Professional Information for PRILIGY®

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

PRILIGY® 30 mg film-coated tablets

PRILIGY® 60 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 30 mg film-coated tablet contains 30 mg of dapoxetine base (as hydrochloride).

Each 60 mg film-coated tablet contains 60 mg of dapoxetine base (as hydrochloride).

Excipient with known effect:

Contains sugar:

PRILIGY 30 contains 46 mg lactose monohydrate.

PRILIGY 60 contains 92 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

The 30 mg film-coated tablets are light grey, round and debossed with “30” inside a triangle on one side.

The 60 mg film-coated tablets are grey, round and debossed with “60” inside a triangle on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRILIGY is indicated for the treatment of premature ejaculation (PE) in men 18 to 64 years of age, who have **all** of the following:

- 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 period of 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 (18 to 64 years of age)

The recommended starting dose is 30 mg, (on demand use) approximately 1 to 3 hours prior to sexual activity. **PRILIGY must not be taken more frequently than once every 24 hours.** PRILIGY must not be taken more frequently than once every 24 hours. 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.

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 prescriber 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.

Special populations

Elderly (age 65 years and over)

Safety and efficacy of PRILIGY have not been established in patients aged 65 years and over as limited data are available in this population.

Children and adolescents

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

Patients with renal impairment

No dose adjustment is required 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 metabolisers 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 metaboliser genotype or in patients concomitantly treated with potent CYP2D6 inhibitors (see sections 4.4 and 4.5).

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).

Method of administration

For oral use.

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

Precautions to be taken before handling or administering PRILIGY

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

4.3 Contraindications

PRILIGY is contraindicated:

- In patients with known hypersensitivity to dapoxetine hydrochloride or to any of the excipients (see section 6.1).
- In significant pathological conditions such as:
  - heart failure (NYHA class II-IV)
  - conduction abnormalities such as AV block or sick sinus syndrome
  - significant ischaemic heart disease

- significant mono or multiple valvular disease
- a history of syncope
- carotid artery stenosis.

- In patients with a history of mania or severe depression.
- For 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).
- For 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).
- PRILIGY is contraindicated in patients experiencing uncontrolled epilepsy.
- PRILIGY is contraindicated in children under the age of 18 years (see section 4.4).
- In concomitant treatment with serotonin reuptake inhibitors [selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine/noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs)] or other medicines 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 medicines. Similarly, these medicines 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, nefazodone, nelfinavir, atazanavir, grapefruit juice, 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 under INDICATIONS. 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 healthcare professionals. PRILIGY should not be used in men with erectile dysfunction (ED) who are using phosphodiesterase-5 (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 healthcare professional. 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 light-headedness soon after standing, he should immediately lie down so his head is lower than the rest of his body or sit down with his head between his knees until the symptoms pass. The prescriber should also inform the patient not to rise quickly after prolonged lying or sitting.

Syncope

Patients should be cautioned to avoid situations where injury could result, including driving or operating hazardous machinery, should syncope or its prodromal symptoms such as dizziness or light-headedness occur (see section 4.8).

Possible prodromal symptoms such as nausea, dizziness/light-headedness, and diaphoresis were reported more frequently among patients treated with PRILIGY compared to placebo.

The frequency of syncope in the PRILIGY clinical development program varied from 0,06 % (30 mg) to 0,23 % (60 mg) for subjects enrolled in the Phase 3 placebo-controlled clinical trials to 0,64 % for Phase 1 non-PE healthy volunteer studies.

Cases of syncope observed in the clinical trials were considered vasovagal in etiology and the majority occurred during the first 3 hours after dosing. Prodromal symptoms, such as nausea, dizziness, light-headedness, palpitations, asthenia, confusion and diaphoresis 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 recognise 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 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.

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.

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, dysrhythmia, hyperthermia, and serotonin syndrome. Use of PRILIGY with recreational drugs with sedative properties such as narcotics and benzodiazepines may further increase somnolence and dizziness.

Medicines with vasodilatation properties

PRILIGY should be prescribed with caution in patients taking medicines 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 section 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 metaboliser genotype, as this may increase exposure levels, which may result in a higher incidence and severity of dose dependent adverse events (see section 4.5).

