COVER OUTSIDE - FRONT

BOOKLET IS GLUED ON TOP

Priligy® 30 mg
Priligy® 60 mg

dapoxetine

COVER INSIDE - FRONT

COVER INSIDE - BACK

COVER OUTSIDE - BACK

PRODUCT NAME

PRILIGY® (dapoxetine hydrochloride) film-coated tablet.

DOSAGE FORMS AND STRENGTHS

30 mg: Round, convex, light grey film-coated tablet debossed with “30” inside a triangle on one side, containing 30 mg of dapoxetine base (as a hydrochloride salt).

60 mg: Round, convex, grey film-coated tablet debossed with “60” inside a triangle on one side, containing 60 mg of dapoxetine base (as a hydrochloride salt).

The chemical name is (+)-(S)-N, N-dimethyl-(α)-[2-(1-naphthalenyloxy) ethyl]- benzenemethanamine hydrochloride.

For excipients, see Pharmaceutical Information - List of Excipients.

CLINICAL INFORMATION

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:

- 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.

Dosage and Administration

For oral use. Tablets should be swallowed whole. 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 should syncope or its prodromal symptoms such as dizziness or lightheadedness occur (see Clinical Information - Warnings and Precautions and Effects on Ability to Drive and Use Machines).

Adult men (18 to 64 years of age)

The recommended starting dose for all patients is 30 mg, taken as needed approximately 1 to 3 hours prior to sexual activity. 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. The maximum recommended

dosing frequency is once every 24 hours.
PRILIGY® may be taken with or without food (see Pharmacological Properties - Pharmacokinetic Properties).
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 Pharmacological Properties - Pharmacokinetic Properties).

Children and Adolescents

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

Patients with Renal Impairment

No dose adjustment is required but caution is advised in patients with mild or moderate renal impairment. PRILIGY® is not recommended for use in patients with severe renal impairment (see Pharmacological Properties - Pharmacokinetic Properties).

Patients with Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment. PRILIGY® is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh class B and C) (see Clinical Information - Contraindications and Pharmacological Properties - Pharmacokinetic

Properties).

Known CYP2D6 poor metabolizers or use with potent CYP2D6 inhibitors

Caution is advised if increasing the dose to 60 mg in a patient known to be a CYP2D6 poor metabolizer or if increasing the dose to 60 mg in a patient concomitantly treated with potent CYP2D6 inhibitors (see Clinical Information - Warnings and Precautions and Interactions).

Patients treated with potent or moderate inhibitors of CYP3A4

Concomitant use of potent CYP3A4 inhibitors is contraindicated. The dose is restricted to 30 mg when used concomitantly with moderate CYP3A4 inhibitors (see Clinical Information – Contraindications, Warnings and Precautions, and Interactions).

Contraindications

PRILIGY® is contraindicated in patients with known hypersensitivity to dapoxetine hydrochloride or to any of the excipients.

PRILIGY® is contraindicated in patients with 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 or significant valvular disease].

PRILIGY® is contraindicated 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 Clinical Information - Interactions).

PRILIGY® is contraindicated 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 Clinical Information - Interactions).
PRILIGY® is contraindicated for 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

Clinical Information - Interactions).
PRILIGY® is contraindicated for concomitant treatment with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazodone, nelfinavir, atazanavir, etc. (see Clinical Information - Interactions).
PRILIGY® is contraindicated in patients with moderate and severe hepatic impairment.

Warnings and Precautions

General

PRILIGY® is only indicated in men with PE. Safety has not been established and there are no data on the ejaculation-delaying effects in men without PE.

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 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 Clinical Information - Interactions and Effects on Ability to Drive and Use Machines).

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 subject 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 incidences among patients treated with doses higher than 60 mg, the recommended maximum daily dose.

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 Clinical Information - Effects on Ability to Drive and Use Machines).

