Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Super P Force 160 60mg/100mg Film-coated Tablets

2. Qualitative and quantitative composition
Each film-coated tablet contains dapoxetine hydrochloride equivalent to 60mg dapoxetine and sildenafil citrate equivalent to 100mg of sildenafil.

Excipient with known effect
Each tablet contains 10mg of lactose.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Film-coated tablet.

A dark blue, heart shaped biconvex film-coated tablet that is plain on both the sides.

4. Clinical particulars

4.1 Therapeutic indications
Dapoxetine and Sildenafil tablets is indicated for the treatment of premature ejaculation (PE) and erectile dysfunction in adult men aged 18 to 64 years.

4.2 Posology and method of administration
Adult men (aged 18 to 64 years)
Super P Force 160 should only be used after the recommended starting dose of 30mg Dapoxetine and 50mg Sildenafil is proven insufficient and no orthostatic reactions were observed.

1 tablet should be taken, as needed, approximately 1 hour prior to sexual activity. The maximum daily dose is 60mg Dapoxetine and 100mg Sildenafil.

Super P Force is not intended for continuous daily use and should only be taken when sexual activity is anticipated.

If taken with food, the onset of activity may be delayed compared to the fasted state.

Elderly (age 65 and over)
The safety and efficacy of Dapoxetine has not been established in patients above the age of 65.

Paediatric population
This medicine is not indicated for individuals below 18 years of age.

Renal Impairment
Caution is advised in patients with mild or moderate renal impairment. Super P Force is not recommended for use in patients with severe renal impairment (see sections 4.4 and 5.2).

Hepatic impairment
Super P Force is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh Class B and C) (see sections 4.3 and 5.2).

Known CYP2D6 poor metabolizers or patients treated with potent CYP2D6 inhibitors
Caution is advised if increasing the dose of Dapoxetine to 60 mg in patients known to be of CYP2D6 poor metabolizer genotype or in patients concomitantly treated with potent CYP2D6 inhibitors (see sections 4.4, 4.5 and 5.2).

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 Dapoxetine and a starting dose of 25 mg Sildenafil in patients concomitantly treated with moderate CYP3A4 inhibitors and caution is advised (see sections 4.3, 4.4 and 4.5).

Use in patients taking other medicinal products
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 (see sections 4.4 and 4.5).

Method of administration
For oral use.

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

Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable, particularly those with cardiac conditions such as:
• Heart failure (NYHA class II-IV)
• Unstable angina
• 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 Super P Force has been discontinued (see section 4.5).

Concomitant treatment with thioridazine, or within 14 days of discontinuing treatment with thioridazine. Similarly, thioridazine should not be administered within 7 days after Dapoxetine has been discontinued (see section 4.5).

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 Super P Force has been discontinued (see section 4.5).

Concomitant treatment of potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazadone, nelfinavir, atazanavir, etc. (see section 4.5).

Moderate and severe hepatic impairment.

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 (see section 4.4).

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).

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.

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 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.

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 Super P Force should be avoided.

The prescriber should counsel the patient in advance that if he experiences possibly prodromal symptoms, such as light-headedness 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.

Cardiovascular risk factors
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 the drug without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors. Subjects with underlying cardiovascular disease were excluded from Phase 3 clinical trials for Dapoxetine. The risk of adverse cardiovascular outcomes from syncope.

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 (see section 5.1). 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 (see section 4.3).

Use with recreational drugs

Patients should be advised not to use Super P Force 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 this drug. These reactions include, but are not limited to, arrhythmia, hyperthermia, and serotonin syndrome. Use of Super P Force 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 Super P Force 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 Super P Force (see sections 4.5 and 4.7).

Suicide/suicidal thoughts
Antidepressants, including SSRIs, increased the risk compared to placebo of suicidal thinking and suicidality in short-term studies in children and adolescents with Major Depressive Disorder and other psychiatric disorders.
Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24. In clinical trials with Dapoxetine for the treatment of premature ejaculation, there was no clear indication of treatment-emergent suicidality in evaluation of possibly suicide-related adverse events evaluated by the Columbia Classification Algorhythm 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 light-headedness occur (see section 4.8).
Possibly prodromal symptoms such as nausea, dizziness/light-headedness, and diaphoresis were reported more frequently among patients treated with Dapoxetine compared to placebo.

