LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Priligy
Dapoxetine hydrochloride
Film-coated tablets, 30 and 60 mg

SE/H/718/01-02/DC

This module reflects the scientific discussion for the approval of Priligy. The procedure was finalised at 2008-12-17. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Janssen-Cilag AB has applied for a marketing authorisation for Priligy, 30 and 60 mg film coated tablets. The active substance is *dapoxetine*. Dapoxetine is a SSRI developed as a p.r.n. treatment of premature ejaculation (PE) in men. The exact mechanism of ejaculatory delay is not completely understood, including the precise role that serotonin reuptake inhibition exerts on this process.
For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Priligy is presented in the form of tablets containing 30 and 60 mg of dapoxetine free base. The excipients are a mixture of lactose monohydrate and microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide, triacetine and black and yellow iron oxides. The tablets are packed in PVC-PE-PVDC/Alu blister.

II.2 Drug Substance

Dapoxetine hydrochloride does not have a monograph in the Ph Eur.

The drug substance is white to slightly yellow powder which is freely soluble in methanol, dichloromethane, propylene glycol and water. The structure of dapoxetine has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Priligy film-coated tablet is formulated using excipients described in the current Ph Eur, except for iron oxides which regarding their quality is referred to the relevant EU Directive. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01). The ingredient magnesium stearate is of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as particle size and solubility of dapoxetine hydrochloride in HCl acid as well as the crystalline form of dapoxetine hydrochloride.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Dapoxetine is a selective serotonin reuptake inhibitor (SSRI) proposed for the treatment of premature ejaculation (PE) in adult men aged 18-64. The anticipated dosage regimen is to be taken on a p.r.n. basis, at a maximum of once daily. The recommended dose is 30 mg or 60 mg, taken approximately 1-3 hours prior to sexual activity. The maximum recommended dose is 60 mg once per day (in a 24-hour period). At multiple dose conditions at 60 mg the AUC for dapoxetine is 2950±1000 ng*h/ml.

III.2 Pharmacology

Primary pharmacodynamics

Dapoxetine was demonstrated to be an inhibitor of serotonin (5-HT) reuptake (IC_{50} = 13.6 nM) *in vitro* in rat brain synaptosomes, while inhibition of norepinephrine and dopamine reuptake was weak (IC_{50} = 1533 and 2033 nM, respectively). In cells expressing the human transcript of the serotonin reuptake transporter, dapoxetine and its metabolites desmethyl dapoxetine, didesmethyl dapoxetine, and 5-OH desmethyl dapoxetine were all demonstrated to be inhibitors of serotonin reuptake with IC_{50} values of 1.12 nM, 1 nM (equipotent), 2.1 nM, and 11.8 nM, respectively. The major human metabolite, dapoxetine-N-oxide, was shown to be a weak inhibitor with an IC_{50} value of 282 nM. In cells expressing the human transcript of the norepinephrine reuptake transporter, dapoxetine and its metabolites dapoxetine-N-oxide, desmethyl dapoxetine, 5-OH desmethyl dapoxetine, and 3-DABP had IC_{50} values of 202 nM, no activity at 10 μM, 40.9 nM, 116 nM, and no activity at 10 μM, respectively, and were thus all weak inhibitors of norepinephrine reuptake. Didesmethyl dapoxetine inhibited norepinephrine reuptake with an IC_{50} value of 32.4 nM. Dapoxetine and its metabolites were weak inhibitors of the dopamine reuptake in cells expressing the human transcript of the dopamine reuptake transporter with IC_{50} values ranging from 1.0-2.0 μM.

In vivo, dapoxetine inhibited serotonin uptake into the brain and platelets of rats with oral ED_{50} values of 6.8 mg/kg and 15.4 mg/kg, respectively. Dapoxetine transiently decreased the concentration of the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) in the brains of rats following a single 10 mg/kg intraperitoneal injection. Dapoxetine antagonized the depletion of brain serotonin by p-chloroamphetamine in rats and mice with ED_{50} values of 15.5 and 4.6 mg/kg, i.p., respectively. At i.p. doses up to 32 mg/kg, dapoxetine did not antagonize the 6-hydroxydopamine-induced depletion of cardiac noradrenaline in mice. Dapoxetine suppressed ingestive behaviors, increased serum corticosterone concentrations in rats, and produced analgesia in the mouse writhing test. These results are all consistent with the inhibitory action of dapoxetine at the serotonin reuptake transporter. *In vivo* administration (SC) of desmethyldapoxetine and didesmethyldapoxetine to the rat inhibited 5-HT uptake *ex*

vivo with ED_{50} values of 1.5 and 4 mg/kg, respectively and NE uptake *ex vivo* with ED_{50} values of 12 and 5 mg/kg, respectively.

