holter monitors, were considered vasovagal in etiology and the majority occurred during the first 3 hours after dosing, after the first dose, or associated with study-related procedures in the clinic setting (such as blood draw and orthostatic maneuvers and blood pressure measurements). Possibly prodromal symptoms, such as nausea, dizziness, lightheadedness, palpitations, asthenia, confusion and diaphoresis generally occurred within the first 3 hours following dosing, and often preceded the syncope. Patients need to be made aware that they could experience syncope at any time with or without prodromal symptoms during their treatment with Dapoxetine Hydrochloride. Prescribers should counsel patients about the importance of maintaining adequate hydration and about how to recognize prodromal signs and symptoms to decrease the likelihood of serious injury associated with falls due to loss of consciousness. If the patient experiences possibly prodromal symptoms, the patient should immediately lie down so his head is lower than the rest of his body or sit down with his head between his knees until the symptoms pass, and be cautioned to avoid situations where injury could result, including driving or operating hazardous machinery, should syncope or other CNS effects occur.

Patients with cardiovascular risk factors

Subjects with underlying cardiovascular disease were excluded from Phase 3 clinical trials. The risk of adverse cardiovascular outcomes from syncope (cardiac syncope and syncope from other causes) is increased in patients with underlying structural cardiovascular disease (e.g., documented outflow obstruction, valvular heart disease, carotid stenosis and coronary artery disease). There are insufficient data to determine whether this increased risk extends to vasovagal syncope in patients with underlying cardiovascular disease.

Use with recreational drugs

Patients should be advised not to use Dapoxetine Hydrochloride 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 Hydrochloride. These reactions include, but are not limited to, arrhythmia, hyperthermia, and serotonin syndrome. Use of Dapoxetine Hydrochloride with recreational drugs with sedative properties such as narcotics and benzodiazepines may further increase somnolence and dizziness.

Ethanol

Patients should be advised not to use Dapoxetine Hydrochloride 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 Hydrochloride.

Medicinal products with vasodilatation properties

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

Moderate CYP3A4 inhibitors

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

Potent CYP2D6 inhibitors

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

Mania

Dapoxetine Hydrochloride 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 Hydrochloride 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 Hydrochloride 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 Hydrochloride to rule out undiagnosed depressive disorders. Concomitant treatment of Dapoxetine Hydrochloride with antidepressants, including SSRIs and SNRIs, is contraindicated. Discontinuation of treatment for ongoing depression or anxiety in order to initiate Dapoxetine Hydrochloride for the treatment of PE is not recommended. Dapoxetine Hydrochloride 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 Hydrochloride should be discontinued.

Haemorrhage

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

Renal impairment

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

Withdrawal effects

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

A double-blind clinical trial in subjects with PE designed to assess the withdrawal effects of 62 days of daily or as needed dosing with 60 mg Dapoxetine Hydrochloride showed mild

withdrawal symptoms with a slightly higher incidence of insomnia and dizziness in subjects switched to placebo after daily dosing.

Eye disorders

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

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on sildenafil

In vitro studies

Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

In vivo studies

Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). Although no increased incidence of adverse events was observed in these patients, when sildenafil is administered concomitantly with CYP3A4 inhibitors, a starting dose of 25 mg should be considered.

Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was administered alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not advised and in any event the maximum dose of sildenafil should under no circumstances exceed 25 mg within 48 hours.

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg three times a day) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics. Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.

When a single 100 mg dose of sildenafil was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady state (500 mg twice daily for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC, C_{max}, t_{max}, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite. Cimetidine (800 mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers.

Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest increases in plasma levels of sildenafil.

Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of sildenafil.

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect of concomitant treatment on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates). In a study of healthy male volunteers, co-administration of the endothelin antagonist, bosentan, (an inducer of CYP3A4 [moderate], CYP2C9 and possibly of CYP2C19) at steady state (125 mg twice a day) with sildenafil at steady state (80 mg three times a day) resulted in 62.6% and 55.4% decrease in sildenafil AUC and C_{max}, respectively. Therefore, concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma concentrations of sildenafil.

Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to result in a serious interaction with sildenafil.

Effects of sildenafil on other medicinal products

In vitro studies

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC₅₀ >150 µM). Given sildenafil peak plasma concentrations of approximately 1 µM after recommended doses, it is unlikely that Sildenafil will alter the clearance of substrates of these isoenzymes.

There are no data on the interaction of sildenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

In vivo studies

Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated.

Riociguat: Preclinical studies showed 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 sildenafil, is contraindicated.

Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing. In three specific drug-drug interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and sildenafil (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, and mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were observed. When sildenafil and doxazosin were administered simultaneously to patients stabilized on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

No significant interactions were shown when sildenafil (50 mg) was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9.

Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid (150 mg).

Sildenafil (50 mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dl.

Pooling of the following classes of antihypertensive medication; diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. In a specific interaction study, where sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 8 mmHg. The corresponding additional reduction in supine diastolic blood pressure was 7 mmHg. These additional blood pressure reductions were of a similar magnitude to those seen when sildenafil was administered alone to healthy volunteers.

Sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

In healthy male volunteers, sildenafil at steady state (80 mg t.i.d.) resulted in a 49.8% increase in bosentan AUC and a 42% increase in bosentan C_{max} (125 mg b.i.d.).

Pharmacodynamic interactions of DAPOXETINE HYDROCHLORIDE

Potential for interaction with monoamine oxidase inhibitors

In patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Animal data on the effects of combined use of an SSRI and MAOIs suggest that these medicinal products may act synergistically to elevate blood pressure and evoke behavioural excitation. Therefore, Dapoxetine hydrochloride 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 hydrochloride has been.

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 hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride 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 Hydrochloride has been discontinued.

CNS active medicinal products

The use of Dapoxetine Hydrochloride 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 Hydrochloride and such medicinal products is required.

Pharmacokinetic interactions

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

In vitro studies in human liver, kidney, and intestinal microsomes indicate dapoxetine is metabolized primarily by CYP2D6, CYP3A4 and flavin monooxygenase 1 (FMO1). Therefore, inhibitors of these enzymes may reduce dapoxetine clearance.

CYP3A4 inhibitors

Potent CYP3A4 inhibitors. Administration of ketoconazole (200 mg twice daily for 7 days) increased the C_{max} and AUC_{inf} of dapoxetine (60 mg single dose) by 35% and 99%, respectively. Considering the contribution of both unbound dapoxetine and desmethyldapoxetine, the C_{max} of

the active fraction may be increased by approximately 25% and the AUC of the active fraction may be doubled if taken with potent CYP3A4 inhibitors.

The increases in the C_{max} and AUC of the active fraction may be markedly increased in a part of the population which lack a functional CYP2D6 enzyme, i.e., CYP2D6 poor metabolizers, or in combination with potent inhibitors of CYP2D6.

Therefore, concomitant use of Dapoxetine hydrochloride 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 hydrochloride.

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

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

Potent CYP2D6 inhibitors

The 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.

PDE5 inhibitors

Dapoxetine Hydrochloride should not be used in patients using PDE5 inhibitors due to possible reduced orthostatic tolerance. The pharmacokinetics of dapoxetine (60 mg) in combination with

tadalafil (20 mg) and sildenafil (100 mg) were evaluated in a single dose crossover study. Tadalafil did not affect the pharmacokinetics of dapoxetine. Sildenafil caused slight changes in dapoxetine pharmacokinetics (22% increase in AUC_{inf} and 4% increase in C_{max}), which are not expected to be clinically significant.

Concomitant use of Dapoxetine Hydrochloride with PDE5 inhibitors may result in orthostatic hypotension. The efficacy and safety of Dapoxetine hydrochloride in patients with both premature ejaculation and erectile dysfunction concomitantly treated with Dapoxetine hydrochloride and PDE5 inhibitors have not been established.

