

**Summary of Product
Characteristics of
Dumax 60 Film Coated Tablet**

1. Name of the medicinal Product

Dumax 60 Film Coated Tablet

2. Qualitative and Quantitative Composition

Each Film Coated Tablet contains

Dapoxetine Hydrochloride

Eq. to Dapoxetine60 mg.

Excipients of known Effect :Lactose BP 113.988 mg,

For the full list of excipients, see Section 6.1.

3 Pharmaceutical form

Film coated tablet

4 Clinical particulars

4.1 Therapeutic indications

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

Dumax should be administered only as on-demand treatment before anticipated sexual activity. Dumax 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 Dumax should not be initiated with the 60 mg dose.

Dumax is not intended for continuous daily use. Dumax should be taken only when sexual activity is anticipated. Dumax 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 Dumax 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 Dumax is appropriate.

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

Elderly (age 65 years and over)

The efficacy and safety of Dumax have not been established in patients age 65 years and over.

Paediatric population

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

Patients with renal impairment

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

Patients with hepatic impairment

Dumax 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

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. Dumax may be taken with or without food (see section 5.1).

Precautions to be taken before handling or administering the medicinal product Before treatment is initiated, see section 4.4 regarding orthostatic hypotension.

4.3 Contraindication

Hypersensitivity to the active substance or to any of the excipients of DUMAX. 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 Dumax 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 Dumax 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 Dumax has been discontinued.

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

4.4 Special warnings and precautions for use

General recommendations

Dumax is only indicated in men with Premature Ejaculation who meet all the criteria listed in sections 4.1 and 5.1. Dumax 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. Dumax 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 Dumax 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 Dumax for the treatment of premature ejaculation, there was no clear indication of treatment-emergent suicidality in evaluation of possibly suicide-related adverse events evaluated by the Columbia Classification Algorithm of Suicide Assessment (C-CASA), Montgomery-Asberg Depression Rating Scale, or Beck Depression Inventory-II.

Syncope

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

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

In the clinical trials, cases of syncope characterized as loss of consciousness, with bradycardia or sinus arrest observed in patients wearing Holter monitors, were considered vasovagal in etiology and the majority occurred during the first 3 hours after dosing, after the first dose, or associated with study-related procedures in the clinic setting (such as blood draw and orthostatic maneuvers and blood pressure measurements). Possibly prodromal symptoms, such as nausea, dizziness, lightheadedness, palpitations, asthenia, confusion and diaphoresis generally occurred within the first 3 hours following dosing, and often preceded the syncope. Patients need to be made aware that they could experience syncope at any time with or without prodromal symptoms during their treatment with Dumax. 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 Dumax 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 Dumax. These reactions include, but are not limited to, arrhythmia, hyperthermia, and serotonin syndrome. Use of Dumax 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 Dumax 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 Dumax.

Medicinal products with vasodilatation properties

Dumax 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

Dumax 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, Dumax 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

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

Haemorrhage

There have been reports of bleeding abnormalities with SSRIs. Caution is advised in patients taking Dumax, 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

Dumax 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 Dumax 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 Dumax has been associated with ocular effects such as mydriasis and eye pain. Dumax 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, Dumax 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 Dumax 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 Dumax 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.

Dumax 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 Dumax 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. Dumax 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 Dumax has been discontinued.

CNS active medicinal products

The use of Dumax 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 Dumax and such medicinal products is required.

Pharmacokinetic interactions

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

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

CYP3A4 inhibitors

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

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

Therefore, concomitant use of Dumax 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 desmethyl dapoxetine, especially in CYP2D6 poor metabolizers. The maximum dose of dapoxetine should be 30 mg if dapoxetine is combined with any of these drugs.

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

Potent CYP2D6 inhibitors

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

PDE5 inhibitors

Dumax should not be used in patients using PDE5 inhibitors due to possible reduced orthostatic tolerance (see section 4.4). The pharmacokinetics of dapoxetine (60 mg) in combination with tadalafil (20 mg) and sildenafil (100 mg) were evaluated in a single dose crossover study. Tadalafil did not affect the pharmacokinetics of dapoxetine. Sildenafil caused slight changes in dapoxetine pharmacokinetics (22% increase in AUC_{inf} and 4% increase in C_{max}), which are not expected to be clinically significant.