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.

Use in children and adolescents under 18 years of age

PRILIGY should not be used in individuals below 18 years of age. Safety and efficacy in children under 18 years of age have not been established. In clinical trials in Major Depressive Disorder, treated with other SSRIs, there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm (see section 4.8).

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 should not be used in men with psychiatric 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 the underlying psychiatric disorder or might be a result of treatment with PRILIGY. Doctors should encourage patients to report any distressing thoughts or feelings at any time and if 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 medicines known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants [TCAs], aspirin, 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 to moderate renal impairment (see sections 4.2 and 4.5).

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.
However, 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 reported in subjects switched to placebo after daily dosing. 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.

Alcohol (ethanol)

Patients should be advised not to use PRILIGY in combination with alcohol.
Combining alcohol with PRILIGY 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 section 4.5).

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 PRILIGY.

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

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

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 medicines 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 dysrhythmias. Medicines 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).

CNS active medicines

The use of PRILIGY in combination with CNS active medicines has not been systematically evaluated in patients with premature ejaculation. Consequently, caution is advised if the concomitant administration of PRILIGY and such medicines is required.

Medicines or herbal products with serotonergic effects

Co-administration with serotonergic medicines (including MAOIs, L-tryptophan, triptans, tramadol, linezolid, SSRIs, lithium and St. John's wort (*Hypericum perforatum*) preparations) may lead to an increased incidence of serotonin associated effects. PRILIGY should not be used concomitantly with other SSRIs or MAOIs and caution is advised and a closer clinical monitoring is required when other serotonergic medicines are used concomitantly with PRILIGY (see sections 4.3 and 4.4).

Pharmacokinetic interactions

Effects of co-administered medicines on dapoxetine hydrochloride

In vitro studies in human liver, kidney, and intestinal microsomes indicate dapoxetine is

metabolised primarily by CYP2D6, CYP3A4 and flavin monooxygenase 1 (FMO1). Therefore, inhibitors of these enzymes may reduce dapoxetine clearance.

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). Therefore, concomitant use of PRILIGY and potent CYP2D6 inhibitors may increase blood concentrations of dapoxetine. This is not expected to result in clinically significant interactions.

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.

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 metabolisers. The maximum dose of dapoxetine should be 30 mg if dapoxetine is combined with any of these medicines (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 metaboliser by geno– or phenotyping. In patients verified to be CYP2D6 extensive metabolisers, 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 metabolisers 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. 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 medicines

Tamsulosin

In a clinical pharmacology study of patients receiving daily doses of tamsulosin with multiple doses

of dapoxetine 30 mg or 60 mg, dapoxetine pharmacokinetics were comparable to those noted in previous studies in healthy subjects, indicating that tamsulosin does not affect dapoxetine pharmacokinetics.

The pharmacokinetics of tamsulosin were similar in the dapoxetine 30 and 60 mg groups and similar on Days 1 and 7, indicating that dapoxetine did not affect 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 dapoxetine 30 or 60 mg 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).

Medicines metabolised 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 approximately 11 % and 19 %, respectively, compared to desipramine administered alone. These differences are not likely to be clinically important. Dapoxetine is unlikely to affect the pharmacokinetics of other CYP2D6 substrates.

Medicines metabolised by CYP3A4

Multiple dosing of dapoxetine (60 mg/day for 6 days) did not inhibit the metabolism of midazolam (8 mg single dose). Therefore, dapoxetine is unlikely to affect the pharmacokinetics of other CYP3A4 substrates.

Medicines metabolised by CYP2C19

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

Medicines metabolised 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.

PDE5 inhibitors

In a single-dose crossover study, dapoxetine (60 mg) did not affect the pharmacokinetics of tadalafil (20 mg) or sildenafil (100 mg).

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

There are no data evaluating the effect of chronic use of warfarin with PRILIGY; therefore, caution is advised when PRILIGY 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).