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

Tamsulosin

Concomitant administration of single or multiple doses of 30 mg or 60 mg dapoxetine to patients receiving daily doses of tamsulosin did not result in changes in the pharmacokinetics of tamsulosin. The addition of dapoxetine to tamsulosin did not result in a change in the orthostatic profile and there were no differences in orthostatic effects between tamsulosin combined with either 30 or 60 mg dapoxetine and tamsulosin alone; however, Dapoxetine hydrochloride should be prescribed with caution in patients who use alpha adrenergic receptor antagonists due to possible reduced orthostatic tolerance.

Medicinal products metabolized by CYP2D6

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

Medicinal products metabolized by CYP3A4

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

Medicinal products metabolized by CYP2C19

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

Medicinal products metabolized by CYP2C9

Multiple dosing of dapoxetine (60 mg/day for 6 days) did not affect the pharmacokinetics or pharmacodynamics of a single 5 mg dose of 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

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

There have been reports of bleeding abnormalities with SSRIs.

Ethanol

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

4.6 Fertility, pregnancy and lactation

Sildenafil is not indicated for use by women.

There are no adequate and well-controlled studies in pregnant or breast-feeding women.

No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil.

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers.

Dapoxetine is not indicated for use by women.

Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy or embryonal/foetal development.

It is not known if either dapoxetine or its metabolites are excreted in human milk.

4.7 Effects on ability to drive and use machines

Sildenafil may have a minor influence on the ability to drive and use machines.

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to Sildenafil, before driving or operating machinery.

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.

4.8 Undesirable effects

Tabulated list of adverse reactions of Sildenafil

In the table below all medically important adverse reactions, which occurred in clinical trials at an incidence greater than placebo are listed by system organ class and frequency (very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $1/1,000$)).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Medically important adverse reactions reported at an incidence greater than placebo in controlled clinical studies and medically important adverse reactions reported through post-marketing surveillance

Infections and infestations	
Uncommon:	Rhinitis
Immune system disorders	
Uncommon:	hypersensitivity
Nervous system disorders	
Very common:	Headache
Common:	Dizziness
Uncommon:	Somnolence, Hypoaesthesia
rare:	Cerebrovascular accident, Transient ischaemic attack, Seizure*, Seizure recurrence*, Syncope
Eye disorders	
common:	Visual colour distortions, Visual disturbance, Vision blurred
Uncommon:	Lacrimation disorders, Eye pain, Photophobia, Photopsia, Ocular hyperaemia, Visual brightness, Conjunctivitis
rare:	Non-arteritic anterior ischaemic optic neuropathy (NAION)*,* Retinal vascular occlusion*, Retinal haemorrhage, Arteriosclerotic retinopathy, Retinal disorder, Glaucoma, Visual field defect, Diplopia, Visual acuity reduced, Myopia, Asthenopia, Vitreous floaters, Iris disorder, Mydriasis, Halo vision, Eye oedema, Eye swelling, Eye disorder, Conjunctival hyperaemia, Eye irritation, Abnormal sensation in eye, Eyelid oedema, Scleral discoloration
Ear and labyrinth disorders	
rare:	Deafness
Uncommon:	Vertigo, Tinnitus
Cardiac disorders	
rare:	Sudden cardiac death*, Myocardial infarction, Ventricular arrhythmia*, Atrial fibrillation, Unstable angina
Uncommon:	Tachycardia, Palpitations
Vascular disorder	
common:	Flushing, Hot flush
Uncommon:	Hypertension, Hypotension