In support of treatment of premature ejaculation, it was shown that acute treatment with dapoxetine modulated the ejaculatory reflex in rats by causing an increase in pudendal motoneuron reflex discharge (PMRD) latency and a reduction in PMRD duration. Mechanistic studies demonstrated that dapoxetine inhibited the ejaculatory expulsion reflex by acting at a supraspinal level, with the lateral paragigantocellular nucleus (LPGi) as a necessary brain structure in mediating the effect. While delaying ejaculation, dapoxetine had no effects on other sexual behavior in the rat.

Secondary pharmacodynamics
A series of *in vitro* secondary pharmacology studies comparing agonist activity of dapoxetine on contractile responses in various smooth tissues and cardiac muscle isolated from rat or Guinea pig, and for its ability to antagonize or enhance the effects of standard agonists or field stimulation were performed. Dapoxetine did not elicit contractile activity in the Guinea pig ileum, rat vas deferens, or rat uterus. It did not antagonize the effects of norepinephrine (vas deferens) or isoproterenol (atria). The response of the ileum to field stimulation was significantly inhibited (40 %) at the highest concentration tested (10 μM). At 10 μM or higher, dapoxetine markedly antagonized acetylcholine (ileum), angiotensin (field-stimulated ileum), and oxytocin (uterus) in a non-competitive manner. Dapoxetine demonstrated significant antagonist activity at the α_{1A}-adrenergic receptor at concentrations > 10 μM with an estimated IC_{50} of 8.3 μM. In consistence with this finding dapoxetine had no agonist activity at the α_1-adrenergic receptor, but exerted a weak antagonist effect when tested in the isolated rabbit thoracic aorta. Notable binding of dapoxetine was measured as > 75 % inhibition of specific binding at 1 μM at the α_{1A}-adrenegic receptor, D1 receptor, 5-HT_{2B} receptor and the 5-HT reuptake transporter when profiled at 145 receptors, ion channels, transporters, and enzymes. When taking affinity constants, plasma protein binding, and relevant clinical dosing and exposure into account the expected maximum of 4 % and 3.1 % binding of dapoxetine and desmethyldapoxetine, respectively, to these receptors is not considered clinically relevant.

Safety pharmacology
A panel of safety pharmacology studies evaluated the potential physiological activity of dapoxetine on cardiovascular, CNS, respiratory, renal, and immunological parameters.

CNS
Slight behavioral changes (hyperreactivity, aggressiveness, and increased vocalization) were observed in mice administered dapoxetine from 3 mg/kg. Seizure activity was significantly reduced at 30 mg/kg as evaluated by electroshock. Hexobarbital-induced sleep time was increased at 30 mg/kg. Systemic exposure of dapoxetine or its active metabolites was not measured. However, in another study following a single oral dose of 25 mg/kg in the mouse the C_{max} and AUC of dapoxetine were 56 ng/mL and 107 ng*h/mL, respectively. This is considerably less than the clinical dapoxetine exposure at the maximum recommended dose of 60 mg (C_{max} ~ 0.5 μg/mL), and firm conclusions regarding effects of dapoxetine on the CNS cannot be drawn from the behavioural study. Nevertheless, CNS effects predictable for an SSRI was observed in the toxicity studies in the rat and the monkey, and in clinical trials in humans and further studies are not warranted.

Cardiovascular
Dapoxetine decreased the membrane K^+-current in hERG-transfected HEK293 cells with an IC_{50} of 3.26 μM. At concentrations of 1 μM and 10 μM, dapoxetine decreased the amplitude, duration, and upstroke of the action potential in isolated rabbit Purkinje fibers, indicating

potential blocking of sodium and calcium currents. In anesthetized Guinea pigs administered dapoxetine intravenously, decreased heart rate (5 mg/kg) and increased blood pressure (2.5 mg/kg through 10 mg/kg) was observed. At cumulative dapoxetine doses of up to 19.38 mg/kg, no effect on the PQ, QRS, or QTc (Bazett) intervals was observed. At a cumulative dose of 39.38 mg/kg, cardiac conduction disturbances were observed, which included increased PQ interval, increased QRS interval, and decreased QTcB interval. The plasma concentrations of dapoxetine ranged from 3902 to 6896 ng/mL (median of 5450 ng/mL) which is approximately 10-fold the clinical C_{max}. There were no biologically significant changes in heart rate or blood pressure in conscious rats administered dapoxetine orally at 27 mg/kg, however, at this dose the exposure is well below the clinical exposure. No significant ECG changes were seen in the anesthetized dog after intravenous infusions at doses up to 10 mg/kg, but there were significant increases in pulmonary arterial pressure, pulmonary vascular resistance, and respiratory rate at 2 and 10 mg/kg. However, in the conscious dog dapoxetine had no significant effects on pulmonary arterial pressure, aortic blood pressure or heart rate when administered intravenously at 2 mg/kg or orally at 150 mg/kg. There were no significant effects on ECG in the 28-day or 9-month repeat dose toxicity studies in the cynomolgus monkey. However, also in these studies clinical exposure was not reached. In 3 clinical studies specifically addressing potential electrophysiological effects on the cardiovascular system there was no consistent pattern of ECG changes and no effects on the QT interval even at a daily dose of 240 mg. It can be concluded that although dapoxetine inhibits the hERG membrane K^+-current effects on the QT interval are unlikely. In the clinical development of dapoxetine syncope was observed. However, the preclinical data do not support an arrythmogenic mechanism as the etiology, rather, the observed antagonism at the α_{1A}-adrenergic receptor suggests a vasovagal effect.

