1.3 PRODUCT INFORMATION

1.3.1 Summary of product Characterstics (SmPC)

The Summary of Product Characteristics has been enclosed in the following pages.

SMPC

SUMMARY OF PHARMACEUTICAL PRODUCT

Dapoxetine Tablets 30mg / 60 mg

1. Name of the Product

Dapoxem 30 (Dapoxetine Tablets 30 mg)

Dapoxem 60 (Dapoxetine Tablets 60 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains

Dapoxetine hydrochloride

equivalent to Dapoxetine 30 mg / 60 mg

3. PHARMACEUTICAL FORM

Film-coated tablet.

Dapoxetine Tablets 30 mg : Grey colored, round, biconvex, filmcoated tablets with plain surface on both sides.

Dapoxetine Tablets 60 mg : Grey colored, round, biconvex, filmcoated tablets with plain surface on both sides.

4.CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

Posology

Adult men (aged 18 to 64 years)

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 Tablets should not be initiated with the 60 mg dose. Dapoxetine Tablets is not intended for continuous daily use. Dapoxetine Tablets should be taken only when sexual activity is anticipated. Dapoxetine Tablets must not be taken more frequently than once every 24 hours. If the individual response to 30 mg is insufficient and the patient has not experienced moderate or severe adverse reactions or prodromal symptoms suggestive of syncope, the dose may be increased to a maximum recommended dose of 60 mg taken as needed approximately 1 to 3 hours prior to sexual activity. The incidence and severity of adverse events is higher with the 60 mg dose. If the patient experienced orthostatic reactions on the starting dose, no dose escalation to 60 mg should be performed.

A careful appraisal of individual benefit risk of Dapoxetine Tablets should be performed by the physician after the first four weeks of treatment (or at least after 6 doses of treatment) to determine whether continuing treatment with Dapoxetine Tablets is appropriate. Data regarding the efficacy and safety of Dapoxetine Tablets beyond 24 weeks are limited. The clinical need of continuing and the benefit risk balance of treatment with Dapoxetine Tablets should be re-evaluated at least every six months. Elderly (age 65 years and over) The efficacy and safety of Dapoxetine Tablets have not been established in patients age 65 years and over.

Paediatric population

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

Patients with renal impairment

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

Patients with hepatic impairment

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

Known CYP2D6 poor metabolizers or patients treated with potent CYP2D6 inhibitors.

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

Patients treated with moderate or potent inhibitors of CYP3A4.

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

Method of administration

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

Precautions to be taken before handling or administering the medicinal product

Before treatment is initiated, see section 4.4 regarding orthostatic hypotension.

4.3 Contraindications

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

Significant pathological cardiac conditions such as:

• Heart failure (NYHA class II-IV)

• Conduction abnormalities such as AV block or sick sinus syndrome

• Significant ischemic heart disease

• Significant valvular disease

• A history of syncope.

A history of mania or severe depression.

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

Moderate and severe hepatic impairment.

4.4 Special warnings and precautions for use

General recommendations

Dapoxetine Tablets is only indicated in men with Premature Ejaculation who meet all the criteria listed in sections 4.1 and 5.1. Dapoxetine Tablets 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 Tablets 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 Tablets 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 Tablets 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 lightheadedness occur. Possibly prodromal symptoms such as nausea, dizziness/lightheadedness, and diaphoresis were reported more frequently among patients treated with Dapoxetine Tablets 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, light headedness, 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 Tablets. 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 Tablets 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 Tablets. These reactions include, but are not limited to, arrhythmia, hyperthermia, and serotonin syndrome. Use of Dapoxetine Tablets 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 Tablets 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 Tablets.

Medicinal products with vasodilatation properties

Dapoxetine Tablets 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 Tablets 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 Tablets 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 Tablets 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 Tablets to rule out undiagnosed depressive disorders. Concomitant treatment of Dapoxetine

Tablets with antidepressants, including SSRIs and SNRIs, is contraindicated. Discontinuation of treatment for ongoing depression or anxiety in order to initiate Dapoxetine Tablets for the treatment of PE is not recommended. Dapoxetine Tablets 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 Tablets should be discontinued.

Haemorrhage

There have been reports of bleeding abnormalities with SSRIs. Caution is advised in patients taking Dapoxetine Tablets, 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 Tablets 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 Tablets 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 Tablets has been associated with ocular effects such as mydriasis and eye pain.

Dapoxetine Tablets 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, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

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 Tablets 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 Tablets has been discontinued.

Potential for interaction with thioridazine

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias. Medicinal products such as Dapoxetine Tablets 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 Tablets 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 Tablets 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 Tablets 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 Tablets has been discontinued.

CNS active medicinal products

The use of Dapoxetine Tablets 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 Tablets 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 Tablets and potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazodone, nelfinavir and atazanavir,

is contraindicated .

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

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

Potent CYP2D6 inhibitors

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

PDE5 inhibitors

Dapoxetine Tablets 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 AUCinf and 4% increase in Cmax), which are not expected to be clinically significant.

Concomitant use of Dapoxetine Tablets with PDE5 inhibitors may result in orthostatic hypotension. The efficacy and safety of Dapoxetine Tablets in patients with both premature ejaculation and erectile dysfunction concomitantly treated with Dapoxetine Tablets and PDE5 inhibitors has 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 Tablets 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 AUCinf of midazolam (8 mg single dose) by approximately 20% (range -60 to +18%). The clinical relevance of the effect on midazolam is likely to be small in most patients. The increase in CYP3A activity may be of clinical relevance in some individuals concomitantly treated with a medicinal product mainly metabolized by CYP3A and with a narrow therapeutic window.