Combining alcohol with PRILIGY® may enhance neurocardiogenic adverse events such as syncope, thereby increasing the risk of accidental injury; therefore, patients should be advised to avoid alcohol with 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 disease.

Orthostatic hypotension

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 Clinical Information - Interactions).

Moderate CYP3A4 inhibitors

The dose is restricted to 30 mg when used concomitantly with moderate CYP3A4 inhibitors such as erythromycin, clarithromycin, fluconazole, amprenavir, fosamprenavir, aprepitant, verapamil, and diltiazem, and caution is advised (see Clinical Information – Dosing and Administration and Interactions).

Potent CYP2D6 inhibitors

Caution is advised if increasing the dose to 60 mg in a patient taking potent CYP2D6 inhibitors or if increasing the dose to 60 mg in a patient known to be a CYP2D6 poor metabolizer, as this may increase exposure levels,

which may result in a higher incidence and severity of dose dependent adverse events (see Clinical Information - Dosing and Administration and Interactions).

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.

Use in children and adolescents under age 18

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 Clinical Information - Contraindications). 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.

Hemorrhage

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 Clinical Information - Interactions).

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 Clinical Information - Dosing and Administration and Pharmacological Properties - Pharmacokinetic Properties).

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 (see Pharmacological Properties - Pharmacodynamic Properties). 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.

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 behavioral 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 Clinical Information - Contraindications).

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 Clinical Information - Contraindications).

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 Clinical Information - Contraindications).

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.

Effects of co-administered medicinal products on dapoxetine hydrochloride

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 (the sum of the unbound exposure of dapoxetine and desmethyldapoxetine) may be increased by approximately 25% and the AUC of the active fraction may be doubled if taken with potent CYP3A4 inhibitors. These 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 (see Clinical Information - Contraindications).

Moderate CYP3A4 inhibitors

Concomitant treatment with moderate CYP3A4 inhibitors such as erythromycin, clarithromycin, fluconazole, amprenavir, fosamprenavir, aprepitant, verapamil and diltiazem may also give rise to significantly increased exposure of dapoxetine and desmethyldapoxetine, especially in CYP2D6 poor metabolizers. Therefore, the maximum dose of PRILIGY® is 30 mg if combined with any of these drugs and caution is advised (see Clinical Information - Dosage and Administration and Warnings and Precautions).

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. Therefore, caution is advised if increasing the dose to 60 mg in a patient taking potent CYP2D6 inhibitors or if increasing the dose to 60 mg in a patient known to be a CYP2D6 poor metabolizer (see Clinical Information

- Dosage and Administration and Warnings and Precautions).

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 Clinical Information - Warnings and Precautions).

Effects of dapoxetine hydrochloride on co-administered medicinal products

Tamsulosin

Concomitant administration of single or multiple doses of 30 mg or 60 mg PRILIGY® to patients receiving daily doses of tamsulosin did not result in changes in the pharmacokinetics of tamsulosin. The addition of PRILIGY® 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 PRILIGY® 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 Clinical Information - Warnings and Precautions).

Medicinal products metabolized by CYP2D6
Multiple doses of PRILIGY® (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. 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 CYP3A
Multiple dosing of PRILIGY® (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 PRILIGY® (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.

Medicinal products metabolized by CYP2C9

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

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

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 Clinical Information - Warnings and Precautions). 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) or the pharmacokinetics of ethanol; however, PRILIGY® in combination with ethanol increased somnolence and significantly decreased self-rated alertness. Pharmacodynamic measures of cognitive impairment (Digit Vigilance Speed, Digit Symbol Substitution Test) did not show a significant separation from placebo with either ethanol or PRILIGY® alone but did show a statistically significant effect when PRILIGY® was coadministered with ethanol versus ethanol alone. 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 PRILIGY® 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 Clinical Information - Warnings and Precautions and Effects on Ability to Drive and Use Machines).

Pregnancy, Breast-feeding and Fertility

PRILIGY® is not indicated for use by women.