Other
Oral doses of dapoxetine at 10 and 100 mg/kg induced slight increases in urine output and creatinine excretion in female rats. At higher dose levels, toxicity limited the ability to evaluate renal function. No effects on primary antibody production were observed in male CD-1 mice following 10 days of dosing with dapoxetine. Dapoxetine did not elicit contractile activity in the Guinea pig or rat ileum. No other studies specifically addressing the gastrointestinal system were performed.

III.3 Pharmacokinetics

The pharmacokinetic and toxicokinetic evaluation of dapoxetine demonstrated approximately dose-proportional pharmacokinetics in all tested species, up to 325 mg/kg/day in rodents. The half-life value for the elimination of dapoxetine from the plasma was shorter in research animals (2 – 7 hours) than in humans (18.1 hours) and oral bioavailability was also lower in rat (~11%) and monkey (~3%) than human (~ 42 %). In repeat dose studies, there was no indication of significant accumulation of dapoxetine or its metabolites.

Following oral administration of a single dose of 25 mg/kg of ^{14}C-dapoxetine to rats, dapoxetine was rapidly and extensively distributed to tissues of absorption and elimination (liver, kidney, lung, spleen, gastrointestinal contents, salivary gland, Harderian gland, and urine). Radioactivity levels in other tissues reflected plasma concentrations. There was a moderate penetration of radioactivity into the central nervous system with AUC values for cerebrum, cerebellum, medulla, and spinal cord ranging from 32 to 66% of the AUC for plasma.

Placental transport was demonstrated in pregnant rats. Tissue-to-maternal plasma ratios at 8 hours after dosing were in uterus and placenta 1.75 and 2.55, respectively, and in amniotic fluid and embryonic tissues 0.23 and 0.39, respectively. The latter increased to ratios greater

than 1 up to 24 hours which indicated that the ^{14}C-dapoxetine and/or metabolites were more slowly excreted from these compartments than maternal plasma. Distribution was not studied in pigmented animals.

Dapoxetine was extensively bound (> 99%), and the metabolites desmethyl dapoxetine, dapoxetine-N-oxide, and didesmethyldapoxetine were highly bound (~ 93 - 99 %) to plasma protein in all species, with the exception of dapoxetine-N-oxide where binding was lower in the dog (~ 85%).

In vitro inhibition studies in human liver microsomes showed that dapoxetine has no effect or weak inhibitory effects toward CYP450s. The most potent inhibitory effect was for CYP2C19 with an IC_{50} of 7.99 μM, which is about 5 times higher than the dapoxetine C_{max} after a 60 mg clinical dose (~ 1.38 μM, ~ 420 ng/mL).

Dapoxetine was classified as a moderate mixed inducer of hepatic enzymes in the rat and the dog. In the repeat dose toxicity studies increases in total hepatic CYP450 content and induction of hepatic CYP1A and CYP2B enzymes were observed in the rat and the monkey. There was little evidence of induction of CYP enzymes in human hepatocytes *in vitro* which is consistent with findings in clinical drug-drug interaction studies. Dapoxetine was not a P-glycoprotein substrate.