Alcohol (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). Similarly, dapoxetine coadministration did not affect ethanol pharmacokinetics. PRILIGY in combination with ethanol increased somnolence and significantly decreased self-rated alertness. Pharmacodynamic measures of cognitive impairment also showed an additive effect when PRILIGY was co-administered with ethanol. Concomitant use of alcohol and PRILIGY 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.

4.6 Fertility, pregnancy and lactation

PRILIGY is not indicated for use by women.

Observational data on a limited number of partner's pregnancies during clinical trials indicate no adverse effects of PRILIGY on pregnancy or on the health of the fetus/new-born child. 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 may influence the ability to drive and use machines. Dizziness, disturbance in attention, syncope, blurred vision and somnolence have been reported in subjects receiving PRILIGY in clinical trials. Therefore, patients should be warned to avoid situations where injury could result, including driving or operating hazardous machinery, should syncope or other CNS effects occur.

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 section 4.4).

4.8 Undesirable effects

Summary of 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).

In children treated with other SSRIs, hostility, suicidal ideation and self-harm have been reported.

Tabulated list of adverse reactions

The safety of PRILIGY was evaluated in 4 224 subjects with premature ejaculation who participated in five double-blind, placebo-controlled clinical trials. Of the 4 224 subjects, 1 616 received PRILIGY 30 mg as needed and 2 608 received 60 mg, either as needed or once daily.

Table 1 presents the adverse drug reactions that have been reported.

Frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100).

Table 1: Adverse drug reactions

System organ class	Very common	Common	Uncommon	Rare
Psychiatric disorders		Insomnia Anxiety Nervousness Libido decreased Depression Apathy Abnormal dreams	Euphoric mood Mood altered Confusional state Sleep disorder Bruxism Disorientation Hypervigilance Abnormal thinking Depressed mood Indifference Initial insomnia Middle insomnia Nightmare Loss of libido Anorgasmia	
Nervous system	Dizziness	Somnolence	Depressed level of	Exertional

disorders	Headache	Tremor Disturbance in attention Paraesthesia	consciousness Dysgeusia Lethargy Syncope Akathisia Syncope vasovagal Dizziness postural Hypersomnia Sedation	dizziness Sudden onset of sleep
Eye disorders		Blurred vision	Mydriasis Eye pain Visual disturbance	
Ear and labyrinth disorders		Tinnitus	Vertigo	
Cardiac disorders			Tachycardia Sinus bradycardia Sinus arrest	
Vascular disorders		Flushing	Hypotension Systolic hypertension Hot flush	
Respiratory, thoracic and mediastinal disorders		Sinus congestion Yawning		
Gastrointestinal disorders	Nausea	Diarrhoea Abdominal pain Dry mouth	Abdominal discomfort Epigastric	Defaecation urgency

		Vomiting Dyspepsia Flatulence Constipation Abdominal distension Abdominal pain upper Stomach discomfort	discomfort	
Skin and subcutaneous tissue disorders		Hyperhidrosis	Pruritus Cold sweat	
Reproductive system and breast disorders		Erectile dysfunction	Ejaculation failure Male orgasmic disorder Paraesthesia of male genitals	
General disorders and administration site conditions		Fatigue Irritability	Asthenia Feeling abnormal Feeling hot Feeling jittery Feeling drunk	
Investigations		Increased blood pressure	Increased heart rate Increased diastolic blood pressure Increased orthostatic	

			blood pressure	

Adverse drug reactions reported in the Phase 2 clinical trials and 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.

Description of selected adverse reactions

Syncope characterised as loss of consciousness has been reported in clinical trials and is considered PRILIGY-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 manoeuvres 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 characterised 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 metaboliser genotype (see sections 4.2, 4.4, and 4.5).

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. paraesthesia 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 PRILIGY is important. It allows continued monitoring of the benefit/risk balance of PRILIGY. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

No case of overdose has been reported.

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, haemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for PRILIGY are known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 18.10 Medicines acting on the genito-urinary system. Others.

Pharmacotherapeutic group: Other urologicals.

ATC code: G04BX14.

Mechanism of action

Dapoxetine is a potent selective serotonin neuronal reuptake inhibitor (SSRI) with an IC_{50} of 1,12 nM and subsequently, potentiates the neurotransmitter's action at pre- and postsynaptic receptors.