Medicinal products metabolized by CYP2C19

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

Medicinal products metabolized by CYP2C9

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

pharmacokinetics of other CYP2C9 substrates.

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

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

Ethanol

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

4.6 Fertility, Pregnancy and lactation

Dapoxetine Tablets 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

Dapoxetine Tablets 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 Tablets .

4.8 Undesirable effects

Summary of the safety profile

Syncope and orthostatic hypotension have been reported in clinical trials.

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

Tabulated list of adverse reactions

The safety of Dapoxetine Tablets 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 Tablets 30 mg as needed and 2608 received 60 mg, either as needed or once daily.

Table 1 presents the adverse reactions that have been reported.

System Organ Class	Very common (> 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10000 to < 1/1000)
Psychiatric disorders		Anxiety, Agitation, Restlessness,Insomnia, Abnormal dreams, Libido decreased	Depression, Depressed mood, Euphoric mood, Mood altered, Nervousness, Indifference, Apathy, Confusional state, Disorientation, Thinking abnormal, Hypervigilance, Sleep disorder, Initial insomnia, Middle insomnia, Nightmare, Bruxism, Loss of	

			libido, Anorgasmia	
Nervous system disorders	Dizziness, Headache	Somnolence, Disturbance in attention, Tremor, Paraesthesia	Syncope, Syncope vasovagal, Dizziness postural, Akathisia, Dysgeusia, Hypersomnia, Lethargy, Sedation, Depressed level of consciousness	Dizziness exertional, Sudden onset of sleep
Eye disorders		Vision blurred	Mydriasis, Eye pain, Visual disturbance, Vertigo	
Cardiac disorders			Sinus arrest, Sinus bradycardia, Tachycardia	
Vascular disorders		Flushing	Hypotension, Systolic hypertension, Hot flush	
Respiratory, thoracic and mediastinal disorders		Sinus congestion, Yawning		
Gastrointestinal disorders	Nausea	Diarrhoea, Vomiting, Constipation, Abdominal pain, Abdominal pain upper, Dyspepsia, Flatulence, Stomach discomfort, Abdominal distension, Dry mouth	Abdominal discomfort, Epigastric discomfort	Defaecation urgency
Skin and subcutaneous tissue disorders		Hyperhidrosis	Pruritis, Cold sweat	
Reproductive system and breast disorders		Erectile dysfunction	Ejaculation failure, Male orgasmic disorder, Paraesthesia	

			of genital male	
General disorders and administration site conditions		Fatigue, Irritability	Asthenia, Feeling hot, Feeling jittery, Feeling abnormal, Feeling drunk	
Investigations		Blood pressure increased	Heart rate increased, Blood pressure diastolic increased, Blood pressure orthostatic increased	

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

Description of selected adverse reactions

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

The occurrence of syncope and possibly prodromal symptoms appears dose dependent as demonstrated by higher incidence among patients treated with higher than recommended doses in Phase 3 clinical trials. Orthostatic hypotension has been reported in clinical trials. The frequency of syncope characterized as loss of consciousness in the Dapoxetine Tablets clinical development program varied depending on the population studied and ranged from 0.06% (30 mg) to 0.23% (60 mg) for subjects enrolled in the Phase 3 placebo-controlled clinical trials to 0.64% (all doses combined) for Phase 1 non-PE healthy volunteer studies.

Other special populations

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

Withdrawal effects

Abrupt discontinuation of chronically administered SSRIs used to treat chronic depressive disorders

has been reported to result in the following symptoms: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia and hypomania. Results of a safety study showed a slightly higher incidence of withdrawal symptoms of mild or moderate insomnia and dizziness in subjects switched to placebo after 62 days of daily dosing.

4.9 Overdose

No case of overdose has been reported. There were no unexpected adverse events in a clinical pharmacology study of Dapoxetine Tablets 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 Tablets are known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Urologicals, ATC code: G04BX14

Mechanism of action

Dapoxetine is a potent selective serotonin reuptake inhibitor (SSRI) with an IC_{50} of 1.12 nM, while its major human metabolites, desmethyldapoxetine (IC_{50} < 1.0 nM) and didesmethyldapoxetine (IC50 = 2.0 nM) are equivalent or less potent (dapoxetine-N-oxide (IC_{50} = 282 nM)).

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

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

action at pre- and postsynaptic receptors.

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 Tablets 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 Tablets 30 mg as needed, and 389 to Dapoxetine Tablets 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 2: Least squares mean and median Average IELT at study end*

Average IELT	**Placebo**	**Dapoxetine Tablets 30 mg**	**Dapoxetine Tablets 60 mg**
Median	1.05 min	1.72 min	1.91 min
Difference from placebo		0.6 min**	0.9 min**

[95% CI]		[0.37, 0.72]	[0.66, 1.06]
Least Squares Mean	1.7 min	2.9 min	3.3 min
Difference from placebo [95% CI]		1.2 min** [0.59, 1.72]	1.6 min** [1.02, 2.16]
*Baseline value carried forward for subjects with no post-baseline data. **Difference was statistically significant (p-value <= 0.001).			

Table 3: Subjects achieving at least a specific level in Average IELT at study end*			
IELT (mins)	**Placebo %**	**Dapoxetine 30 mg %**	**Dapoxetine 60 mg %**
≥1.0	51.6	68.8	77.6
≥2.0	23.2	44.4	47.9
≥3.0	14.3	26.0	37.4
≥4.0	10.4	18.4	27.6
≥5.0	7.6	14.3	19.6
≥6.0	5.0	11.7	14.4
≥7.0	3.9	9.1	9.8
≥8.0	2.9	6.5	8.3
* Baseline value carried forward for subjects with no post-baseline data.			