Dapoxetine was extensively metabolized in rats, monkeys, and humans. No metabolites were identified in human that were not observed in the test animals, although the relative abundance showed some inter-species variability. In human, multiple Phase I metabolites were formed primarily via N-demethylation, napthyl hydroxylation, and N-oxidation by multiple CYP enzymes (cytochrome P450) including CYP3A4 and CYP2D6. In one *in vitro* study comparing the metabolite formation in liver microsomes from five different species, including human, the most abundant circulating human metabolite, dapoxetine-N-oxide, was detected with only weak signals, and a positive blank. In another study using human liver microsomes dapoxetine-N-oxide was detected only at trace levels. Of importance, it was also shown that dapoxetine-N-oxide was mainly formed by flavin-containing monooxygenase 1 (FMO1) by renal microsomes. In one additional study *in vitro* formation of dapoxetine-N-oxide in rat and mouse liver microsomes was confirmed, as well as in mouse and rat renal microsomes. The dapoxetine-N-oxide, plus the less abundant minor metabolites desmethyl dapoxetine and didesmethyl dapoxetine, were also detected in mouse, rat, and monkey plasma, however not at equal abundance. Another metabolite, 3-DAPB (3- dimethylaminobenzene propanol), was more abundant in rat plasma than in human. Most of the Phase I metabolites were further metabolized (Phase II) to glucuronides and sulfates and excreted in the urine in monkey and human.

The kidney was the primary excretory organ for metabolites of dapoxetine in human, monkey and mouse, while the liver was the primary excretory organ in rat and dog. The profiles for human and monkey urine were quite similar. Furthermore, most major metabolites seen in human urine were also observed in rat urine. Little or no parent drug or unconjugated metabolite was detected in urine. Notably, dapoxetine-N-oxide was neither detected in urine or feces in any species, nor was it demonstrated to be further metabolised.

III.4 Toxicology

Single- dose toxicity

Oral single-dose toxicity studies were adequately performed in the mouse, rat, dog, and rhesus monkey (nasogastric gavage). Approximate oral lethal doses of dapoxetine HCl were 1175, ≥ 1450, > 400, and > 200 mg/kg, respectively. Dose-related clinical signs observed included difficulty breathing, dilated papillary reflex, tremors, hypoactivity, excess salivation, emesis, anorexia, weight loss, and abnormal stool and were consistent with exaggerated pharmacologic activity. Clinical signs were reversible upon cessation of dosing. Single dose studies were also performed in the rat and cynomolgus monkey following iv injection at doses up to 5 mg/kg without deaths and any obvious signs of toxicity observed. In addition, dapoxetine, desmethyldapoxetine, didesmethyldapoxetine, and dapoxetine-N-oxide exposure was confirmed in the rat and cynomolgus monkey.

Repeat-dose toxicity

A large number of repeat-dose studies were performed in the rat, dog, and cynomolgus monkey using the oral route of exposure and ranging from 2 weeks to 9 months of duration.

In repeat-dose studies in the rat decreased mean body weight, weight gain, and food consumption was observed. Major clinical signs observed were labored breathing and a clear oral discharge. The liver was identified as a target organ with observed moderate-to-marked centrilobular fatty change, centrilobular/midzonal hepatocellular hypertrophy and vacuolation, increased liver-to-body weight percentage, and induction of hepatic CYP1A and CYP2B activity. At the maximum tolerated dose in the rat, 225 mg/kg/day, the margin to the clinical exposure (AUC) to dapoxetine and dapoxetine-N-oxide is approx. 2-fold and no margin, respectively. At high doses (from 892 mg/kg/day yielding an exposure margin of approx. > 10-fold for dapoxetine) renal tubule degeneration was also observed.

Also in mice the kidney was identified as a target organ with nephropathy and urolithiasis observed at high dietary doses (from 776 mg/kg/day), apparently without exposure margins to the clinical exposure. However, this finding is considered as an exacerbation of rodent-specific age-related progressive nephropathy and is of low clinical relevance.

In the dog, emesis, increased salivation, mydriasis, slow and/or incomplete papillary light response, increased lacrimation, hypoactivity, and sporadic tremors were observed from 50 mg/kg/day, and were attributed to exaggerated pharmacological activity. ECG examination showed no treatment related changes in cardiac rhythm, conduction or alterations in heart rate. A significant increase in CYP450 was observed from 50 mg/kg/day. Hepatic porphyria was diagnosed in dogs given daily dapoxetine doses of 150 mg/kg for 6 months. This lesion was not observed in any dog given 15 or 50 mg/kg for 6 months or in dogs administered 150 mg/kg/day for 3 months. The effects on the liver in dogs given 150 mg/kg/day of dapoxetine for 6 months are consistent with those seen with other SSRIs.

In a 28 day study in the cynomolgus monkey no treatment-related changes were observed in electrocardiograms, hematologic or serum chemistry parameters, body weights, or gross or microscopic tissue examinations at 100 mg/kg/day. Also in the cynomolgus monkey, an increase in hepatic CYP450 was observed. Clinical signs observed were ataxia, emesis, and hypothermia. Deaths occurred at 200 mg/kg/day and were precluded by dilated pupils, emesis, ataxia, tremors, hypoactivity, excessive salivation, nonformed feces and poor apetite. The cause of death was not discernable from macroscopic and microscopic observations and was attributed to exaggerated pharmacologic effects. Of importance, these deaths occurred following continuous use and were preceded by progressive CNS-signs that were not observed in humans and that would lead to drug discontinuation. Moreover, when reducing the dose

recovery of CNS-symptoms was observed. It can be concluded that the clinical relevance of this finding is limited.