Medicinal products with vasodilatation properties
Dapoxetine and Sildenafil 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 (see section 4.5). This is most likely to occur within 4 hours post dosing. In order to minimise the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil and dapoxetine treatment. Initiation of sildenafil at a dose of 25 mg should be considered (see section 4.2). In

addition, physicians should advise patients what to do in the event of postural hypotensive symptoms

Moderate CYP3A4 inhibitors
Caution is advised in patients taking moderate CYP3A4 inhibitors and the dose is restricted to 30 mg (see sections 4.2 and 4.5).

Potent CYP2D6 inhibitors
Caution is advised if increasing the dose of Dapoxetine 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 (see sections 4.2, 4.5 and
5.2).

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

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

Depression and/or psychiatric disorders
Men with underlying signs and symptoms of depression should be evaluated prior to treatment with Dapoxetine to rule out undiagnosed depressive disorders. Concomitant treatment of Dapoxetine with antidepressants, including SSRIs and SNRIs, is contraindicated (see section 4.3). Discontinuation of treatment for ongoing depression or anxiety in order to initiate Dapoxetine for the treatment of PE is not recommended. Dapoxetine is not indicated for psychiatric disorders and should not be used in men with these disorders, such as schizophrenia, or in those suffering with co-morbid depression, as worsening of symptoms associated with depression cannot be excluded. This could be the result of underlying psychiatric disorder or might be a result of medicinal product therapy. Physicians should encourage patients to report any distressing thoughts or feelings at any time and if signs and symptoms of depression develop during treatment, Dapoxetine should be discontinued.

Haemorrhage
There have been reports of bleeding abnormalities with SSRIs. Caution is advised in patients taking Dapoxetine, particularly in concomitant use with medicinal products known to affect platelet function (e.g., atypical antipsychotics and phenothiazines, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs [NSAIDs], anti-platelet agents) or anticoagulants (e.g., warfarin), as well as in patients with a history of bleeding or coagulation disorders (see section 4.5).

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.

Renal impairment
Dapoxetine is not recommended for use in patients with severe renal impairment and caution is advised in patients with mild or moderate renal impairment (see sections 4.2 and 5.2).

Withdrawal effects
Abrupt discontinuation of chronically administered SSRIs used to treat chronic depressive disorders has been reported to result in the following symptoms: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia and hypomania.
A double-blind clinical trial in subjects with PE designed to assess the withdrawal effects of 62 days of daily or as needed dosing with 60 mg Dapoxetine showed mild withdrawal symptoms with a slightly higher incidence of insomnia and dizziness in subjects switched to placebo after daily dosing (see section 5.1).

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

Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil and other PDE5 inhibitors (see section 4.8). 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 (see section 4.8). Patients should be advised that in the event of any sudden visual defect, they should stop taking Super P Force and consult a physician immediately (see section 4.3).

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

Women
Super P Force is not indicated for use by women.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions:
Dapoxetine
Potential for interaction with monoamine oxidase inhibitors

In patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Animal data on the effects of combined use of an SSRI and MAOIs suggest that these medicinal products may act synergistically to elevate blood pressure and evoke behavioural excitation. Therefore, Dapoxetine should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, an MAOI should not be administered within 7 days after Dapoxetine has been discontinued (see section 4.3).

Potential for interaction with thioridazine
Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias. Medicinal products such as Dapoxetine that inhibit the CYP2D6 isoenzyme appear to inhibit the metabolism of thioridazine and the resulting elevated levels of thioridazine are expected to augment the prolongation of the QTc interval. Dapoxetine should not be used in combination with thioridazine or within 14 days of discontinuing treatment with thioridazine. Similarly, thioridazine should not be administered within 7 days after Dapoxetine has been discontinued (see section 4.3).

Medicinal/herbal products with serotonergic effects
As with other SSRIs, co-administration with serotonergic medicinal/herbal products (including MAOIs, L-tryptophan, triptans, tramadol, linezolid, SSRIs, SNRIs, lithium and St. John's Wort (Hypericum perforatum) preparations) may lead to an incidence of serotonin associated effects. Dapoxetine should not be used in combination with other SSRIs, MAOIs or other serotonergic medicinal/herbal products or within 14 days of discontinuing treatment with these medicinal/herbal products. Similarly, these medicinal/herbal products should not be administered within 7 days after Dapoxetine has been discontinued (see section 4.3).

CNS active medicinal products
The use of Dapoxetine in combination with CNS active medicinal products (e.g., antiepileptics, antidepressants,

antipsychotics, anxiolytics, sedative hypnotics) has not been systematically evaluated in patients with premature ejaculation. Consequently, caution is advised if the concomitant administration of Dapoxetine and such medicinal products is required.

