1. NAME OF THE MEDICINAL PRODUCT

Priligy 30 mg film–coated tablets
Priligy 60 mg film–coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film–coated tablet contains dapoxetine hydrochloride equivalent to 30 mg or 60 mg dapoxetine.

Excipient with known effect: Lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film–coated tablet.
The 30 mg film–coated tablets are light grey, round, convex and debossed with "30" inside a triangle on one side.
The 60 mg film–coated tablets are grey, round, convex and debossed with "60" inside a triangle on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

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

The following conditions were fulfilled in the clinical studies of PE:
- 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.

4.2 Posology and 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. 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 4.4).

Adult men (aged 18 to 64 years)

Before treatment is initiated, the physician should obtain a careful medical history focusing on past orthostatic events and also perform an orthostatic test (blood pressure and pulse rate, supine and standing). If the patient discloses a history suggestive of orthostatic reactions or an orthostatic test shows this kind of reaction, treatment with Priligy should be avoided.

The recommended starting dose for all patients is 30 mg, taken as needed approximately 1 to 3 hours prior to sexual activity. The maximum recommended dosing frequency is once every 24 hours. If the

effect of 30 mg is insufficient and the side effects are acceptable, the dose may be increased to the maximum recommended dose of 60 mg.

If the patient experienced orthostatic reactions on the starting dose, no dose escalation to 60 mg should be performed.

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

The physician who elects to use Priligy for the treatment of premature ejaculation should evaluate the risks and patient–reported benefits of the medicinal product after the first four weeks of treatment or after 6 doses to assess the patient risk–benefit balance and to determine whether continuing treatment with Priligy is appropriate.

Elderly (age 65 years and over)

Safety and efficacy of Priligy have not been established in patients age 65 years and over as limited data are available in this population (see section 5.2).

Children and adolescents

Priligy should not be used in individuals below 18 years of age.

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 is 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).

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 (second– or third–degree AV block or sick sinus syndrome) not treated with a permanent pacemaker
- Significant ischemic heart disease
- Significant valvular disease.

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. Safety has not been established and there are no data on the ejaculation–delaying effects in men without Premature Ejaculation.

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

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).

Syncope

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.

Possibly prodromal symptoms such as nausea, dizziness/lightheadedness, and diaphoresis were reported more frequently among patients treated with Priligy compared to placebo. In patients receiving 30 mg Priligy in Phase 3 clinical trials, nausea was reported in 11.0%, dizziness in 5.8% and hyperhidrosis/diaphoresis in 0.8%. In patients receiving 60 mg Priligy in Phase 3 clinical trials, nausea was reported in 21.2%, dizziness in 11.7% and hyperhidrosis/diaphoresis in 1.5%. In addition, 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.

Cases of syncope characterized as loss of consciousness observed in the clinical trials 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).

Combining alcohol with dapoxetine may 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.

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.

Orthostatic hypotension

An orthostatic test should be performed before initiating therapy. In case of a history of documented or suspected orthostatic reaction, treatment with Priligy should be avoided (see section 4.2).

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. In addition, Priligy should be prescribed with caution in patients taking medicinal products with vasodilatation properties (such as alpha adrenergic receptor antagonists, nitrates, PDE5 inhibitors) 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).

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.

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.

Co−morbid depression and 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 no evidence of withdrawal syndrome and little evidence of withdrawal symptoms with only a slightly higher incidence of mild or moderate insomnia and dizziness in subjects switched to placebo after daily dosing (see section 5.1). Consistent results were seen in a second double−blind clinical trial with a 24−week treatment phase of 30 and 60 mg doses as needed followed by a 1−week withdrawal assessment period.

Eye disorders

As with other SSRIs, 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, the 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 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

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. However, Priligy should be prescribed with caution in patients who use PDE5 inhibitors due to possible reduced orthostatic tolerance (see section 4.4).

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

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.

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).

4.6 Pregnancy and lactation

Priligy is not indicated for use by women.

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

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

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.

Syncope characterized as loss of consciousness 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 clinic setting (such as blood draw and orthostatic maneuvers and blood pressure measurements). Prodromal symptoms often preceded the syncope (see section 4.4).