At the NOAELs observed in the repeat dose studies in the rat, dog, or monkey, there are no exposure margins to dapoxetine or dapoxetine-N-oxide at the proposed clinical dose of 60 mg. In 1- and 3-month rat studies the NOAEL was 25 mg/kg/day and in 6-month studies the NOAEL was 13-15 mg/kg/day. However, the liver findings in the rat and the dog can be attributed to the observed enzyme induction. There was no marked signs of induction of CYP enzymes in human hepatocytes *in vitro*, suggesting low clinical relevance. In the 9-month study in the cynomolgus monkey, the NOAEL was the highest administered dose (75 mg/kg/day). This gives an exposure to dapoxetine and dapoxetine-N-oxide of equal to and 10 % of the clinical AUC, respectively, as well as half and 20 %, respectively, of the clinical C_{max}. The highest tolerated dose was however achieved since deaths occurred at 200 mg/kg/day in the 28-day study (see discussion above).

Genotoxicity
The genotoxicity of dapoxetine and dapoxetine-N-oxide has been adequately studied with respect to gene mutations in bacteria and mammalian cells and chromosome aberrations *in vitro* and *in vivo*. Additionally, tests of primary DNA damage and sister chromatid exchange *in vivo* have been conducted. No genotoxicity was evident from these studies. Noteworthy, there was an increase in cells with polyploidy observed in the *in vitro* chromosomal aberration study in CHO cells (10.5, 2.5, and 5.5 % at 50, 55, and 60 μg/mL + S9, respectively). This finding is considered as non-DNA reactive and may in this case be of limited clinical relevance.

The clinical relevance of the submitted additional negative *in vivo* study investigating sister chromatid exchange in the Chinese hamster cannot be fully assessed since no toxicokinetics or ADME-profiling of the Chinese hamster were provided.

Carcinogenicity
The carcinogenic potential of dapoxetine was evaluated in a 2-year oral study in the rat. Based on the number of surviving animals/sex/group dosing was discontinued early for the treated female groups (Week 90) and the high dose male group (Week 97). Statistically significantly increased mortality was observed in the high dose groups (225 mg/kg/day). A minimal increase in hepatocellular adenoma was observed in the high dose males and females. However, this finding can be attributed to the induction of hepatic enzymes, which was not observed in humans, and is considered of low clinical significance. A minimal increase was also observed for thyroid follicular cell carcinoma in the low dosed male group, however without a dose-response relationship. Non-neoplastic findings were observed in the liver (M and F), lung, trachea, and mesenteric lymph node (F) at 225 mg/kg/day (NOEL 75 mg/kg/day). The systemic exposure of dapoxetine, or its metabolites, was not measured in the study. It can however be concluded from other toxicokinetic studies that the systemic exposure (AUC) to both dapoxetine and dapoxetine-N-oxide at 225 mg/kg/day in the rat is approximately 2-fold the clinical exposure at 60 mg.

A 26-week oral carcinogenicity study was performed in transgenic Tg.rasH2 mice and was provided together with a toxicokinetic bridging study confirming systemic exposure following 15 days oral dosing at 200 mg/kg with C_{max} of 419 and 620 ng/mL (males) and AUC_{0-24} of 1000 and 1020 ng*h/mL (males) for dapoxetine and dapoxetine-N-oxide, respectively. The high dose group was terminated early due to high mortality rates and it can be concluded that the carcinogenicity of dapoxetine has been studied in the mouse up to 100 mg/kg. The systemic exposure levels in male mice following 15 days oral dosing at 100 mg/kg were 126 and 218 ng/mL (C_{max}) and 455 and 529 ng*h/mL (AUC_{0-24}) for dapoxetine and dapoxetine-N-

oxide, respectively. This is clearly below the C_{max} of 498 ng/mL and $AUC_{0-\infty}$ of 2640 ng*h/mL observed for dapoxetine in humans. Nevertheless, the MTD was reached and higher dosing is not feasible. The limited exposure obtained in the mouse carcinogenicity study is adequately reflected in the SPC. Non-neoplastic findings were observed in the nasal cavities (exudative inflammation along with mucous gland hyperplasia and squamous metaplasia with subsequent hyperplasia) already at 25 mg/kg/day. This finding was attributed to local exposure following oral gavage and is not considered to be clinically relevant. Other target organs, also previously noted, were the trachea (chronic inflammation) from 100 mg/kg/day, and kidneys (nephropathy with infarction, degeneration and necrosis of the tubules) at 200 mg/kg/day.