Use during pregnancy

There is no evidence of teratogenicity, embryotoxicity, or fetotoxicity in rats or rabbits that received up to 100 mg/kg (rats) or 75 mg/kg (rabbits).

There is no evidence to suggest that dapoxetine exposure has an effect on a partner's pregnancy based on limited observational data from the clinical trial database. There are no adequate and well-controlled studies of dapoxetine in pregnant women.

Use during breast-feeding

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

Effects on 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 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 Clinical Information - Warnings and Precautions and Interactions).

Adverse Reactions

Clinical Trial Data

The safety of PRILIGY® was evaluated in 6081 subjects with premature ejaculation who participated in five double-blind, placebo-controlled clinical trials. Of the subjects evaluated, 4222 received PRILIGY®: 1615 received PRILIGY® 30 mg as needed and 2607 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 Clinical Information - Warnings and Precautions).
Orthostatic hypotension has been reported in clinical trials (see Clinical Information - Warnings and Precautions).
The most common adverse drug reactions (≥ 5%) reported during clinical trials were headache, dizziness, nausea, diarrhea, insomnia and fatigue. The most common events leading to discontinuation were nausea (2.2% of PRILIGY®-treated subjects) and dizziness (1.2% of PRILIGY®-treated subjects).
Adverse drug reactions reported by ≥ 1% of PRILIGY®-treated subjects in

these trials are shown in Table 1.

Table 1: Adverse Drug Reactions Reported by ≥ 1% of PRILIGY®-treated Subjects in 5 Double-Blind, Placebo-Controlled Clinical Trials of PRILIGY®

System/organ class Adverse drug reaction	PLACEBO (n=1857) %	PRILIGY® 30 mg as needed (n=1616[1]) %	PRILIGY® 60 mg as needed (n=2106[1]) %	PRILIGY® 60 mg once daily[2] (n=502) %
Investigations Blood pressure increased[3]	0.2	0.4	1.1	2 2

Nervous system disorders				
Dizziness[4]	2.2	5.8	11.0	14 9
Headache	4.8	5.6	8.8	11 2
Somnolence[5]	0.6	3.1	4.8	4 0
Tremor	0.2	0.5	0.9	1 6
Disturbance in attention	0.5	0.4	0.8	2 6
Paresthesia	0.3	0.4	0.8	1 2
Eye disorders				
Vision blurred[6]	0.4	0.2	0.6	2 0
Ear and labyrinth disorders				
Tinnitus	0.4	0.2	0.5	1 2

Respiratory, thoracic and mediastinal disorders				
Sinus congestion	0.3	0.7	1.0	1 6
Yawning	0	0.4	0.9	1 2
Gastrointestinal disorders				
Nausea	2.2	11.0	22.2	17.1
Diarrhea[7]	1.7	3.5	6.9	9.4
Abdominal pain[8]	1.2	2.2	2.6	4.4
Dry mouth	0.7	1.2	2.6	3.4
Vomiting	0.4	1.0	2.3	1 8
Dyspepsia	0.4	0.9	1.4	0 8
Flatulence	0.1	0.4	0.9	1.4
Constipation	0.3	0.3	0.4	1 8
Abdominal distension	0.3	0.1	0.6	1 0

Skin and subcutaneous tissue disorders Hyperhidrosis	0.2	0.8	1.2	3 0
Vascular disorders Flushing[9]	0.3	0.9	1.3	1.4
General disorders and administration site conditions Fatigue Irritability	1.2 0.8	2.0 0.1	4.1 1.1	9 2 3 6
Reproductive system and breast disorders Erectile dysfunction	1.6	2.3	2.6	1 2

Psychiatric disorders				
Insomnia[10]	1.6	2.3	4.3	9 0
Anxiety	0.5	1.1	2.0	2 2
Nervousness[11]	0.5	0.6	1.2	3 0
Libido decreased[12]	0.4	0.6	0.9	1.4
Depression[13]	0.6	0.4	0.9	1 2
Apathy[14]	0.1	0.4	0.2	1 0
Abnormal dreams[15]	0.3	0.2	0.4	2 0