Orthostatic hypotension has been reported in clinical trials (see section 4.4).

The most common adverse drug reactions reported during clinical trials were headache, dizziness, nausea, diarrhoea, insomnia and fatigue. The most common adverse events leading to discontinuation were nausea (2.2% of Priligy−treated subjects) and dizziness (1.2% of Priligy−treated subjects).

Table 1 presents the adverse reactions that have been reported.

Table 1: Frequency of Adverse Reactions

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, Nervousness, Nightmare, Sleep disorder, Bruxism, Euphoric mood, Indifference, Apathy, Mood altered, Initial insomnia, Middle insomnia, Anorgasmia, Confusional state, Hypervigilance, Thinking abnormal, Disorientation, Loss of libido	
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, 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 long–term open–label extension trial were consistent with those reported in the double–blind studies and no additional adverse drug reactions were reported.

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

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.

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). In the rat, dapoxetine inhibits the ejaculatory expulsion reflex by acting at a supraspinal level within the lateral paragigantocellular nucleus (LPGi) as a necessary brain structure for the effect. 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, causing an increase in pudendal motoneuron reflex discharge (PMRD) latency and a reduction in PMRD duration.

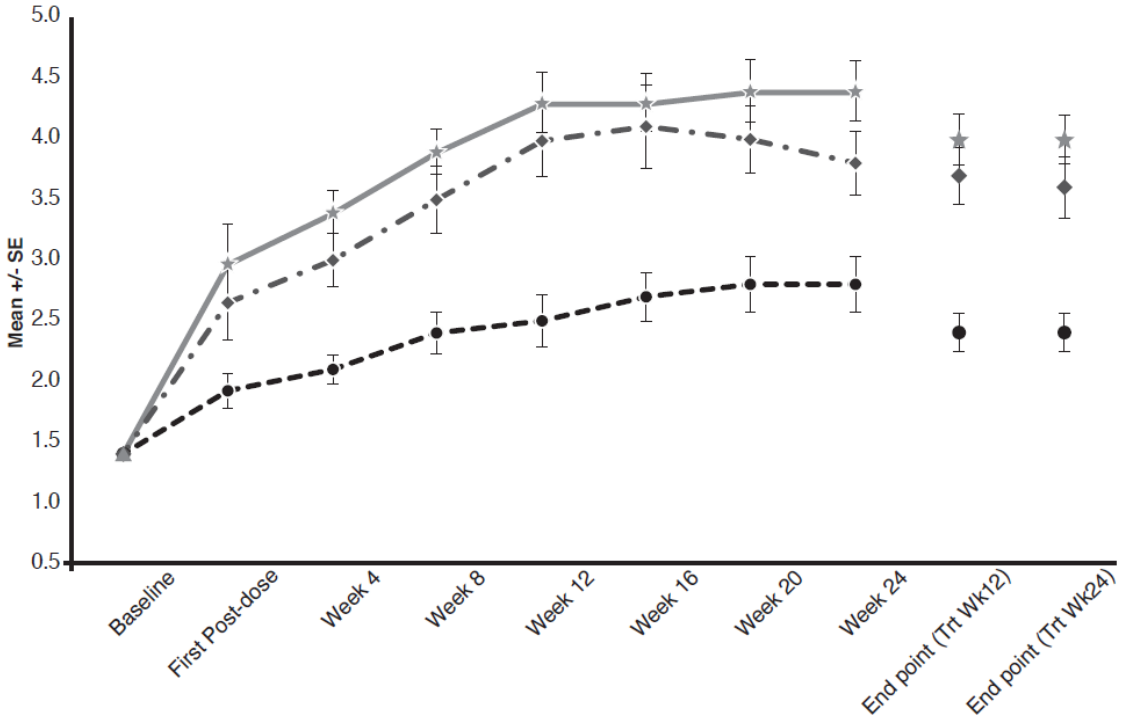
Clinical trials

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 enrollment. In four of the studies, subjects had an intravaginal ejaculatory latency time (IELT; time from vaginal penetration to the moment of intravaginal ejaculation) of $\leq$ 2 minutes in a minimum of 75% of evaluable sexual intercourse events during the baseline period. In the fifth study, subjects had the same entry criteria; however, IELT was not measured using a stopwatch. 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. In four studies, the primary endpoint of average IELT was measured using a stopwatch during each episode of sexual intercourse.