The Applicant has also undertaken a 26-week topical carcinogenicity study in Tg.Ac mouse at 375, 750, and 1500 mg/kg/day. In this study, an increased incidence and multiplicity of squamous cell papillomas was observed. This finding suggests that dapoxetine may act as a tumor promoter when administered topically at dose levels of 750 mg/kg/day or higher. However, the relevance of this finding for the intended oral clinical use of dapoxetine is limited.

Reproductive and developmental toxicity
Dapoxetine did not affect male or female fertility at doses up to 174 and 100 mg/kg/day, respectively. In addition, no apparent treatment-related effects on sperm motility, epididymal sperm count or testis histopathology was observed in the cynomolgus monkey following 39 weeks of treatment at 75 mg/kg/day or after the 4-week recovery. Dapoxetine was not teratogenic in the rat or the rabbit at doses up to 100 and 75 mg/kg, respectively. Reduced fetal body weight and an increased incidence of incomplete ossification were observed in the rat at 100 mg/kg/day. Reduced fetal body weight was observed in the rabbit at 75 mg/kg/day. Fetal viability was not affected. The NOAEL for maternal toxicity was 7.5 mg/kg/day and for fetuses 25 mg/kg/day. Plasma exposure of dapoxetine or its metabolites was not measured in any of the embryo-fetal studies. Placental transfer of radioactivity has been demonstrated in pregnant rats administered a single oral dose of ^{14}C-labeled dapoxetine, demonstrating exposure to the fetuses, although at a low level and not distinguished between dapoxetine and metabolites. The lack of ADME data and toxicokinetics in the rabbit is a drawback. However, signs of exaggerated SSRI-pharmacological activity (prone position, lateral recumbency, convulsions, dilated pupils, ataxia, cyanosis, rales, rapid and labored respiration) were observed in the maternal animals. The lack of a peri/postnatal study and juvenile toxicity studies is acceptable since only adult males will be treated with this product. Dapoxetine and its metabolites were excreted in monkey semen at levels similar to plasma. The potential risk to a fertile or pregnant partner, or to her fetus following the estimated exposure to dapoxetine through semen is considered as negligible.

Other
The dependence potential was studied in the male rat following repeat administration of dapoxetine up to 500 mg/kg/day for 14 days followed by a 10-day withdrawal period. No signs of dependence or withdrawal were evident.

Dapoxetine absorbs light in the wavelength 290 - 700 nm. There are no studies addressing distribution in pigmented animals. Nevertheless, the phototoxicity potential of dapoxetine and dapoxetine-N-oxide has been adequately addressed in *in vitro* and *in vivo* studies. Both dapoxetine and dapoxetine-N-oxide was phototoxic *in vitro* but no phototoxicity was observed *in vivo*. The lack of photogenotoxicity and photocarcinogenicity studies is accepted. It can be concluded that dapoxetine is not phototoxic when administered orally.

III.5 Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) consisting of a PBT-assessment stopping at log Kow < 3.5, a Phase I $PEC_{surfacewater}$ calculation using a refined Fpen, and acute toxicity studies in algae, *Daphnia*, and fish was provided. However, the results indicate that dapoxetine has a log R > 4.5 (5.13) at pH 8.9, which is within environmentally relevant pHs (i.e. 4-9 in surface water). Consequently, a bioconcentration study in accordance with OECD 305 is required. A definite conclusion on the PBT status can therefore still not be reached. In addition, the refined $PEC_{surfacewater}$ could not be accepted and a complete Phase II assessment is required before a conclusion on the environmental risk can be made. The Applicant has committed to perform and submit a full Phase II assessment by December 2009.

III.6 Discussion on the non-clinical aspects

Dapoxetine should be classified as a selective serotonine reuptake inhibitor (SSRI), whilst the metabolites desmethyldapoxetine and didesmethyl dapoxetine based on their dual inhibition at the serotonine reuptake transporter and norepinephrine reuptake transporter should be considered as serotonine norepinephrine reuptake inhibitors (SNRI). The contribution of desmethyldapoxetine, didesmethyldapoxetine, and dapoxetine-N-oxide to the overall pharmacologic activity is considered of low clinical relevance when taking into account their respective IC_{50} and ED_{50} at inhibition of serotonin and norepinephrine reuptake, systemic exposure (C_{max}), level of protein binding, and anticipated free plasma concentration.