Dapoxetine major human metabolites, desmethyldapoxetine (IC_{50} < 1,0 nM) and didesmethyldapoxetine (IC_{50} = 2,0 nM) are equivalent or less potent (dapoxetine-N-oxide (IC_{50} = 282 nM)).

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 6 081 subjects were randomized. Subjects were 18 years of age or older with a history of PE in most 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.

Results of all randomised studies were consistent. Efficacy was demonstrated after 12 weeks of

treatment. One study had a treatment duration of 24 weeks. In the study, 1 162 subjects were randomised, 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 in Table 2 below and the cumulative distribution of subjects who achieved at least a specific level in Average IELT at study end are in Table 3 below. Other studies and pooled analysis of the data at Week 12 gave consistent results.

Table 2: Least squares mean and medical 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*

Average IELT	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 an absolute bioavailability of 42 %.

Following single oral doses of 30 mg and 60 mg in the fasted state, peak plasma concentrations of dapoxetine were 297 ng/mL after 1,01 hours, and 498 ng/mL after 1,27 hours, respectively. Ingestion of a high fat meal modestly reduced peak concentrations of dapoxetine and slightly delayed the time for dapoxetine to reach peak concentrations; however, the extent of absorption was not affected by consumption of a high fat meal. These changes are not clinically significant. PRILIGY can be taken with or without food.

Distribution

Greater 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 14C-dapoxetine, dapoxetine was extensively metabolised 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, suggesting that this metabolite does not contribute significantly to the actions of dapoxetine. In a single dose clinical pharmacology study using 60 mg PRILIGY, plasma levels in poor metabolisers of CYP2D6 were higher than in extensive metabolisers (approximately 31 % higher for C_{max} and 36 % higher for AUC_{inf}). In the two multidose Phase 3 studies, where the CYP2D6 metaboliser status was identified, a total of 120 poor metabolisers and 1 598 extensive metabolisers were enrolled and

treated with PRILIGY. No overall differences were seen in efficacy or safety between poor and extensive metabolisers.

Additionally, no differences were observed in the pharmacokinetics of patients with premature ejaculation compared with healthy volunteers.

Elimination

Dapoxetine was primarily eliminated in the urine, mainly as conjugated metabolites; unchanged active substance was not detected in the urine. Following oral administration, dapoxetine has an initial half-life of approximately 1,5 hours, with plasma levels less than 5 % of peak concentrations by24 hours after dosing. There was minimal accumulation of dapoxetine following daily dosing. Dapoxetine terminal half-life was 19,3 hours. The terminal half-life of DED was approximately 19 hours.

Pharmacokinetics in special populations

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. In all of these subjects, only a small fraction (<1 %) of dapoxetine was recovered in the urine intact over 3-4 days. No dose adjustment is necessary in patients with mild or moderately impaired renal function. Dapoxetine pharmacokinetics have not been evaluated in patients requiring renal dialysis. There are limited data in patients with severe renal impairment. Patients with severe renal impairment may have the potential for poor tolerance or greater variability in exposure; therefore, use of PRILIGY in patients with severe renal impairment is not recommended.

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).

5.3 Preclinical safety

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 $AUC_{0\text{-}24\ hr}$) 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 tumours 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

Colloidal anhydrous silica

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose.

Tablet coating

Hypromellose

Lactose monohydrate

Titanium dioxide (E171)

Triacetin

Black iron oxide (E172)

Yellow iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Keep blister strips in the outer carton until required for use.

6.5 Nature and contents of container

PVC-PE-PVDC/Alu opaque blister strips of 1, 2, 3, 6, and 18 film-coated tablets. The blisters are packed into an outer container. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor

10 Church Street

Durbanville 7551

Tel. no.: 087 551 3245

8. REGISTRATION NUMBERS

PRILIGY® 30 mg: 43/18.10/0692

PRILIGY® 60 mg: 43/18.10/0693

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 November 2015

10. DATE OF REVISION OF THE TEXT

15 August 2025