Results of all randomized studies were consistent. In a representative study with the longest treatment duration (24 weeks), 1162 subjects were randomized, 385 to placebo, 388 to Priligy 30 mg as needed, and 389 to Priligy 60 mg as needed. The mean IELT at baseline and study endpoint for all treatment

groups is shown in Figure 1. Increases in mean average IELT at the week 24 endpoint were statistically significant ($p<0.001$) in both Priligy groups versus placebo. The magnitude of IELT prolongation was related to baseline IELT and was variable between individual subjects. The clinical relevance of Priligy treatment effects are described below in terms of patient reported response rates.

Figure 1: Mean (+/- SE) in Average IELT (min) over Time-Study R096769-PRE-3001



	Sample size (N) for each visit in Figure 1									
	Baseline	First Post-dose	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Endpoint Wk 12	Endpoint Wk 24
Placebo	382	339	332	280	238	221	195	182	339	339
DPX 30 mg PRN	385	363	356	303	264	240	221	218	363	363
DPX 60 mg PRN	387	355	347	287	249	229	214	198	355	355

Treatment Group:
---○ PLACEBO ---◇ DPX 30 MG PRN ---☆ DPX 60 MG PRN
End Point (TRT WK 12) = LPOCF to Week 12. End Point (TRT WK 24) = LPOCF to Week 24

LPOCF is last post–baseline observation carried forward.

In addition to the primary endpoint of average IELT, meaningful treatment benefit to the patient in the above study was demonstrated using a definition of treatment response consisting of a composite of 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 beginning at Week 4 and up to and including Week 24 ($p=0.003$ for dapoxetine 30 mg versus placebo at Week 16, all other comparisons $p\leq0.001$). Significant decrease in subject distress and significant improvement in subject satisfaction with sexual intercourse were also observed. Improvements at weeks 12 and 24 for the key secondary endpoints are presented in Table 2.

Table 2: Percentage of Subjects with Improvement in Key Secondary Endpoints Study R096769-PRE-3001

Key Secondary Endpoint (at LPOCF)*	Placebo %	Priligy 30 mg %	Priligy 60 mg %
Treatment Response Composite (change ≥ 2 in control and ≤ -1 in distress)	(n=346)	(n=359)	(n=353)
Week 12	12.1	27.3*	34.0*
Week 24	13.0	25.3*	37.1*
Change ≤ -1 in Distress	(n=347)	(n=360)	(n=353)
Week 12	46.1	63.1*	65.4*
Week 24	47.8	60.0*	68.6*
Change ≥ 1 in Satisfaction	(n=347)	(n=359)	(n=353)
Week 12	31.7	51.3*	56.1*
Week 24	35.7	48.5*	55.8*

* p-value <0.001 for Priligy versus placebo; LPOCF is last post−baseline observation carried forward

Table 3 provides the distribution of response outcome 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.

Table 3: CGIC Summary at Week 24 (LPOCF)*; Study R096769-PRE-3001

CGIC Response Outcome	Placebo n (%)	Priligy 30 mg n (%)**	Priligy 60 mg n (%)**
No Change or Worse***	236 (68.0%)	152 (42.3%)	97 (27.6%)
Slightly Better	57 (16.4%)	97 (27.0%)+	117 (33.2%)+
Better	41 (11.8%)	74 (20.6%)	96 (27.3%)
Much Better	13 (3.7%)	36 (10.0%)	42 (11.9%)
Total	347 (100%)	359 (100%)	352 (100%)

*LPOCF is last post−baseline observation carried forward

**Two−sided p-value < 0.001 for both Priligy 30 mg versus placebo and Priligy 60 mg versus placebo (using the van Elteren test controlling the baseline IELT stratum and pooled center that showed the distributions of CGIC in Priligy groups were statistically significantly better than the placebo group)