Respiratory, thoracic and mediastinal disorders	
common:	Nasal congestion
rare:	Throat tightness, Nasal oedema, Nasal dryness
Uncommon:	Epistaxis, Sinus congestion
Gastrointestinal disorders	
common:	Nausea, Dyspepsia
Uncommon:	Gastro oesophageal reflux disease, Vomiting, Abdominal pain upper, Dry mouth
rare:	Hypoaesthesia oral
Skin and subcutaneous tissue disorders	
Uncommon:	Rash
rare:	Stevens-Johnson Syndrome (SJS)*, * Toxic Epidermal Necrolysis (TEN) *
Musculoskeletal and connective tissue disorders	
Uncommon:	Myalgia, Pain in extremity
Renal and urinary disorders	
Uncommon:	Haematuria
Reproductive system and breast disorders	
rare:	Penile haemorrhage, Priapism*, Haemospermia, Erection increased
General disorders and administration site conditions	
Rare:	Irritability
Uncommon:	Heart rate increased

*Reported during post-marketing surveillance only

**Visual colour distortions: Chloropsia, Chromatopsia, Cyanopsia, Erythroopsia and Xanthopsia

***Lacrimation disorders: Dry eye, Lacrimal disorder and Lacrimation increased

Tabulated list of adverse reactions of Sildenafil

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.

Psychiatric disorders	
common:	Anxiety, Agitation, Restlessness, Insomnia, Abnormal dreams, Libido decreased
Uncommon	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
Nervous system disorders	
Very common:	Dizziness, Headache
Common:	Somnolence, Disturbance in attention, Tremor, Paraesthesia
Uncommon:	Syncope, Syncope vasovagal, Dizziness postural, Akathisia, Dysgeusia, Hypersomnia, Lethargy, Sedation, Depressed level of consciousness
rare:	Dizziness exertional, Sudden onset of sleep
Eye disorders	
common:	Vision blurred
Uncommon:	Mydriasis, Eye pain, Visual disturbance
Ear and labyrinth disorders	
common:	Tinnitus
Uncommon:	Vertigo
Cardiac disorders	
Uncommon:	Sinus arrest, Sinus bradycardia, Tachycardia
Vascular disorder	
common:	Flushing
Uncommon:	Hypotension, Systolic hypertension, Hot flush
Respiratory, thoracic and mediastinal disorders	
common:	Sinus congestion, Yawning
Gastrointestinal disorders	
Very common:	Nausea
common:	Diarrhoea, Vomiting, Constipation, Abdominal pain, Abdominal pain upper, Dyspepsia, Flatulence, Stomach discomfort, Abdominal distension, Dry mouth
Uncommon:	Abdominal discomfort, Epigastric discomfort
rare:	Defaecation urgency
Skin and subcutaneous tissue disorders	
common:	Hyperhidrosis

uncommon:	Pruritis, Cold sweat
Reproductive system and breast disorders	
common:	Erectile dysfunction
Uncommon	Ejaculation failure, Male orgasmic disorder, Paraesthesia of genital male
General disorders and administration site conditions	
Uncommon:	Heart rate increased, Blood pressure diastolic increased, Blood pressure orthostatic increased
common:	Fatigue, Irritability

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 hydrochloride 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Sildenafil Citrate

In single dose volunteer studies of doses up to 800 mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased. Doses of 200 mg did not result in increased efficacy but the incidence of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision) was increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

Dapoxetine Hydrochloride

No case of overdose has been reported.

There were no unexpected adverse events in a clinical pharmacology study of Dapoxetine Hydrochloride 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 hydrochloride are known.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals; Drugs used in erectile dysfunction. ATC Code: G04B E03.

Mechanism of action

Sildenafil is an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

Pharmacodynamic effects

Studies in vitro have shown that sildenafil is selective for PDE5, which is involved in the erection process. Its effect is more potent on PDE5 than on other known phosphodiesterases. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina. At maximum recommended doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE 2, 3, 4, 7, 8, 9, 10 and 11. In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility.

Clinical efficacy and safety

Two clinical studies were specifically designed to assess the time window after dosing during which sildenafil could produce an erection in response to sexual stimulation. In a penile plethysmography (RigiScan) study of fasted patients, the median time to onset for those who obtained erections of 60% rigidity (sufficient for sexual intercourse) was 25 minutes (range 12-

37 minutes) on sildenafil. In a separate RigiScan study, sildenafil was still able to produce an erection in response to sexual stimulation 4-5 hours post-dose.