1 One randomized patient never received study medication
2 Treatment duration up to approximately 70 days
3 Also includes blood pressure diastolic increased and blood pressure orthostatic increased
4 Also includes dizziness postural and dizziness exertional

[5] Also includes hypersomnia and sudden onset of sleep
[6] Also includes visual disturbance
[7] Also includes defacation urgency
[8] Also includes abdominal pain upper, stomach discomfort, abdominal discomfort and epigastric discomfort
[9] Also includes hot flush
[10] Also includes middle insomnia and initial insomnia
[11] Also includes agitation and restlessness
[12] Also includes loss of libido
[13] Also includes depressed mood
[14] Also includes indifference
[15] Also includes nightmare

Additional adverse drug reactions that occurred in < 1% of PRILIGY®-treated subjects are listed below in Table 2.

Table 2: Adverse Drug Reactions Reported by < 1% of PRILIGY®-treated Subjects in 5 Double-Blind, Placebo-Controlled Clinical Trials of PRILIGY®

System/organ class Adverse drug reaction
Cardiac disorders
Tachycardia[1]
Sinus bradycardia
Sinus arrest

Nervous system disorders
Depressed level of consciousness[2]
Dysgeusia
Lethargy
Syncope[3]
Akathisia
Eye disorders
Mydriasis (see Clinical Information - Warnings and Precautions)
Eye pain
Ear and labyrinth disorders
Vertigo

Skin and subcutaneous tissue disorders
Pruritus
Cold sweat
Vascular disorders
Hypotension
Systolic hypertension
General disorders and administration site conditions
Asthenia
Feeling abnormal
Feeling hot
Feeling jittery
Feeling drunk

Reproductive system and breast disorders
Ejaculation failure
Male orgasmic disorder[4]
Paraesthesia of genital male
Psychiatric disorders
Euphoric mood
Mood altered
Confusional state
Sleep disorder
Bruxism
Disorientation
Hypervigilance
Thinking abnormal

[1] Also includes heart rate increased
[2] Also includes sedation
[3] Also includes syncope vasovagal
[4] Also includes anorgasmia (also moved from Psychiatric disorders system organ class)

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.

Overdose

There have been no reports of overdose during clinical trials.

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.

PHARMACOLOGICAL PROPERTIES

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 center, 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 with 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

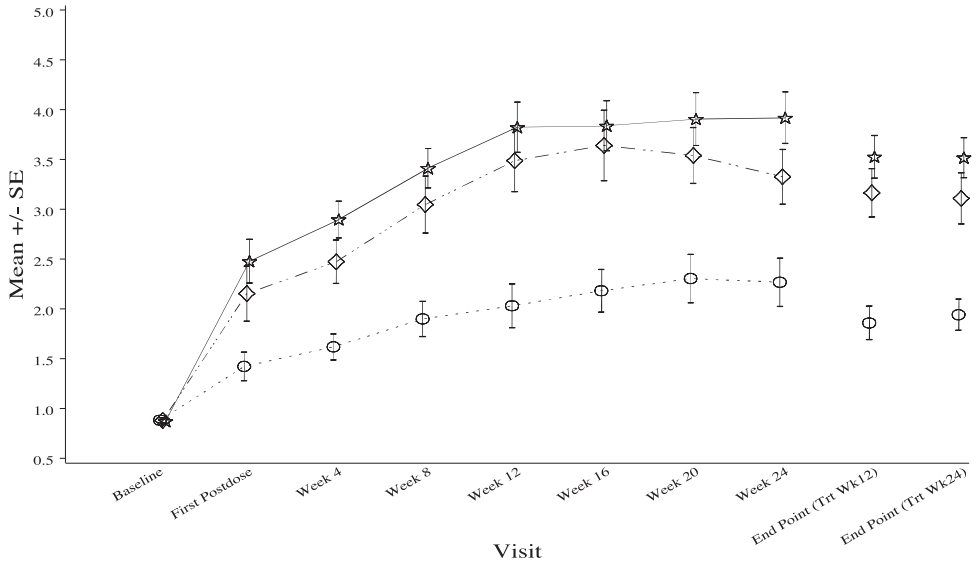
The effectiveness of PRILIGY® in the treatment of premature ejaculation has been established in five double-blind, placebo-controlled clinical trials, in which a total of 6081 subjects were randomized. Subjects were 18 years of