Pharmacokinetic interactions

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

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

CYP3A4 inhibitors

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

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

Therefore, concomitant use of Dapoxetine and potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazodone, nelfinavir and atazanavir, is contraindicated. Grapefruit juice is also a potent CYP3A4 inhibitor and should be avoided within 24 hours prior to taking Dapoxetine (see section 4.3).

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 (see sections 4.2, 4.4 and below).

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

Potent CYP2D6 inhibitors
The Cmax and AUCinf of dapoxetine (60 mg single dose) increased by 50% and 88%, respectively, in the presence of
fluoxetine (60 mg/day for 7 days). Considering the contribution of both unbound dapoxetine and
desmethyldapoxetine, the Cmax of the active fraction may be increased by approximately 50% and the AUC of the
active fraction may be doubled if taken with potent CYP2D6 inhibitors. These increases in the Cmax and AUC of the
active fraction are similar to those expected for CYP2D6 poor metabolizers and may result in a higher incidence and
severity of dose dependent adverse events (see section 4.4).

PDE5 inhibitors
Dapoxetine should not be used in patients using PDE5 inhibitors due to possible reduced orthostatic tolerance (see
section 4.4). 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 AUCinf and 4% increase in Cmax),
which are not expected to be clinically significant.
Concomitant use of Dapoxetine with PDE5 inhibitors may result in orthostatic hypotension (see section 4.4). The efficacy
and safety of Dapoxetine in patients with both premature ejaculation and erectile dysfunction concomitantly treated with
Dapoxetine 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 should be
prescribed with caution in patients who use alpha adrenergic receptor antagonists due to possible reduced

orthostatic tolerance (see section 4.4).

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

Medicinal products metabolized by CYP3A4
Multiple dosing of dapoxetine (60 mg/day for 6 days) decreased the AUCinf of midazolam (8 mg single dose) by
approximately 20% (range -60 to +18%). The clinical relevance of the effect on midazolam is likely to be small in
most patients. The increase in CYP3A activity may be of clinical relevance in some individuals concomitantly treated
with a medicinal product mainly metabolized by CYP3A and with a narrow therapeutic window.

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

Medicinal products metabolized by CYP2C9
Multiple dosing of dapoxetine (60 mg/day for 6 days) did not affect the pharmacokinetics or pharmacodynamics of a
single 5 mg dose of 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 (see section 4.4). 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 (see section 4.4).

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 co-administered 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 (see sections 4.4 and 4.7)

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 Cmax 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 (see section 4.4) 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 Cmax and a 210% increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics (see section 4.2). 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, Cmax, tmax, 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 Cmax, 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 (see section 5.1), 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 (see section 4.3).

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 (see section 4.3).

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 (see sections 4.2 and 4.4). 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 (see section 5.1).

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 Cmax (125 mg b.i.d.).

4.6 Fertility, pregnancy, and lactation

Super P Force 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 (see section 5.3).
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.

Super P Force 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 and sildenafil in clinical trials. Therefore, patients should be warned to avoid situations where injury could result, including driving or operating hazardous machinery.

4.8 Undesirable effects

4.9 Overdose

No case of dapoxetine overdose has been reported.

There were no unexpected adverse events in a clinical pharmacology study of dapoxetine with daily doses up to 240 mg (two 120 mg doses given 3 hours apart). In general, symptoms of overdose with SSRIs include serotonin-mediated adverse reactions such as somnolence, gastrointestinal disturbances such as nausea and vomiting, tachycardia,
tremor, agitation and dizziness.

In single dose volunteer studies of doses up to 800 mg of Sildenafil, 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. Due to high protein binding and large volume of distribution of dapoxetine hydrochloride and sildenafil, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for dapoxetine are known.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Dapoxetine
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 didesmethyldapoxetine (IC50 = 2.0 nM) are equivalent or less potent (dapoxetine-N-oxide (IC50 = 282 nM)).

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

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

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 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.

Results of all randomized studies were consistent. Efficacy was demonstrated after 12 weeks of treatment. One study enrolled patients both outside and within the EU and had a treatment duration of 24 weeks. In the study, 1162 subjects were randomized, 385 to placebo, 388 to Dapoxetine 30 mg as needed, and 389 to Dapoxetine 60 mg as needed.

The mean and median Average IELT at study end are presented in Table 2 below and the cumulative distribution of subjects who achieved at least a specific level in Average IELT at study end are presented in Table 3 below. Other studies and pooled analysis of the data at Week 12 gave consistent results.

[Table Here]

The magnitude of IELT prolongation was related to baseline IELT and was variable between individual subjects. The clinical relevance of Dapoxetine treatment effects was further demonstrated in terms of various patient reported outcome measures and a responder analysis.