Sildenafil causes mild and transient decreases in blood pressure which, in the majority of cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 100 mg oral dosing of sildenafil was 8.4 mmHg. The corresponding change in supine diastolic blood pressure was 5.5 mmHg. These decreases in blood pressure are consistent with the vasodilatory effects of sildenafil, probably due to increased cGMP levels in vascular smooth muscle. Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG.

In a study of the hemodynamic effects of a single oral 100 mg dose of sildenafil in 14 patients with severe coronary artery disease (CAD) (>70% stenosis of at least one coronary artery), the mean resting systolic and diastolic blood pressures decreased by 7% and 6% respectively compared to baseline. Mean pulmonary systolic blood pressure decreased by 9%. Sildenafil showed no effect on cardiac output, and did not impair blood flow through the stenosed coronary arteries.

A double-blind, placebo-controlled exercise stress trial evaluated 144 patients with erectile dysfunction and chronic stable angina who regularly received anti-anginal medicinal products (except nitrates). The results demonstrated no clinically relevant differences between sildenafil and placebo in time to limiting angina.

Mild and transient differences in colour discrimination (blue/green) were detected in some subjects using the Farnsworth-Munsell 100 hue test at 1 hour following a 100 mg dose, with no effects evident after 2 hours post-dose. The postulated mechanism for this change in colour discrimination is related to inhibition of PDE6, which is involved in the phototransduction cascade of the retina. Sildenafil has no effect on visual acuity or contrast sensitivity. In a small size placebo-controlled study of patients with documented early age-related macular degeneration (n=9), sildenafil (single dose, 100 mg) demonstrated no significant changes in the visual tests conducted (visual acuity, Amsler grid, colour discrimination simulated traffic light, Humphrey perimeter and photostress).

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers.

Further information on clinical trials

In clinical trials sildenafil was administered to more than 8000 patients aged 19-87. The following patient groups were represented: elderly (19.9%), patients with hypertension (30.9%), diabetes mellitus (20.3%), ischaemic heart disease (5.8%), hyperlipidaemia (19.8%), spinal cord injury (0.6%), depression (5.2%), transurethral resection of the prostate (3.7%), radical prostatectomy (3.3%). The following groups were not well represented or excluded from clinical trials: patients with pelvic surgery, patients post-radiotherapy, patients with severe renal or hepatic impairment and patients with certain cardiovascular conditions.

In fixed dose studies, the proportions of patients reporting that treatment improved their erections were 62% (25 mg), 74% (50 mg) and 82% (100 mg) compared to 25% on placebo. In controlled clinical trials, the discontinuation rate due to sildenafil was low and similar to placebo.

Across all trials, the proportion of patients reporting improvement on sildenafil were as follows: psychogenic erectile dysfunction (84%), mixed erectile dysfunction (77%), organic erectile dysfunction (68%), elderly (67%), diabetes mellitus (59%), ischaemic heart disease (69%), hypertension (68%), TURP (61%), radical prostatectomy (43%), spinal cord injury (83%), depression (75%). The safety and efficacy of sildenafil was maintained in long term studies.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Sildenafil in all subsets of the paediatric population for the treatment of erectile dysfunction.

DAPOXETINE HYDROCHLORIDE

Pharmacotherapeutic group: Other Urologicals, ATC code: G04BX14

Mechanism of action

Dapoxetine is a potent selective serotonin reuptake inhibitor (SSRI) with an IC₅₀ of 1.12 nM, while its major human metabolites, desmethyldapoxetine (IC₅₀ < 1.0 nM) and didesmethylapoxetine (IC₅₀ = 2.0 nM) are equivalent or less potent (dapoxetine-N-oxide (IC₅₀ = 282 nM)).