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 ≤ 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 (R096769-PRE-3001) 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 average 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 (LPOCF) 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:- - -o PLACEBO - - -◊ DPX 30 MG PRN - - -* DPX 60 MG PRN
End Point (TRT WK12) = LPOCF to Week 12. End Point (TRT WK24) = 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″0.001). Significant decrease in subject distress and significant improvement in subject satisfaction with sexual intercourse were also observed. Improvements at Weeks 12 and 24 (LPOCF) for the key secondary endpoints are presented in Table 3.

Table 3: 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

Other secondary patient reported outcome (PRO) endpoints were assessed in the clinical trials including clinical global impression of change in condition,

CGIC, a commonly used measure in which patients assess the status of their condition. Patients were asked to compare their premature ejaculation from the start of the study, with response options ranging from much better to much worse. Endpoints for CGIC showed statistically significant improvement compared to placebo when tested at the nominal significance level of 0.05 (2-sided). CGIC results by treatment group reported at the end of the above study are shown in Table 4.

Table 4: Results of Clinical Global Impression of Change in Condition at Study Endpoint (LPOCF*); Study R096769-PRE-3001

CGIC Response Outcome	Placebo n (%)	PRILIGY® 30mg n (%)	PRILIGY® 60mg 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
**No Change or Worse includes No Change, Slightly Worse, Worse or Much Worse
***At least Slightly Better CGIC response rate includes Slightly Better, Better and

Much Better: 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

In a study with a 12-week treatment duration (R096769-PRE-3003), conducted in Asian-Pacific countries, 1067 subjects were randomized, 357 to placebo, 354 to PRILIGY® 30 mg as needed, and 356 to PRILIGY® 60 mg as needed. The mean average IELT at baseline and study endpoint for all treatment groups is shown in Figure 2. Increases in mean average IELT at the Week 12 endpoint (LPOCF) were statistically significant ($p<0.001$) in both PRILIGY® groups versus placebo.