A responder was defined as a subject who had at least a 2-category increase in control over ejaculation plus at least a 1-category decrease in ejaculation-related distress. A statistically significantly greater percentage of subjects responded in each of the Dapoxetine groups versus placebo at the end of the study Week 12 or 24. There was a higher percentage of responders in the dapoxetine 30 mg (11.1% - 95% CI [7.24; 14.87]) and 60 mg (16.4% - 95% CI [13.01; 19.75]) groups compared with the placebo group at Week 12 (pooled analysis).

The clinical relevance of Dapoxetine treatment effects is represented by treatment group for the subject's Clinical Global Impression of Change (CGIC) outcome measure, in which patients were asked to compare their premature ejaculation from the start of the study, with response options ranging from much better to much worse. At study end (Week 24), 28.4% (30 mg group) and 35.5% (60 mg group) of subjects reported their condition to be " better" or " much better" , compared to 14% for placebo, while 53.4% and 65.6% of subjects treated with dapoxetine 30 mg and 60 mg, respectively, reported their condition to be at least " slightly better" , compared to 28.8% for placebo.

Sildenafil
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 PDE2, 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 (see section 4.6).

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 (see section 4.3).

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.

5.2 Pharmacokinetic properties

Dapoxetine

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: Noxidation, 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 (see section 5.1). The unbound exposures (AUC and Cmax) of DED are approximately 50% and 23%, respectively, of the unbound exposure of dapoxetine.

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

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

Race
Analyses of single dose clinical pharmacology studies using 60 mg dapoxetine indicated no statistically significant differences between Caucasians, Blacks, Hispanics and Asians. A clinical study conducted to compare the pharmacokinetics of dapoxetine in Japanese and Caucasian subjects showed 10% to 20% higher plasma levels (AUC and peak concentration) of dapoxetine in Japanese subjects due to lower body weight. The slightly higher exposure is not expected to have a meaningful clinical effect.

Elderly (age 65 years and over)
Analyses of a single dose clinical pharmacology study using 60 mg dapoxetine showed no significant differences in pharmacokinetic parameters (Cmax, AUCinf, Tmax) between healthy elderly males and healthy young adult males.

The efficacy and safety has not been established in this population (see section 4.2).

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 (see sections 4.2 and 4.4).

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 (see sections 4.2 and 4.3).

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 of Dapoxetine 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 (see section 4.2). The safety of Dapoxetine in poor metabolizers of CYP2D6 is of particular concern with concomitant administration of other medicinal products that may inhibit the metabolism of dapoxetine such as moderate and potent CYP3A4 inhibitors (see sections 4.2 and 4.3).

Sildenafil

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 Cmax 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 tmax of 60 minutes and a mean reduction in Cmax of 29%.

Distribution
The mean steady state volume of distribution (Vd) 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.

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.

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).

Pharmacokinetics in special patient groups
Elderly
Healthy, elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 90% higher plasma concentrations of sildenafil and the active N-desmethyl metabolite compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration was approximately 40%.

Renal insufficiency

In volunteers with mild to moderate renal impairment (creatinine clearance = 30-80 mL/min), the pharmacokinetics of sildenafil were not altered after receiving a 50 mg single oral dose. The mean AUC and Cmax of the N-desmethyl metabolite increased up to 126% and up to 73% respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant. In volunteers with severe renal impairment (creatinine clearance <30 mL/min), sildenafil clearance was reduced, resulting in mean increases in AUC and Cmax of 100% and 88% respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and Cmax values were significantly increased by 200% and 79% respectively.

Hepatic insufficiency
In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84%) and Cmax (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

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.

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

6. Pharmaceutical particulars

6.1 List of excipients

Croscarmellose Sodium
Lactose
Maize Starch
Povidone K30
Colloidal Anhydrous Silica
Magnesium Stearate
Hypromellose E15
Titanium Dioxide
Brilliant Blue
Isopropyl Alcohol
Dichloromethane

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage:

Store below 30℃

6.5 Nature and contents of container

Commercial Presentation: 4's, 10's, 20's, 30's & 100's
1 x 4's (4 tablets are packed in one PVC-blister and 1 such PVC-blister is kept in one carton along with package insert).

6.6 Special precautions for disposal and other handling:

Not applicable.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:

Manufacturing site address:

Local Technical Representative:

8. Marketing authorization number

CTD9648

9. Date of first registration

20-02-2024

10. Date of revision of the text:

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