SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Priligy 30 mg film–coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film–coated tablet contains dapoxetine hydrochloride equivalent to 30 mg dapoxetine.

Excipient with known effect: Lactose. Each 30 mg tablet contains 45.88 mg of lactose.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film–coated tablet.
Light grey, round, convex, approximately 6.5 mm in diameter and debossed with “30” inside a triangle on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Priligy is not intended for continuous daily use. Priligy should be taken only when sexual activity is anticipated. Priligy 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 (see section 4.4).

A careful appraisal of individual benefit risk of Priligy 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 Priligy is appropriate.

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

Elderly (age 65 years and over)

The efficacy and safety of Priligy have not been established in patients age 65 years and over (see section 5.2).

Paediatric Population
There is no relevant use of Priligy in this population in the indication of premature ejaculation.

Patients with renal impairment

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

Patients with hepatic impairment

Priligy is contraindicated in patients with moderate and severe hepatic impairment (Child–Pugh Class B and C) (see sections 4.3 and 5.2).

Known CYP2D6 poor metabolizers or patients treated with potent CYP2D6 inhibitors

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

Patients treated with moderate or potent inhibitors of CYP3A4

Concomitant use of potent CYP3A4 inhibitors is contraindicated. The dose should be restricted to 30 mg in patients concomitantly treated with moderate CYP3A4 inhibitors and caution is advised (see sections 4.3, 4.4 and 4.5).

<u>Method of administration</u>

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. Priligy may be taken with or without food (see section 5.2).

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 Priligy has been discontinued (see section 4.5).

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

Concomitant treatment with serotonin reuptake inhibitors [selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs)] or other medicinal/herbal products with serotonergic effects [e.g., L–tryptophan, triptans, tramadol, linezolid, lithium, St. John's Wort (*Hypericum perforatum*)] or within 14 days of discontinuing treatment with these medicinal/herbal products. Similarly, these medicinal/herbal products should not be administered within 7 days after Priligy has been discontinued (see section 4.5).

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

Moderate and severe hepatic impairment.

4.4 Special warnings and precautions for use

General recommendations

Priligy is only indicated in men with Premature Ejaculation who meet all the criteria listed in sections 4.1 and 5.1. Priligy 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. Priligy should not be used in men with erectile dysfunction (ED) who are using PDE5 inhibitors (see section 4.5).

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 Priligy 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 Priligy 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 (see section 4.8).

Possibly prodromal symptoms such as nausea, dizziness/lightheadedness, and diaphoresis were reported more frequently among patients treated with Priligy 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 Priligy. 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 (see section 4.7).

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 Priligy 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 Priligy. These reactions include, but are not limited to, arrhythmia, hyperthermia, and serotonin syndrome. Use of Priligy 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 Priligy 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 Priligy (see sections 4.5 and 4.7).

Medicinal products with vasodilatation properties

Priligy should be prescribed with caution in patients taking medicinal products with vasodilatation properties (such as alpha adrenergic receptor antagonists and nitrates) due to possible reduced orthostatic tolerance (see section 4.5).

Moderate CYP3A4 inhibitors

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

Potent CYP2D6 inhibitors

Caution is advised if increasing the dose to 60 mg in patients taking potent CYP2D6 inhibitors or if increasing the dose to 60 mg in patients known to be of CYP2D6 poor metabolizer genotype, as this may increase exposure levels, which may result in a higher incidence and severity of dose dependent adverse events (see sections 4.2, 4.5 and 5.2).

Mania

Priligy 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, Priligy 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

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

Haemorrhage

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

Renal impairment

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

Withdrawal effects

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

A double−blind clinical trial in subjects with PE designed to assess the withdrawal effects of 62 days of daily or as needed dosing with 60 mg Priligy showed mild withdrawal symptoms with a slightly higher incidence of insomnia and dizziness in subjects switched to placebo after daily dosing (see section 5.1).

Eye disorders

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

Lactose intolerance

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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, Priligy 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 Priligy has been discontinued (see section 4.3).

Potential for interaction with thioridazine

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias. Medicinal products such as Priligy 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. Priligy 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 Priligy has been discontinued (see section 4.3).

Medicinal/herbal products with serotonergic effects

As with other SSRIs, co−administration with serotonergic medicinal/herbal products (including MAOIs, L−tryptophan, triptans, tramadol, linezolid, SSRIs, SNRIs, lithium and St. John's Wort (*Hypericum perforatum)* preparations) may lead to an incidence of serotonin associated effects. Priligy 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 Priligy has been discontinued (see section 4.3).

CNS active medicinal products

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

Pharmacokinetic interactions

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

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

CYP3A4 inhibitors

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

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

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

Moderate CYP3A4 inhibitors. Concomitant treatment with moderate CYP3A4 inhibitors (e.g., erythromycin, clarithromycin, fluconazole, amprenavir, fosamprenavir, aprepitant, verapamil, diltiazem) may also give rise to significantly increased exposure of dapoxetine and desmethyldapoxetine, especially in CYP2D6 poor metabolizers. The maximum dose of dapoxetine should be 30 mg if dapoxetine is combined with any of these drugs (see sections 4.2, 4.4 and below).

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

Potent CYP2D6 inhibitors

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

PDE5 inhibitors

Priligy 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 Priligy with PDE5 inhibitors may result in orthostatic hypotension (see section 4.4). The efficacy and safety of Priligy in patients with

both premature ejaculation and erectile dysfunction concomitantly treated with Priligy 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, Priligy should be prescribed with caution in patients who use alpha adrenergic receptor antagonists due to possible reduced orthostatic tolerance (see section 4.4).