The magnitude of IELT prolongation was related to baseline IELT and was variable between individual subjects. The clinical relevance of Priligy 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 a1-category decrease in ejaculation-related distress. A statistically significantly greater percentage of subjects responded in each of the Priligy 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]) groupscompared with the placebo group at Week 12 (pooled analysis).

The clinical relevance of Priligy 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 ejaculationfrom 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.

5.2 Pharmacokinetic properties

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 Tablets 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, C-dapoxetine, dapoxetine was extensively metabolized to multiple metabolites primarily through the following biotransformational pathways: N-oxidation, N-demethylation, naphthyl hydroxylation, glucuronidation and sulfation. There was evidence of presystemic first-pass metabolism after oral administration.

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

Elimination

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

Pharmacokinetics in special populations

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

Race

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

lower body weight. The slightly higher exposure is not expected to have a meaningful clinical effect.

Elderly (age 65 years and over)

Analyses of a single dose clinical pharmacology study using 60 mg Dapoxetine showed no significant differences in pharmacokinetic parameters (Cmax, AUCinf, Tmax) between healthy elderly males and healthy young adult males. The efficacy and safety has not been established in this population.

Renal impairment

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

Hepatic impairment

In patients with mild hepatic impairment, unbound Cmax of Dapoxetine is decreased by 28% and unbound AUC is unchanged. The unbound Cmax and AUC of the active fraction (the sum of the unbound exposure of dapoxetine and desmethyldapoxetine) were decreased by 30% and 5%, repectively. In patients with moderate hepatic impairment unbound Cmax of dapoxetine is essentially unchanged (decrease of 3%) and unbound AUC is increased by 66%. The unbound Cmax and AUC of the active fraction were essentially unchanged and doubled, respectively. In patients with severe hepatic impairment, the unbound Cmax of Dapoxetine was decreased by 42% but the unbound AUC was increased by approximately 223%. The Cmax and AUC of the active fraction had similar changes.

CYP2D6 Polymorphism

In a single dose clinical pharmacology study using 60 mg Dapoxetine, plasma concentrations in poor metabolizers of CYP2D6 were higher than in extensive metabolizers of CYP2D6 (approximately 31% higher for Cmax and 36% higher for AUCinf of Dapoxetine and 98% higher for Cmax and 161% higher for AUCinf of desmethyldapoxetine). The active fraction of Dapoxetine Tablets may be increased by approximately 46% at Cmax and by approximately 90% at AUC. This increase may result

in a higher incidence and severity of dose dependent adverse events. The safety of Dapoxetine Tablets in poor metabolizers of CYP2D6 is of particular concern with concomitant administration of other medicinal products that may inhibit the metabolism of Dapoxetine such as moderate and potent CYP3A4 inhibitors.

5.3 Preclinical safety data

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 excipient(s)

Lactose monohydrate, Microcrystalline cellulose PH 102, Croscarmellose sodium (Ac-Di-Sol),

Colloidal Silicon Dioxide, Magnesium stearate.

Coating: Polyvinyl Alcohol, Talc, Titanium dioxide, Macrogol, Lecithin, Ferrosoferric oxide, Iron oxide red & Iron oxide yellow.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30^0C. Protect from light and moisture. Keep out of reach of children.

6.5 Nature and contents of container

10 Tablets of Dapoxetine Tablets 30 mg / 60 mg are packed with PVC/PVdC film on one side and Aluminium foil on the other side in the form of a blister pack and such 1 or 3 blister packs are further packed in a printed carton along with instructions for use.

7. MARKETING AUTHORISATION HOLDER

MSN LABORATORIES PRIVATE LIMITED,

(Formulations Division),

Plot No. 42, Anrich Industrial Estate,

Bollaram, Sangareddy Dist-502 325,

Telangana, India.

1.3.2 Labelling (outer & inner labels)

The artworks of container label, carton & Pack Insert for DAPOXEM 60 (Dapoxetine Tablets 60 mg) are enclosed in the following pages.

℞ **DAPOXEM 60**

Dapoxetine Tablets 60 mg

Each film-coated tablet contains:
Dapoxetine hydrochloride
equivalent to Dapoxetine 60 mg

Dosage :
As directed by the Physician.

Do not store above 30°C.
Protect from light and moisture.

Keep out of reach of children

Manufactured by:
MSN Laboratories Private Limited
(Formulations Division), Plot No. 42,
Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325,
Telangana, INDIA.

Mfg. Lic No.: 38/MD/AP/2007/F/CC

℞ **DAPOXEM 60**

Dapoxetine Tablets 60 mg

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Mfg. Lic No.: 38/MD/AP/2007/F/CC