The rat and the monkey are considered as adequate species for the non-clinical evaluation. The ADME profile of dapoxetine in the mouse following oral exposure was not fully evaluated. However, based on available data on *in vitro* metabolism, *in vivo* plasma toxicokinetics following topical exposure, and excretion data also the mouse can be considered as a relevant non-clinical species. It should be noted that quantitative differences in exposure to the most abundant human metabolite dapoxetine-N-oxide was apparent in all animal species tested. Metabolism and toxicokinetic data are lacking in the rabbit, Guinea pig, and Chinese hamster. Consequently, their relevance as non-clinical species cannot be fully assessed.

A panel of safety pharmacology studies evaluated the potential physiological activity of dapoxetine on cardiovascular, CNS, respiratory, renal, and immunological parameters. Single dose toxicity studies were performed in the mouse, rat, dog, rhesus monkey, and cynomolgus monkey. A large number of repeat-dose studies were performed in the rat, dog, and cynomolgus monkey using the oral route of exposure and ranging from 2 weeks to 9 months of duration. Male and female fertility and embryo-fetal development were studied in the rat and the rabbit. Dapoxetine was found non-genotoxic in standard genotoxicity tests. Carcinogenicity studies were performed in the rat and in transgenic mouse.

Based on the results from the non-clinical studies no special hazard for humans was revealed when considering the treatment of premature ejaculation (PE) in adult men aged 18-64.

IV. CLINICAL ASPECTS

IV.1 Introduction

(If no introduction, suggest deleting this header and renumbering those below.)

IV.2 Pharmacokinetics

Absorption

Dapoxetine has a moderate and variable bioavailability (42%, range 15-76%, n=8). The reasons for the limited bioavailability may be first pass metabolism, possibly low solubility, and active efflux. Marked efflux was observed in a Caco-2 cells study. The transporter has not been identified but is not Pgp and may also not be BCRP or MRP2. The applicant will perform additional transport studies in MDCKII cells over a wide and clinically relevant concentration range. These studies will be completed and submitted as a post-approval commitment. The Applicant will submit the full reports by the end of 2009. If no transport is observed in these transporter systems, further studies will be planned in an effort to identify the efflux transporter(s) involved in the transport of dapoxetine. An inhibition of an efflux transporter could increase the exposure of drug and metabolites due to increased bioavailability of dapoxetine. Involvement of an uptake transporter may also not be excluded. The bioavailability decreases at doses above 100 mg. Tmax is approximately 1-2 hours.

The tablet used in the pivotal clinical studies and the main part of the pharmacokinetic studies is the same as intended for marketing with the exception of the debossing. Bioequivalence has been shown between this tablet and a capsule used in some early studies. Concomitant food intake slightly reduced Cmax and slightly increased the bioavailability of dapoxetine. The tablet was taken irrespectively of food intake in the clinical studies.

Distribution and protein binding

Vss was estimated to 162±59 L after iv administration. Dapoxetine is highly protein bound and has a fu of about 0.3-0.4%. The fu of the active metabolite DED is 1.46% in vitro.

Elimination

The terminal half-life of dapoxetine is about 29 hours but it appears to have 3 phases of disposition and 24 hours after a 60 mg dose, concentrations of only about 5-6% of Cmax are observed. The metabolite desmethyl dapoxetine (DED) has a similar half-life. The mode of elimination of dapoxetine is not completely clear. It seems to include a large number of pathways including phase II metabolism giving rise to a large number of metabolites. Only 51% of the drug related material in the circulation has been identified. Unchanged dapoxetine accounted for 24% of the AUC of radioactive material after a radiolabelled oral dose. Main metabolites include DED, and dapoxetine-N-oxide. Main primary eliminaton pathways apparently include CYP3A4 catalysed formation of DED, FMO1 catalysed formation of dapoxetine-N-oxide and CYP2D6 catalysed formation of hydroxy-dapoxetine. DED then appears to be further metabolised by CYP2D6 to hydroxyl-DED and then conjugated. The elimination of DED has not been fully characterised. There is little renal or biliary excretion of unchanged dapoxetine. The pharmacokinetics appears dose-linear up to 100 mg q.d. and is not significantly time-dependent. Steady state of dapoxetine and DED is reached approximately at the third day of a 60 mg q.d. treatment. The intra-individual variability appears low and the inter-individual variability low to moderate.

Pharmacokinetics of metabolites

Dapoxetine is mainly eliminated through metabolism and has some active metabolites. The metabolites appear to have a lower protein binding relying on inter-study comparisons. One of the metabolites, desmethyldapoxetine (DED) has similar activity to the parent compound and about 70% lower unbound systemic exposure than dapoxetine. Thus, dependent on the degree of distribution to target site, it may contribute to some of the pharmacological effect of dapoxetine, especially when the metabolite exposure is increased.