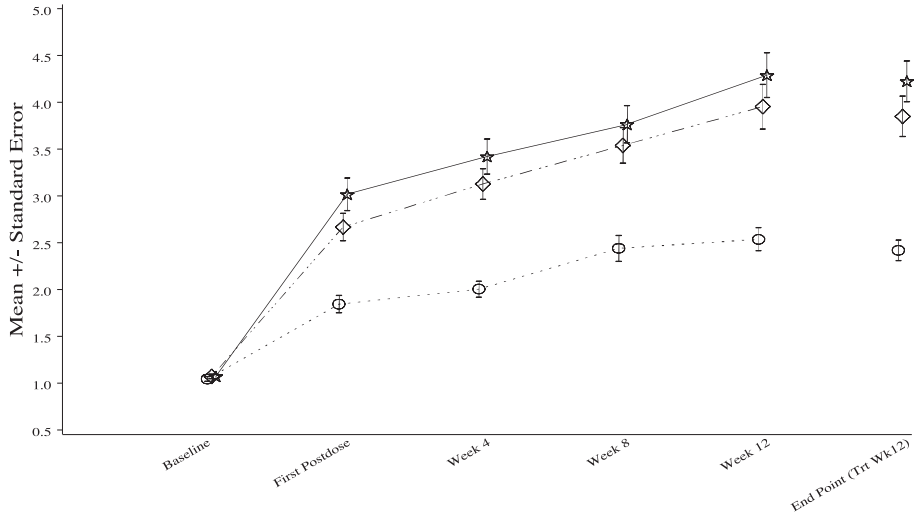


Figure 2: Mean (+/- SE) in Average IELT (min) over Time Study R096769-PRE-3003

	Sample size (N) for each visit in Figure 2					
	Baseline	First Post-dose	Wk 4	Wk 8	Wk 12	Endpoint (Treatment Wk12)
Placebo	357	342	341	312	295	342
DPX 30 mg PRN	354	333	333	309	281	333
DPX 60 mg PRN	356	331	329	299	278	331

Treatment Group:- - -o PLACEBO - - -◊ DPX 30 MG PRN - - -* DPX 60 MG PRN
End Point (TRT WK12) = LPOCF to Week 12.
LPOCF is last post-baseline observation carried forward.

In addition to the primary endpoint of average IELT, meaningful treatment benefit to the patient in study R096769-PRE-3003 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 the first post-dose IELT measurement and up to and including Week 12 ($p<0.001$). Significant decrease in subject distress and significant improvement in subject satisfaction with sexual intercourse were also observed. Improvements at Week 12 endpoint (LPOCF) for the key secondary endpoints are presented in Table 5.

Table 5: Percentage of Subjects with Improvement in Key Secondary Endpoints at Week 12; Study R096769-PRE-3003

Key Secondary Endpoint (LPOCF[1])	Placebo % (n=341)	PRILIGY® 30 mg % (n=329)	PRILIGY® 60 mg % (n=336)
Treatment Response Composite (change ≥ 2 in control and ≤ -1 in distress)	21.7	34.7[1]	37.2[1]
Change ≤-1 in Distress	56.0	66.6[1]	72.7[1,2]
Change ≥ 1 in Satisfaction	57.8	69.3[1]	75.9[1]

[1] p-value <0.001 for PRILIGY® versus placebo; LPOCF is last post-baseline observation carried forward

[2] n=337 (One subject had a result in the distress but not in the composite and satisfaction responses.)

Other secondary patient reported outcome (PRO) endpoints were also assessed in study R096769-PRE-3003 including clinical global impression of change in condition, CGIC, a commonly used measure in which patients assess the status of their condition. Patients were asked to compare their premature ejaculation from the start of the study, with response options ranging from much better to much worse. Endpoints for CGIC showed statistically significant improvement compared to placebo when tested at the nominal significance level of 0.05 (2-sided). CGIC results by treatment group reported at the end of study R096769-PRE-3003 are shown in Table 6.

Table 6: Results of Clinical Global Impression of Change in Condition at Study Endpoint (LPOCF[1]); Study R096769-PRE-3003

CGIC Response Outcome	Placebo n (%)	PRILIGY® 30 mg n (%)	PRILIGY® 60 mg n (%)
No Change or Worse[2]	161 (47 2%)	94 (28.6%)	70 (20 8%)
Slightly Better[3]	105 (30 8%)	112 (34 0%)	127 (37.7%)
Better	53 (15.5%)	78 (23.7%)	93 (27 6%)
Much Better	22 (6.5%)	45 (13.7%)	47 (13 9%)
Total	341 (100%)	329 (100%)	337 (100%)

[1] LPOCF is last post-baseline observation carried forward
[2] No Change or Worse includes No Change, Slightly Worse, Worse or Much Worse
[3] At least Slightly Better CGIC response rate (includes Slightly Better, Better and Much

Better): Placebo (52.8%), PRILIGY® 30 mg (71.4%) and PRILIGY® 60 mg (79.2%) 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.

In the two multidose Phase 3 studies, where the CYP2D6 metabolizer status was identified, a total of 120 poor metabolizers and 1598 extensive metabolizers were enrolled and treated with PRILIGY®. No overall

differences were seen in efficacy or safety between poor and extensive metabolizers.