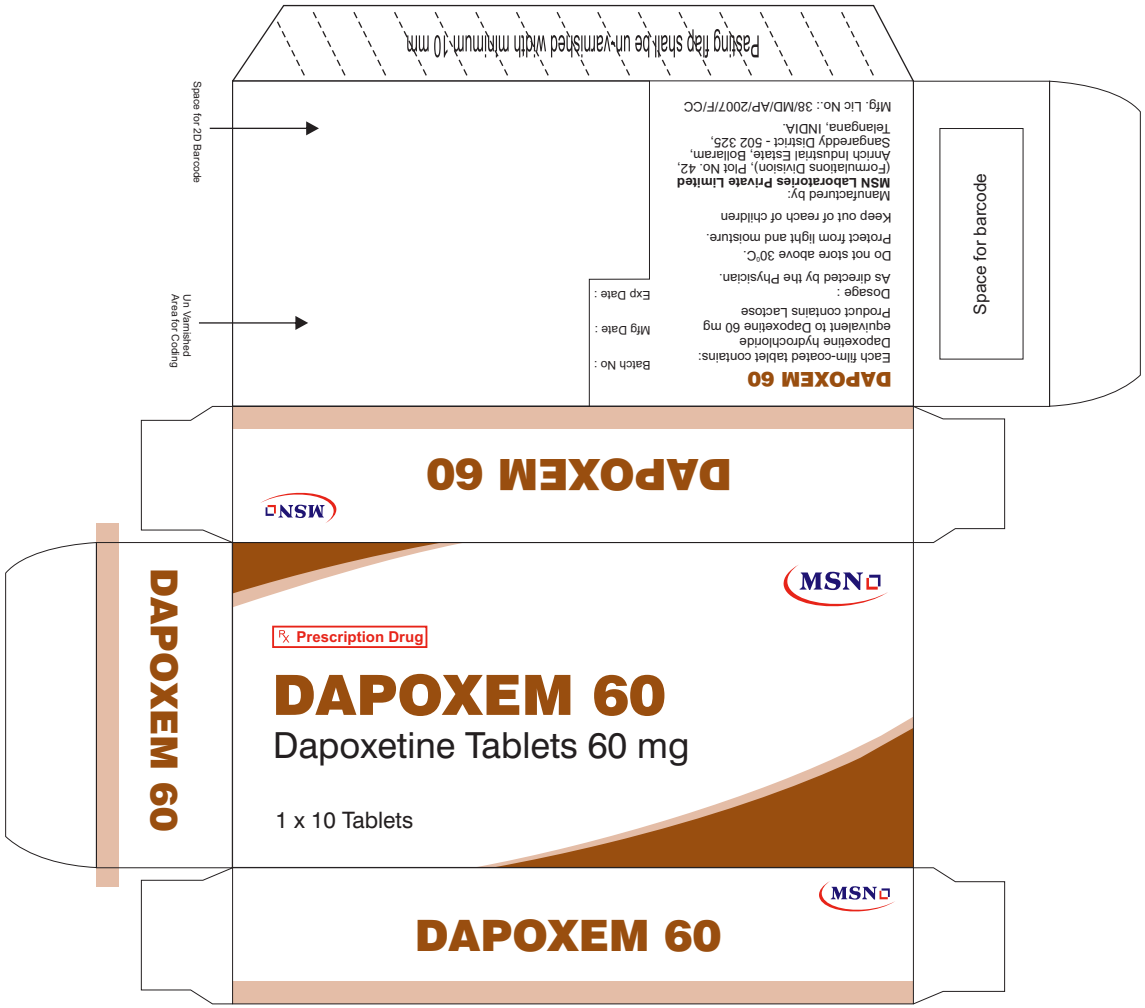
Black

Art work same size
size (4+60+20+10+20+60+4)
Total Foil Width 178 mm
OPZ 25 mm
Print repeat 25.3 mm

Blister Size : 85 x 38 mm

Blister Foil

Test	Specification
1. Description	Printed hard tempered aluminium foil with VMCH coating on the sealing side.
2. Thickness of Aluminium	0.018 to 0.022 mm
3. Width	178 ± 1.0 mm (177 – 179 mm)
4. Aluminium foil GSM VMCH Coating GSM	49.86 to 58.54 GSM 4 to 6 GSM
5. Pin Holes	Nil
6. Ink Adhesion Test	No Ink Lifting
7. Inner Core Diameter	76 ± 1 mm



DIMENSIONS : 90 X 18 X 43 mm
Cyber XL Board 300 gsm, UV Varnish except over printing area.

PANTONE 724 C PANTONE 286 C PANTONE 485 C Black

DIMENSIONS : 90 X 25 X 43 mm

Cyber XL Board 300 gsm, UV Varnish except over printing area.

PANTONE 724 C PANTONE 273 C PANTONE 485 C Black

Table 3: Subjects achieving at least a specific level in Average IELT at study end*			
IELT (mins)	**Placebo %**	**Dapoxetine 30 mg %**	**Dapoxetine 60 mg %**
≥1.0	51.6	68.8	77.6
≥2.0	23.2	44.4	47.9
≥3.0	14.3	26.0	37.4
≥4.0	10.4	18.4	27.6
≥5.0	7.6	14.3	19.6
≥6.0	5.0	11.7	14.4
≥7.0	3.9	9.1	9.8
≥8.0	2.9	6.5	8.3
* Baseline value carried forward for subjects with no post-baseline data.			

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 a1-category decrease in ejaculation-related distress. A statistically significantly greater percentage of subjects responded ineach of the Dapoxetine groups versus placebo at the end of the study Week 12 or 24. There was a higher percentage ofresponders in the dapoxetine 30 mg (11.1% - 95% CI [7.24; 14.87]) and 60 mg (16.4% - 95% CI [13.01; 19.75]) groupscompared with the placebo group at Week 12 (pooled analysis).
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Pharmacokinetic properties

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 Tablets 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, C-dapoxetine, dapoxetine was extensively metabolized to multiple metabolites primarily through the following biotransformational pathways: N-oxidation, N-demethylation, naphthyl hydroxylation, glucuronidation and sulfation. There was evidence of presystemic first-pass metabolism after oral administration.
Intact dapoxetine and dapoxetine-N-oxide were the major circulating moieties in the plasma. In vitro binding and transporter studies show that dapoxetine-N-oxide is inactive. Additional metabolites including desmethyldapoxetine and didesmethyldapoxetine account for less than 3% of the total circulating drug –related materials in plasma. In vitro binding studies indicate that DED is equipotent to dapoxetine and didesmethyldapoxetine has approximately 50% of the potency of dapoxetine. The unbound exposures (AUC and Cmax) of DED are approximately 50% and 23%, respectively, of the unbound exposure of dapoxetine.