Medicinal products metabolized by CYP2D6

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

Medicinal products metabolized by CYP3A4

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

Medicinal products metabolized by CYP2C19

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

Medicinal products metabolized by CYP2C9

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

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

There are no data evaluating the effect of chronic use of warfarin with dapoxetine; therefore, caution is advised when dapoxetine is used in patients taking warfarin chronically (see section 4.4). In a pharmacokinetic study, dapoxetine (60 mg/day for 6 days) did not affect the pharmacokinetics or pharmacodynamics (PT or INR) of warfarin following a single 25 mg dose.

There have been reports of bleeding abnormalities with SSRIs (see section 4.4).

Ethanol

Coadministration of a single dose of ethanol, 0.5 g/kg (approximately 2 drinks), did not affect the pharmacokinetics of dapoxetine (60 mg single dose); however, dapoxetine in combination with ethanol increased somnolence and significantly decreased self–rated alertness. Pharmacodynamic measures of cognitive impairment (Digit Vigilance Speed, Digit Symbol Substitution Test) also showed an additive effect when dapoxetine was 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 Priligy (see sections 4.4 and 4.7).

4.5 Interaction with other medicinal products and other forms of interaction

Priligy 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 Priligy (see sections 4.4 and 4.5).

4.6 Fertility, Pregnancy and lactation

Priligy is not indicated for use by women.

Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy or embryonal/foetal development (see section 5.3).

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

4.7 Effects on ability to drive and use machines

Priligy 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 Priligy (see sections 4.4 and 4.5).

4.8 Undesirable effects

Summary of the safety profile

Syncope and orthostatic hypotension have been reported in clinical trials (see section 4.4).

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 Priligy–treated subjects) and dizziness (1.2% of Priligy–treated subjects).

Tabulated list of adverse reactions

The safety of Priligy was evaluated in 4224 subjects with premature ejaculation who participated in five double–blind, placebo–controlled clinical trials. Of the 4224 subjects, 1616 received Priligy 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 (≥ 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	

Table 1: Frequency of Adverse Reactions (MedDRA)

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		Erectile dysfunction	Ejaculation failure, Male	

Table 1: Frequency of Adverse Reactions (MedDRA)

breast disorders			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 (see section 4.4).

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 Priligy 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 (see sections 4.2, 4.4, 4.5 and 5.2).

Withdrawal effects

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

Results of a safety study showed a slightly higher incidence of withdrawal symptoms of mild or moderate insomnia and dizziness in subjects switched to placebo after 62 days of daily dosing.

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

4.9 Overdose

No case of overdose has been reported.

There were no unexpected adverse events in a clinical pharmacology study of Priligy 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 Priligy 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} < 1.0nM) and didesmethyldapoxetine (IC_{50} = 2.0 nM) are equivalent or less potent (dapoxetine-N-oxide (IC_{50} = 282nM)).

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 Priligy 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 Priligy 30 mg as needed, and 389 to Priligy 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**	**Priligy 30 mg**	**Priligy 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 (mins)	**Placebo %**	**Priligy 30 mg %**	**Priligy 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 a 1−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]) groups compared 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 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 desmethyldapoxetine (DED) increase by approximately 50% when compared to single dose AUC values.

Ingestion of a high fat meal modestly reduced the C_{max} (by 10%) and modestly increased the AUC (by 12%) of dapoxetine and slightly delayed the time for dapoxetine to reach peak concentrations. These changes are not clinically significant. Priligy 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 ^{14}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 (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 Priligy, 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 (see section 4.2).

Renal impairment

A single-dose clinical pharmacology study using a 60 mg dapoxetine dose was conducted in subjects with mild (CrCL 50 to 80 mL/min), moderate (CrCL 30 to < 50 mL/min), and severe renal impairment (CrCL < 30 mL/min) and in subjects with normal renal function (CrCL > 80 mL/min). No clear trend for an increase in dapoxetine AUC with decreasing renal function was observed. AUC in subjects with severe renal impairment was approximately 2-fold that of subjects with normal renal function, although there are limited data in patients with severe renal impairment. Dapoxetine pharmacokinetics have not been evaluated in patients requiring renal dialysis (see sections 4.2 and 4.4).

Hepatic impairment

In patients with mild hepatic impairment, unbound 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%, repectively. 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 (see sections 4.2 and 4.3).

CYP2D6 Polymorphism

In a single dose clinical pharmacology study using 60 mg dapoxetine, plasma concentrations in poor metabolizers of CYP2D6 were higher than in extensive metabolizers of CYP2D6 (approximately 31% higher for 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 Priligy 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 Priligy in poor metabolizers of CYP2D6 is of particular concern with concomitant administration of other medicinal products that may inhibit the metabolism of dapoxetine such as moderate and potent CYP3A4 inhibitors (see sections 4.2 and 4.3).

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 monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Tablet coating:

Lactose monohydrate
Hypromellose
Titanium dioxide (E171)
Triacetin
Iron Oxide Black (E172)
Iron Oxide Yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions and is not sensitive to light or moisture.

6.5 Nature and contents of container

Child-resistant PVC–PE–PVDC/Alu blister in packages of 1, 2, 3 and 6 film–coated tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Phoenix Labs Unlimited Company,
Suite 12, Bunkilla Plaza,
Bracetown Business Park,
Clonee,
Co. Meath,
Ireland.

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