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%). 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 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; 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

More than 99% of dapoxetine is bound *in vitro* to human serum proteins. The active metabolite desmethyldapoxetine 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. Additional metabolites include desmethyldapoxetine, which is equipotent to dapoxetine, and didesmethyldapoxetine, which

has approximately 50% of the potency of dapoxetine. Taking into account potency and unbound plasma concentrations, only desmethyldapoxetine may contribute to the effects of dapoxetine *in vivo* (see Pharmacological Properties – Pharmacokinetic Properties).

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 desmethyldapoxetine is similar to that of dapoxetine.

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. Dapoxetine pharmacokinetics have not been evaluated in patients requiring renal dialysis. There are limited data in patients with severe renal impairment (see Clinical Information – Dosing and Administration and Warnings and Precautions).

Hepatic impairment

In patients with mild hepatic impairment, unbound C_{max} of dapoxetine is

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

In patients with severe hepatic impairment, the unbound C_{max} of dapoxetine was decreased by 42% but the unbound AUC was increased by approximately 223%. The C_{max} and AUC of the active fraction had similar changes (see Clinical Information – Dosing and Administration and Contraindications).

CYP2D6 Polymorphism
In a single dose clinical pharmacology study using 60 mg PRILIGY®, plasma concentrations in poor metabolizers of CYP2D6 were higher than in extensive metabolizers (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. Thus the active fraction of PRILIGY® may be increased by approximately 46% at C_{max} and by approximately 90% for AUC. This increase may result in a higher incidence and severity of dose dependent adverse events. 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 Clinical Information – Dosing and

Administration, Contraindications and Warnings and Precautions.)
Plasma concentrations of dapoxetine and desmethyldapoxetine in CYP2D6 ultrarapid metabolizers are expected to be decreased.

NON-CLINICAL INFORMATION

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.
Daily topical administration for 6 months to Tg.AC transgenic mice at 375, 750, or 1500 mg/kg/day produced some tumor promoter activity (papillomas at the application site) at 750 mg/kg/day or higher. Systemic medicinal product exposure, as measured by AUC of dapoxetine and its major human metabolites, was approximately 1 to 2 fold the exposures in males given the Maximum Recommended Human Dose (MRHD) of 60 mg. The topical exposure model is not relevant for orally administered medicinal products.
Dapoxetine and its major human metabolite were not mutagenic in the *in vitro* bacterial Ames assay or the forward mutation test in mouse lymphoma cells. Dapoxetine was not clastogenic in the *in vitro* chromosomal aberration

test in Chinese hamster ovary cell or the *in vivo* mouse micronucleus assay.
Based on data from the 2-year rat carcinogenicity study, 6-month Tg.rasH2 carcinogenicity study, and genetic toxicology studies, dapoxetine is not expected to have carcinogenic risk.
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.

PHARMACEUTICAL INFORMATION

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
Black iron oxide (E172)
Yellow iron oxide (E172)

Incompatibilities

Not applicable

Shelf Life

See expiry date on the outer pack.

Storage Conditions

Do not store above 30°C.
Keep out of (the sight and) reach of children.

Nature and Contents of Container

PVC-PE-PVDC/aluminum push-through blister

Pack sizes of 1, 2, 3 and 6 tablets
Not all pack sizes may be marketed

Instructions for Use and Handling

No special requirements.

Instructions for Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

MANUFACTURED BY

See outer carton.

HOLDER:
Berlin-Chemie AG,
Glienicker Weg 125, 12489 Berlin, Germany

DATE OF REVISION OF THE TEXT
17-April-2012 based on CCDS 05-March-2012

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Impianto definitivo per la stampa

Informazioni Tecniche

Prodotto:PIL Priligy		Paese: Libano
N° identif.	Cod. laetus:	Cod. parte:
Storia:		Codice PF:
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Colori: Black		
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