Elimination

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

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Race

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

Elderly (age 65 years and over)

Analyses of a single dose clinical pharmacology study using 60 mg Dapoxetine showed no significant differences in pharmacokinetic parameters (Cmax, AUCinf, Tmax) between healthy elderly males and healthy young adult males. The efficacy and safety has not been established in this population.

Renal impairment

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

Hepatic impairment

In patients with mild hepatic impairment, unbound Cmax of Dapoxetine is decreased by 28% and unbound AUC is unchanged. The unbound Cmax and AUC of the active fraction (the sum of the unbound exposure of dapoxetine and desmethyldapoxetine) were decreased by 30% and 5%, repectively. In patients with moderate hepatic impairment unbound Cmax of dapoxetine is essentially unchanged (decrease of 3%) and unbound AUC is increased by 66%. The unbound Cmax and AUC of the active fraction were essentially unchanged and doubled, respectively. In patients with severe hepatic impairment, the unbound Cmax of Dapoxetine was decreased by 42% but the unbound AUC was increased by approximately 223%. The Cmax and AUC of the active fraction had similar changes.

CYP2D6 Polymorphism

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

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.

PHARMACEUTICAL PARTICULARS

List of excipient(s)

Lactose monohydrate, Microcrystalline cellulose, Croscarmellose sodium, Colloidal Silicon Dioxide, Magnesium stearate, and Purified Water.

Coating: Poly vinyl alcohol, Talc, Titanium dioxide, poly ethylene glycol, lecithin, ferroso ferricoxide, Iron oxide yellow and Iron oxide Red.

Incompatibilities

Not applicable.

Special precautions for storage

Do not store above 30°C. Protect from light and moisture.

Keep out of reach of children.

Identification

Dapoxetine Tablets 30 mg: Grey colored, round, biconvex, film coated tablets with plain surface on both sides.

Dapoxetine Tablets 60 mg: Grey colored, round, biconvex, film coated tablets with plain surface on both sides.

PACKING INFORMATION

DAPOXEM 30: Blister pack of 10 Tablets & Carton of 30’s.

DAPOXEM 60: Blister pack of 10 Tablets & Carton of 30’s

Manufactured by:
MSN Laboratories Private Limited
(Formulations Division),
Plot No. 42, Anrich Industrial Estate,
Bollaram, Sangareddy District - 502 325,
Telangana, INDIA.

Date of Revision of text: February 2017

Prescription only medication

DAPOXEM 30/60

(Dapoxetine Tablets 30 mg / 60 mg)

COMPOSITION

DAPOXEM 30
Each film coated tablet contains:
Dapoxetine hydrochloride
equivalent to Dapoxetine 30 mg

DAPOXEM 60
Each film coated tablet contains:
Dapoxetine hydrochloride
equivalent to Dapoxetine 60 mg

Product contains Lactose

PHARMACEUTICAL FORM
Film-coated tablet.

CLINICAL PARTICULARS

Therapeutic indications

Dapoxetine Tablets is indicated for the treatment of premature ejaculation (PE) in adult men aged 18 to 64 years.
Dapoxetine Tablets 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 Tablets should be administered only as on-demand treatment before anticipated sexual activity. Dapoxetine Tablets should not be prescribed to delay ejaculation in men who have not been diagnosed with PE.

Posology and method of administration

Posology

Adult men (aged 18 to 64 years)

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 Tablets should not be initiated with the 60 mg dose. Dapoxetine Tablets is not intended for continuous daily use. Dapoxetine Tablets should be taken only when sexual activity is anticipated. Dapoxetine Tablets must not be taken more frequently than once every 24 hours. If the individual response to 30 mg is insufficient and the patient has not experienced moderate or severe adverse reactions or prodromal symptoms suggestive of syncope, the dose may be increased to a maximum recommended dose of 60 mg taken as needed approximately 1 to 3 hours prior to sexual activity. The incidence and severity of adverse events is higher with the 60 mg dose. If the patient experienced orthostatic reactions on the starting dose, no dose escalation to 60 mg should be performed.
A careful appraisal of individual benefit risk of Dapoxetine Tablets should be performed by the physician after the first four weeks of treatment (or at least after 6 doses of treatment) to determine whether continuing treatment with Dapoxetine Tablets is appropriate. Data regarding the efficacy and safety of Dapoxetine Tablets beyond 24 weeks are limited. The clinical need of continuing and the benefit risk balance of treatment with Dapoxetine Tablets should be re-evaluated at least every six months. Elderly (age 65 years and over) The efficacy and safety of Dapoxetine Tablets have not been established in patients age 65 years and over.

Paediatric population

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

Patients with renal impairment

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

Patients with hepatic impairment

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

Known CYP2D6 poor metabolizers or patients treated with potent CYP2D6 inhibitors.

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

Patients treated with moderate or potent inhibitors of CYP3A4.

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

Method of administration

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

Precautions to be taken before handling or administering the medicinal product

Before treatment is initiated, see Special warnings and Precautions for use. regarding orthostatic hypotension.

Contraindications

Hypersensitivity to the active substance or to any of the excipients used in the formulation.
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 Tablets 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 Tablets 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 Tablets 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.

Special warnings and precautions for use

General recommendations

Dapoxetine Tablets is only indicated in men with Premature Ejaculation who meet all the criteria listed in sections Therapeutic indications and Pharmacodynamic properties. Dapoxetine Tablets 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 Tablets 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 Tablets 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 Tablets 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 lightheadedness occur. Possibly prodromal symptoms such as nausea, dizziness/lightheadedness, and diaphoresis were reported more frequently among patients treated with Dapoxetine Tablets 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, light headedness, 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 Tablets. 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 Tablets 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 Tablets. These reactions include, but are not limited to, arrhythmia, hyperthermia, and serotonin syndrome. Use of Dapoxetine Tablets 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 Tablets 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 Tablets.