***No Change or Worse includes No Change, Slightly Worse, Worse or Much Worse

+At least Slightly Better CGIC response rate: Placebo (32%), Priligy 30 mg (57.7%) and Priligy 60 mg (72.4%) with p-value < 0.0001 for Priligy 30 mg versus placebo and Priligy 60 mg versus placebo

The withdrawal effects of chronic daily and as needed dosing with 60 mg Priligy in the treatment of premature ejaculation were evaluated in a placebo−controlled, double−blind, parallel−group study in which 1238 subjects were randomized. Subjects received placebo or 60 mg Priligy either once daily or as needed for 62 days followed by a withdrawal assessment period of 7 days of additional Priligy treatment or placebo. Withdrawal effects after abrupt cessation of therapy were measured using the Discontinuation Emergent Signs and Symptoms (DESS), a clinician−rated instrument that queries for symptoms and signs associated with the discontinuation of serotonin reuptake inhibitor treatment. For each subject, discontinuation syndrome was defined as an increase in the weekly DESS score by at least 4 points from Day 63 to Day 70. In this study, there was no clear evidence of discontinuation (withdrawal) syndrome upon abrupt discontinuation of Priligy therapy. Consistent with the lack of discontinuation syndrome based on DESS, adverse event data showed little evidence of withdrawal symptoms. Similar results were seen in a second double−blind clinical trial with a 24−week treatment phase of 30 and 60 mg doses as needed followed by a 1−week withdrawal assessment period.

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%).

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 appears to have a rapid distribution with a mean steady state volume of distribution of 162 L. Following intravenous administration in humans, mean estimated initial, intermediate, and terminal half–life values for dapoxetine were 0.10, 2.19, and 19.3 hours respectively.

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 in a clinical study designed to explore the metabolism 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 species in the plasma. *In vitro* studies show that dapoxetine–N–oxide was inactive in a battery of *in vitro* binding and transporter studies. Additional metabolites include desmethyldapoxetine and didesmethyldapoxetine, which account for less than 3% of the circulating medicinal product–related material. *In vitro* binding studies indicate that DED is equipotent to dapoxetine and didesmethyldapoxetine has approximately 50% of the potency of dapoxetine. The unbound exposure of DED is approximately 1/2 of the free exposure of dapoxetine. The unbound C_{max} of DED is estimated to be 20–25% of dapoxetine C_{max} in the absence of intrinsic or extrinsic factors that may change exposure levels.

Elimination

The metabolites of dapoxetine were primarily eliminated in the urine as conjugates. Unchanged active substance was not detected in the urine. Dapoxetine has a rapid elimination, as evidenced by a low concentration (less than 5% of peak) 24 hours after dosing. There was minimal accumulation of dapoxetine following daily dosing. The terminal half–life is approximately 19 hours following oral administration. The half-life of DED is similar to that of dapoxetine.

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.

Renal impairment

In a single dose clinical pharmacology study using 60 mg dapoxetine, no correlation was noted between creatinine clearance and dapoxetine C_{max} or AUC_{inf} in subjects with mild (creatinine clearance 50 to 80 mL/min), moderate (creatinine clearance 30 to < 50 mL/min), and severe (creatinine clearance < 30 mL/min) renal impairment. Dapoxetine pharmacokinetics have not been evaluated in patients requiring renal dialysis. There are limited data in patients with severe renal impairment (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%, 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 (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).

Plasma concentrations of dapoxetine and DED in CYP2D6 ultrarapid metabolizers are expected to be decreased.

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

The expiry date is stated on the packaging.

6.4 Special precautions for storage

Do not store above 30 degrees Celsius

6.5 Nature and contents of container

PVC–PE–PVDC/Alu blister in packages of 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. PRODUCT LICENCE HOLDER

A. Menarini Singapore Pte. Ltd.
30 Pasir Panjang Road
#08-32 Mapletree Business City
Singapore 117440

8. DATE OF REVISION OF THE TEXT

April 2022