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

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

Tamsulosin

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

Medicinal products metabolized by CYP2D6

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

Medicinal products metabolized by CYP3A4

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

Medicinal products metabolized by CYP2C19

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

Medicinal products metabolized by CYP2C9

Multiple dosing of dapoxetine (60 mg/day for 6 days) did not affect the pharmacokinetics or pharmacodynamics of a single 5 mg dose of 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 Dumax (see sections 4.4 and 4.7).

4.6 Fertility, pregnancy and lactation

Dumax 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

Dumax has minor or moderate influence on the ability to drive and use machines. Dizziness, disturbance in attention, syncope, blurred vision and somnolences 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 Dumax.

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 Dumax-treated subjects) and dizziness (1.2% of Dumax -treated subjects).

Tabulated list of adverse reactions

The safety of Dumax was evaluated in 4224 subjects with premature ejaculation who participated in five double-blind, placebo-controlled clinical trials. Of the 4224 subjects, 1616 received Dumax 30 mg as needed and 2608 received 60 mg, either as needed or once daily.

Table 1 presents the adverse reactions that have been reported.

Table 1: Frequency of Adverse Reactions (MedDRA)				
System Organ Class	Very common ($> 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1000$ to $< 1/100$)	Rare ($\geq 1/10000$ 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 (see section 4.4), Eye pain, Visual disturbance	
Ear and labyrinth disorders		Tinnitus	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 (see section 4.4). The frequency of syncope characterized as loss of consciousness in the

Dumax 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 of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS)

<https://pv.pharmacyboardkenya.org>

4.9 Overdose

No case of overdose has been reported.

There were no unexpected adverse events in a clinical pharmacology study of Dumax 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 Dumax 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 IC₅₀ of 1.12 nM, while its major human metabolites, desmethyldapoxetine (IC₅₀ < 1.0 nM) and didesmetyldapoxetine (IC₅₀ = 2.0 nM) are equivalent or less potent (dapoxetine-N-oxide (IC₅₀ = 282 nM)).

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

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

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

Clinical efficacy and safety

The effectiveness of Dumax 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 Dumax 30 mg as needed, and 389 to Dumax 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	Dumax 30 mg	Dumax 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).			

Table 3: Subjects achieving at least a specific level in Average IELT at study end*			
IELT (minutes)	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 Dumax treatment effects was further demonstrated in terms of various patient reported outcome measures and a responder analysis.

A responder was defined as a subject who had at least a 2-category increase in control over

ejaculation plus at least a 1-category decrease in ejaculation-related distress. A statistically significantly greater percentage of subjects responded in each of the Dumax groups versus placebo at the end of the study Week 12 or 24. There was a higher percentage of responders in the dapoxetine 30 mg (11.1% - 95% CI [7.24; 14.87]) and 60 mg (16.4% - 95% CI [13.01; 19.75]) groups compared

with the placebo group at Week 12 (pooled analysis).

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

5.2 Pharmacokinetic properties

Absorption

Dapoxetine is rapidly absorbed with maximum plasma concentrations (C_{max}) occurring approximately 1-2 hours after tablet intake. The absolute bioavailability is 42% (range 15–76%), and dose proportional increases in exposure (AUC and C_{max}) are observed between the 30 and 60 mg dose strengths. Following multiple doses, AUC values for both dapoxetine and the active metabolite desmethyl dapoxetine (DED) increase by approximately 50% when compared to single dose AUC values.

Ingestion of a high fat meal modestly reduced the C_{max} (by 10%) and modestly increased the AUC (by 12%) of dapoxetine and slightly delayed the time for dapoxetine to reach peak concentrations. These changes are not clinically significant. Dapoxetine can be taken with or without food.

Distribution

More than 99% of dapoxetine is bound *in vitro* to human serum proteins. The active metabolite desmethyldapoxetine (DED) is 98.5% protein bound. Dapoxetine has a mean steady state volume of distribution of 162 L.