Medicinal products with vasodilatation properties

Dapoxetine Tablets 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 Tablets 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.

Single Colour Black

Dimensions (Front - 280 x 400 mm - Back - 280 x 400 mm)

Folded size 70 x 36 mm

BIBLE PAPER 40 GSM

Seizure

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

Haemorrhage

There have been reports of bleeding abnormalities with SSRIs. Caution is advised in patients taking Dapoxetine Tablets, 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 Tablets 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 Tablets 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 Tablets has been associated with ocular effects such as mydriasis and eye pain. Dapoxetine Tablets 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, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

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 Tablets 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 Tablets has been discontinued.

Potential for interaction with thioridazine

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias. Medicinal products such as Dapoxetine Tablets 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 Tablets 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 Tablets 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 Tablets 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 Tablets has been discontinued.

CNS active medicinal products

The use of Dapoxetine Tablets 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 Tablets 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 Tablets and potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazodone, nelfinavir and atazanavir, is contraindicated .
Moderate CYP3A4 inhibitors. Concomitant treatment with moderate CYP3A4 inhibitors (e.g., erythromycin, clarithromycin,fluconazole, amprenavir, fosamprenavir, aprepitant, verapamil, diltiazem) may also give rise to significantly increased exposure of dapoxetine and desmethyldapoxetine, especially in CYP2D6 poor metabolizers. The maximum dose of dapoxetine should be 30 mg if dapoxetine is combined with any of these drugs.
These two measures apply to all patients unless the patient has been verified to be a CYP2D6 extensive metabolizer by geno- or phenotyping. In patients verified to be CYP2D6 extensive metabolizers, a maximum dose of 30 mg is advised if dapoxetine is combined with a potent CYP3A4 inhibitor and caution is advised if dapoxetine in 60 mg doses is taken concomitantly with a moderate CYP3A4 inhibitor.

Potent CYP2D6 inhibitors

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

PDE5 inhibitors

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

Medicinal products metabolized by CYP2D6

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

Medicinal products metabolized by CYP3A4

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

Medicinal products metabolized by CYP2C19

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

Medicinal products metabolized by CYP2C9

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

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

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

Ethanol

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

Fertility Pregnancy and lactation

Dapoxetine Tablets 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.

Effects on ability to drive and use machines

Dapoxetine Tablets 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 Tablets .

Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

The safety of Dapoxetine Tablets 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 Tablets 30 mg as needed and 2608 received 60 mg, either as needed or once daily.
Table 1 presents the adverse reactions that have been reported.

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

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

Description of selected adverse reactions

Syncope characterized as loss of consciousness, with bradycardia or sinus arrest observed in patients wearing Holter monitors, has been reported in clinical trials and is considered medicinal product-related. The majority of cases occurred during the first 3 hours after dosing, after the first dose or associated with study-related procedures in the clinical setting (such as blood draw and orthostatic maneuvers and blood pressure measurements). Prodromal symptoms often preceded the syncope.
The occurrence of syncope and possibly prodromal symptoms appears dose dependent as demonstrated by higher incidence among patients treated with higher than recommended doses in Phase 3 clinical trials. Orthostatic hypotension has been reported in clinical trials. The frequency of syncope characterized as loss of consciousness in the Dapoxetine Tablets 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 continuedmonitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report anysuspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard.

Overdose

No case of overdose has been reported. There were no unexpected adverse events in a clinical pharmacology study of Dapoxetine Tablets 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 Tablets are known.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Other Urologicals, ATC code: G04BX14

Mechanism of action

Dapoxetine is a potent selective serotonin reuptake inhibitor (SSRI) with an IC_{50} of 1.12 nM, while its major human metabolites, desmethyldapoxetine (IC_{50} < 1.0 nM) and didesmethyldapoxetine (IC_{50} = 2.0 nM) are equivalent or less potent (dapoxetine-N-oxide (IC_{50} = 282 nM)).
Human ejaculation is primarily mediated by the sympathetic nervous system. The ejaculatory pathway originates from a spinal reflex centre, mediated by the brain stem, which is influenced initially by a number of nuclei in the brain (medial preoptic and paraventricular nuclei).
The mechanism of action of dapoxetine in premature ejaculation is presumed to be linked to the inhibition of neuronal reuptake of serotonin and the subsequent potentiation of the neurotransmitter's action at pre- and postsynaptic receptors.
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 Tablets 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 Tablets 30 mg as needed, and 389 to Dapoxetine Tablets 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 2: Least squares mean and median Average IELT at study end*

Average IELT	Placebo	Dapoxetine Tablets 30 mg	Dapoxetine Tablets 60 mg
Median	1.05 min	1.72 min	1.91 min
Difference from placebo [95% CI]		0.6 min** [0.37, 0.72]	0.9 min** [0.66, 1.06]
Least Squares Mean	1.7 min	2.9 min	3.3 min
Difference from placebo [95% CI]		1.2 min** [0.59, 1.72]	1.6 min** [1.02, 2.16]

*Baseline value carried forward for subjects with no post-baseline data.
**Difference was statistically significant (p-value <= 0.001).

1.3.3 Package Insert (also known as patient information PIL)

Patient Information leaflet for DAPOXEM 60 (Dapoxetine Tablets 60 mg) has been enclosed in the following pages.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Dapoxem 30(Dapoxetine Tablets 30 mg)

Dapoxem 60(Dapoxetine Tablets 60 mg)

Dapoxetine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See possible side effects.