Human ejaculation is primarily mediated by the sympathetic nervous system. The ejaculatory pathway originates from a spinal reflex centre, mediated by the brain stem, which is influenced initially by a number of nuclei in the brain (medial preoptic and paraventricular nuclei).

The mechanism of action of dapoxetine in premature ejaculation is presumed to be linked to the inhibition of neuronal reuptake of serotonin and the subsequent potentiation of the neurotransmitter's action at pre- and postsynaptic receptors.

In the rat, dapoxetine inhibits the ejaculatory expulsion reflex by acting at a supraspinal level within the lateral paragigantocellular nucleus (LPGi). Post ganglionic sympathetic fibers that innervate the seminal vesicles, vas deferens, prostate, bulbourethral muscles and bladder neck cause them to contract in a coordinated fashion to achieve ejaculation. Dapoxetine modulates this ejaculatory reflex in rats.

Clinical efficacy and safety

The effectiveness of Dapoxetine hydrochloride in the treatment of premature ejaculation has been established in five double-blind, placebo-controlled clinical trials, in which a total of 6081 subjects were randomized. Subjects were 18 years of age or older and had a history of PE in the majority of intercourse experiences in the 6-month period prior to enrolment. Premature ejaculation was defined according to the DSM-IV diagnostic criteria: short ejaculatory time (an intravaginal ejaculatory latency time [IELT; time from vaginal penetration to the moment of intravaginal ejaculation] of ≤ 2 minutes measured using a stopwatch in four studies), poor control over ejaculation, marked distress or interpersonal difficulty due to the condition.

Subjects with other forms of sexual dysfunction, including erectile dysfunction, or those using other forms of pharmacotherapy for the treatment of PE were excluded from all studies.

5.2 Pharmacokinetic properties

Absorption

Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 41% (range 25-63%). After oral dosing of sildenafil AUC and C_{max} increase in proportion with dose over the recommended dose range (25-100 mg).

When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in t_{max} of 60 minutes and a mean reduction in C_{max} of 29%.

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 hydrochloride can be taken with or without food.

Distribution

The mean steady state volume of distribution (V_d) for sildenafil is 105 l, indicating distribution into the tissues. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is approximately 440 ng/mL (CV 40%). Since sildenafil (and its major circulating N-desmethyl metabolite) is 96% bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil of 18 ng/mL (38 nM). Protein binding is independent of total drug concentrations.

In healthy volunteers receiving sildenafil (100 mg single dose), less than 0.0002% (average 188 ng) of the administered dose was present in ejaculate 90 minutes after dosing.

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

Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% that of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half life of approximately 4 h.

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 total body clearance of sildenafil is 41 L/h with a resultant terminal phase half-life of 3-5 h. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of administered oral dose).

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.

5.3 Preclinical safety data

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

Maize Starch	BP
Lactose	BP
Microcrystalline Cellulose	BP
Polyvinyl Pyrolidone	BP
Isopropyl Alcohol	BP
Colloidal Anhydrous Silica	BP
Sodium Lauryl Sulphate	BP
Croscarmellose Sodium	BP
Magnesium Stearate	BP
Colorcoat MB4S- HPC5 120621A (Red)	IH
Insta Coat Solution Transparent	IH
Isopropyl alcohol	IH
Dichloromethane	BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 Months

6.4 Special precaution for storage

Store at temperature should not exceeding 30°C. Protect from light.

6.5 Nature and contents of container

Primary Packing materials:

Printed Alu foil and PVC foil

Secondary Packaging Material:

Printed Carton and Printed Insert

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing authorization holder

McW Healthcare Private Limited
286, 287A, 287B, Sector E, Industrial Area,
Sanwer Road, Indore (M.P.), INDIA
Website: - www.mcwhealthcare.com

8. Marketing authorization number(s)

XXXX

9. Date of first authorization/renewal of the authorization

XXXX

10. Date of revision of the text

XXXX