Biotransformation

In vitro studies suggest that dapoxetine is cleared by multiple enzyme systems in the liver and kidneys, primarily CYP2D6, CYP3A4, and flavin monooxygenase (FMO1). Following oral dosing of ¹⁴C-dapoxetine, dapoxetine was extensively metabolized to multiple metabolites primarily through the following biotransformational pathways: N-oxidation, N-demethylation, naphthyl hydroxylation, glucuronidation and sulfation. There was evidence of presystemic first-pass metabolism after oral administration.

Intact dapoxetine and dapoxetine-N-oxide were the major circulating moieties in the plasma. *In vitro* binding and transporter studies show that dapoxetine-N-oxide is inactive. Additional metabolites including desmethyldapoxetine and didesmethyl dapoxetine 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 didesmethyl dapoxetine has approximately 50% of the potency of dapoxetine (see section 5.1). The unbound exposures (AUC and C_{max}) of DED are approximately 50% and 23%, respectively, of the unbound exposure of dapoxetine.

Elimination

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

Pharmacokinetics in special populations

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

Race

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

Elderly (age 65 years and over)

Analyses of a single dose clinical pharmacology study using 60 mg dapoxetine showed no significant differences in pharmacokinetic parameters (C_{max}, AUC_{inf}, T_{max}) between

healthy elderly males and healthy young adult males. The efficacy and safety has not been established in this population.

Renal impairment

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

Hepatic impairment

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

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

CYP2D6 Polymorphism

In a single dose clinical pharmacology study using 60 mg dapoxetine, plasma concentrations in poor metabolizers of CYP2D6 were higher than in extensive metabolizers of CYP2D6 (approximately 31% higher for C_{max} and 36% higher for AUC_{inf} of dapoxetine and 98% higher for C_{max} and 161% higher for AUC_{inf} of desmethyldapoxetine). The active fraction

of Dumax may be increased by approximately 46% at C_{max} and by approximately 90% at AUC. This increase may result in a higher incidence and severity of dose dependent adverse events (see section 4.2). The safety of Dumax in poor metabolizers of mCYP2D6 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 (C_{max} and AUC_{0-24 hr}) at the maximum tolerated doses in some studies approached those observed in man. However, the body weight normalized dose multiples were greater than 100-fold. There were no clinically relevant safety hazards identified in any of these studies.

In studies with oral administration, dapoxetine was not carcinogenic to rats when administered daily for approximately two years at doses up to 225 mg/kg/day, yielding approximately twice the exposures (AUC) seen in human males given the Maximum Recommended Human Dose (MRHD) of 60 mg. Dapoxetine also did not cause tumors in Tg. rasH2 mice when administered at the maximum possible doses of 100 mg/kg for 6 months and 200 mg/kg for 4 months. The steady state exposures of dapoxetine in mice following 6-months oral administration at 100 mg/kg/day were less than the single dose exposures observed clinically at 60 mg.

There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats and no adverse signs of embryotoxicity or fetotoxicity in the rat or rabbit. Reproductive toxicity studies did not include studies to assess the risk of adverse effects after exposure during the peri-post-natal period.

6 Pharmaceutical particulars

6.1 List of excipients

Tablet core:

Lactose

Microcrystalline cellulose

(101) Pregelatinised

Starch Croscarmellose

sodium Colloidal

anhydrous silica

Magnesium stearate

Spectracol Erythrosine

HS LK Purified Water

Coating Materials:

Hypromellose 5 cps

Titanium dioxide

Purified Talc

Propylene Glycol

Spectracol Erythrosine HS LK

Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 Months

6.4 Special precautions for storage

"Do not store above 30⁰C. Keep away from light and wet place."

6.5 Nature and contents of container

4 tablets are packed in Aluminium-PVDC blister strip. Such 1 strip is packed in one carton along with leaflet.

6.6 Special precautions for disposal and other handling

This medicinal product should not be disposed of via waste water or household waste. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

Company Name: Eskayef
Pharmaceuticals Limited

8. Marketing Authorization Number

Kenya : H2018/4865/560ER

9. Date of first authorisation/renewal of the authorisation

H2018/4865/560ER

10. Date of revision of the text

18.02.2014