In this leaflet:

1. What Dapoxetine Tablets is and what it is used for

Dapoxetine Tablets contains an active substance called 'dapoxetine'. This belongs to a group of medicines called “selective serotonin re-uptake inhibitors‟ (SSRIs). Dapoxetine Tablets may also be known as a “urological‟ medicine.

Dapoxetine Tablets increases the time it takes to ejaculate and can improve the control over the ejaculation. This may reduce the frustration or worry about fast ejaculation.

Dapoxetine Tablets is used to treat premature ejaculation in adult men aged 18 to 64 years.

Premature ejaculation is when a man ejaculates with little sexual stimulation and before the man wants. This can cause problems for the man and may cause problems in sexual relationships.

2. What you need to Know before you take Dapoxetine Tablets

Do not take Dapoxetine Tablets if:

- You are allergic to dapoxetine or any of the other ingredients of Dapoxetine Tablets (listed in section 6)
- You have heart problems, such as heart failure or problems with the heart rhythm
- you have a history of fainting
- you have ever had mania (symptoms include feeling over−excited, irritable or not being able to think clearly) or severe depression
- you have moderate or severe liver problems.

You are taking:

- Medicines for depression called 'monoamine oxidase inhibitors' (MAOIs)
- Thioridazine used for schizophrenia
- Other medicines for depression
- Lithium a medicine for bipolar disorder
- Linezolid an antibiotic used to treat infections
- Tryptophan a medicine to help you sleep
- St John‟s wort an herbal medicine
- Tramadol used to treat serious pain
- Medicines used to treat migraines.

Do not take Dapoxetine Tablets at the same time as any of the medicines listed above. If you have taken any of these medicines, you will need to wait 14 days after you stop taking it before you can start taking Dapoxetine Tablets. Once you have stopped taking Dapoxetine Tablets, you will need to wait 7 days before taking any of the medicines listed above. If you are not sure about what to do, talk to your doctor or pharmacist before taking Dapoxetine Tablets.

- Certain medicines for fungal infection, including ketoconazole and itraconazole
- Certain medicines for HIV, including ritonavir, saquinavir, nelfinavir and atazanavir
- Certain antibiotics for treating infection, including telithromycin
- Nefazodone- an antidepressant

  Also see section **“Other medicines and Dapoxetine Tablets”**)

Do not take Dapoxetine Tablets if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Dapoxetine Tablets.

Children and adolescents

This medicine should not be used in children or adolescents under age 18 years.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Dapoxetine Tablets if:

- You have not been diagnosed with premature ejaculation
- You also have another sexual problem, such as erectile dysfunction
- You have a history of dizziness from low blood pressure
- You use recreational drugs such as ecstasy, LSD, narcotics or benzodiazepines
- You drink alcohol (see section " Dapoxetine Tablets with food, drink and alcohol")
- You have ever had a mental health problem such as depression, mania (symptoms include feeling over−excited, irritable or not being able to think clearly), bipolar disorder (symptoms include serious mood swings between mania and depression) or schizophrenia (a psychiatric disease)
- You have epilepsy
- You have a history of bleeding or blood clotting problems
- You have kidney problems
- You have, or are at risk of, high pressure in the eye (glaucoma).

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking this medicine.

Before you start taking this medicine, your doctor should perform a test to make sure that your blood pressure doesn't drop too much when you stand up from lying down.

Other medicines and Dapoxetine Tablets

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. This includes medicines you get without a prescription, such as herbal medicines. This is because Dapoxetine Tablets can affect the way some other medicines work. Also some other medicines can affect the way Dapoxetine Tablets works. Therefore, use of other medicines may affect the maximum dose of Dapoxetine Tablets you're allowed to take.

Do not take Dapoxetine Tablets at the same time as any of the following medicines:

Medicines for depression called 'monoamine oxidase inhibitors' (MAOIs)

- Thioridazine used for schizophrenia
- Other medicines for depression
- Lithium − a medicine for bipolar disorder

- Linezolid − an antibiotic used to treat infections
- Tryptophan − a medicine to help you sleep
- St John's wort − a herbal medicine
- Tramadol − used to treat serious pain
- Medicines used to treat migraines.

Do not take Dapoxetine Tablets at the same time as any of the medicines listed above. If you have taken any of these medicines, you will need to wait 14 days after you stop taking it before you can start taking Dapoxetine Tablets. Once you have stopped taking Dapoxetine Tablets, you will need to wait 7 days before taking any of the medicines listed above. If you are not sure about what to do, talk to your doctor or pharmacist before taking this medicine.

- Certain medicines for fungal infection, including ketoconazole and itraconazole
- Certain medicines for HIV, including ritonavir, saquinavir, nelfinavir and atazanavir
- Certain antibiotics for treating infection, including telithromycin
- Nefazodone − an antidepressant.

Tell your doctor or pharmacist if you are taking any of the following medicines:

- Medicines for mental health problems other than depression
- Non-steroidal anti-inflammatory medicines such as ibuprofen or acetylsalicyclic acid
- Medicines to thin your blood, such as warfarin
- Certain medicines used to treat erectile dysfunction, such as sildenafil, tadalafil or vardenafil, as these medicines may lower your blood pressure, possibly upon standing
- Certain medicines used to treat high blood pressure and chest pain (angina) (such as verapamil and diltiazem), or enlarged prostate, as these medicines may also lower your blood pressure, possibly upon standing
- Certain other medicines for fungal infection, such as fluconazole
- Certain other medicines for HIV, such as amprenavir and fosamprenavir
- Certain other antibiotics for treating infection, such as erythromycin and clarithromycin
- Aprepitant − used to treat nausea.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking this medicine.

Dapoxetine Tablets with food, drink and alcohol

- This medicine can be taken with or without food.
- You should take this medicine with at least one full glass of water.
- Avoid alcohol when taking this medicine.
- The effects of alcohol such as feeling dizzy, sleepy and having slow reactions, may be increased if taken with this medicine.
- Drinking alcohol while taking this medicine may increase your risk of injury from fainting or from other side effects.

Pregnancy, breast−feeding and fertility

This medicine should not be taken by women.

Driving and using machines

You may feel sleepy, dizzy, faint, have difficulty concentrating and blurred vision while taking this medicine. If you experience any of these or similar effects, you should avoid driving or operating hazardous machinery. The effects of alcohol may be increased if taken with this medicine and you may be more at risk of injury from fainting or from other side effects if you take this medicine with alcohol.

Dapoxetine Tablets contains lactose

This medicine contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Dapoxetine Tablets

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- The recommended dose is 30 mg. Your doctor may increase the dose to 60 mg.
- Only take the medicine 1 to 3 hours before sexual activity is anticipated.
- Do not take this medicine more than once every 24 hours or every day.
- Swallow the tablets whole to avoid a bitter taste, with at least one full glass of water. This may help lower your chance of fainting (see ‘Fainting and low blood pressure’ in section 4).
- This medicine can be taken with or without food.
- This medicine should not be used by men under 18 or over 65 years of age.

- Discuss your Dapoxetine Tablets treatment with your doctor after the first 4 weeks or after 6 doses to see whether you should continue treatment. If treatment is continued, you should see your doctor again to discuss this at least every six months.

If you take more Dapoxetine Tablets than you should

Tell your doctor or pharmacist if you have taken more tablets than you should. You may feel sick or be sick.

If you stop taking Dapoxetine Tablets

Talk to your doctor before you stop taking this medicine. You may have problems sleeping and feel dizzy after you stop taking this medicine, even if you have not taken it every day.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Dapoxetine Tablets and see your doctor straight away if:

- You have fits (seizures)
- You faint or feel light headed when you stand up
- You notice any changes in your mood
- You have any thoughts of suicide or harming yourself.

If you notice any of the above, stop taking this medicine and see your doctor straight away.

Fainting and low blood pressure

This medicine can make you faint or make your blood pressure drop when you stand up. To help lower the chance of this happening:

- Take this medicine with at least one full glass of water.
- Do not take this medicine if you are dehydrated (you do not have enough water in your body

This can happen if:

  - You have not had anything to drink in the past 4 to 6 hours
  - You have been sweating for a long time
  - You have an illness where you have a high temperature, diarrhoea or being sick.
- If you feel like you might faint (such as feeling sick, feeling dizzy, light headed, confused, sweaty or an abnormal heart beat), or feel light headed when you stand up, immediately lie down so your head is lower than the rest of your body or sit down with your head between your

knees until you feel better. This will stop you from falling and hurting yourself if you do fain

- Do not stand up quickly after you have been sitting or lying down for a long time.
- Do not drive or use any tools or machines if you feel faint when taking this medicine.
- Tell your doctor if you faint when taking this medicine.

Very common side effects (may affect more than 1 in 10 men):

- Feeling dizzy
- Headache
- Feeling sick.

Common side effects (may affect up to 1 in 10 men):

- Feeling irritable, anxious, agitated or restless
- Feeling numb or having ‘pins and needles’
- Difficulty getting or keeping an erection
- Sweating more than normal or flushing
- Diarrhoea, constipation or having wind
- Stomach pain, bloating or being sick
- Problems sleeping or strange dreams
- Feeling tired or sleepy, yawning
- Blocked nose (nasal congestion)
- A rise in blood pressure
- Difficulty concentrating
- Shaking or trembling
- Lower interest in sex
- Ringing in the ears
- Blurred vision
- Indigestion
- Dry mouth.

Uncommon side effects (may affect up to 1 in 100 men):

- Fainting or feeling dizzy upon standing (see advice above)
- Change in mood, feeling overly excited or feelings of paranoia
- Feeling confused, disoriented or unable to think clearly

- Slow or irregular heartbeat or increase in heart rate
- Loss of sex drive, problems reaching orgasm
- Feeling weak, sedated, lethargic or fatigued
- Feeling depressed, nervous or indifferent
- Feeling hot, jittery, abnormal or drunk
- Vision problems, eye pain or dilated pupils
- Low or high blood pressure
- Feeling itchy or cold sweat
- Spinning sensation
- Abnormal taste
- Teeth grinding.

Rare side effects (may affect up to 1 in 1,000 men):

- Feeling dizzy following exertion
- Sudden onset of sleep
- Urgency of bowel action.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Dapoxetine Tablets

- This medicinal product does not require any special storage conditions.
- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.
- Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Dapoxetine Tablets contains

The active substance is dapoxetine. Each tablet contains 30 mg or 60 mg dapoxetine as a hydrochloride salt.

The other ingredients are:

- Tablet core: Lactose monohydrate, Microcrystalline cellulose, Croscarmellose sodium, Colloidal silicon dioxide, Magnesium stearate.
- Tablet coating: Polyvinyl alcohol-part, Talc,Titanium dioxide, Macrogol, Lecithin, Ferrosoferric oxide, Iron oxide yellow & Iron oxide red

What Dapoxetine Tablets looks like and contents of the pack

Dapoxetine Tablets 30 mg are Grey colored, round, biconvex, film coated tablets with plain surface on both sides.

Dapoxetine Tablets 60 mg are Grey colored, round, biconvex, film coated tablets with plain surface on both sides.

Dapoxetine Tablets are available as blister pack containing 10 tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

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