Special populations
The pharmacokinetics in special populations and the consequences of drug interactions have been calculated using both parent drug exposure as well as exposure of active moiety, the sum of the unbound exposure of dapoxetine and DED assuming equal distribution to the target site (the CNS). As DED is likely to be more hydrophilic than dapoxetine, active moiety is a worst case estimation by assuming equal distribution of DED and dapoxetine to the CNS. Cmax may be the parameter mainly correlated to the cardiovascular adverse effects, while AUC may in part be related to these effects, it is generally used as a general exposure parameter for the exposure studied in comparison with the exposure obtained in the specific populations and during interactions. The highest dose on which safety data is available is 100mg, which was associated with a relatively marked increase in adverse events.

Cmax and AUC of active moiety (unbound concentration of activity equivalents) in CYP2D6 PMs are increased by 46% and 90%, respectively. The parent drug total Cmax and AUC are increased by 31 and 36%, respectively. Although there is a large overlap in exposure between PMs and EMs, this means that PMs treated with 60 mg will obtain an mean exposure of parent drug similar to what is obtained in EMs treated with 100 mg. The mean AUC of active moieties will be similar to a 120 mg dose. The data also applies to treatment with potent CYP2D6 inhibitors. Caution is advised when the dose is increased to 60 mg in CYP2D6 PMs or in patients treated with a potent CYP2D6 inhibitor.

The exposure of dapoxetine and DED is increased in moderate and severe hepatic impairment. The increase in AUC of active moiety is 120% in moderate hepatic impairment while Cmax is unchanged. The mean Cmax and AUC of unbound parent drug is increased by approximately 55 and 121%, respectively. In severe hepatic impairment, mean Cmax was unchanged and AUC of active moiety is increased by 333%.. The AUC of unbound parent drug was increased by 330%. Moderate and severe hepatic impairment is contraindicated. Impaired renal function does not significantly affect the pharmacokinetics of dapoxetine or DED. Treatment of patients with severe renal impairment is not recommended.

Interactions
Dapoxetine is a mild inhibitor of CYP2D6 and seems to be a weak CYP3A4 inducer in vivo. In vitro induction studies indicated CYP2A6 induction in 2 out of 3 donors. The enzyme activities were generally reduced at the highest concentration in the in vitro induction study and this may indicate cytotoxicity. In addition, some enzyme inhibition was observed, to some extent questioning the sensitivity of the study to detect induction as mRNA monitoring would have been needed to exclude induction of the inhibited enzymes. Dapoxetine affects the B-A/A-B permeability ratio of the Pgp substrate digoxin in vitro but due to the low solubility, the concentrations reached in the intestine are not considered sufficiently high for Pgp inhibition to be obtained.

Potent CYP2D6 inhibition is likely to give similar exposures as obtained in PMs. Thus reference is given to the CYP2D6 PM discussion above. Treatment with fluoxetine (potent CYP2D6 inhibitor, mild CYP3A4 inhibitor) increased dapoxetine and DED exposure (by 88 and 114%, respectively). The increase in dapoxetine exposure was greater than the increase observed in CYP2D6 PMs indicating that an additional mechanism of the interaction also was present. The role of CYP3A4 is not completely clear in this interaction. The potent CYP3A4 inhibitor ketoconazole also increased dapoxetine ad DED exposure to a greater extent than indicated from the in vitro metabolism studies. There was a 23% increase in Cmax and 88% increase in AUC of active moiety and a 35 and 99% increase in parent drug Cmax and AUC, respectively. Treatment with potent CYP3A4 inhibitors in patients who are CYP2D6 PMs or on potent CYP2D6 inhibitors may give rise to markedly increased exposure. It is difficult to

estimate the DED exposure resulting from inhibition of both CYP2D6 and CYP3A but the AUC is expected to be increased 3.6-fold. (CL/F is reduced by 25% in absence of CYP2D6 and by 47% during inhibition of CYP3A4, which makes a 72% reduction of CL when these situations are combined.) The applicant suggests a contraindication for use of potent 3A4 inhibitors. This is endorsed. The applicant proposes a caution in section 4.4 for use of moderate CYP3A4 inhibitors as well as for potent CYP2D6 inhibitors. Even moderate 3A4 inhibitors may give rise to AUC of dapoxetine or active moiety which are well above the AUC obtained with 100 mg. The extent of increase in Cmax is unknown. The observed adverse effects appears mainly to be related to Cmax but is probably also partly related to rate of decline in concentrations (AUC). Furthermore, if the interaction results in AUCs for which there is no safety data, this has to be considered in the treatment recommendations. The dose should be restricted to 30 mg in patients treated with a moderate CYP3A4 inhibitor and caution is advised. The recommendations for concomitant use of CYP3A4 inhibitors have been made to suite all patients (including CYP2D6 PMs). However, the increase in exposure will not be as marked in CYP2D6 EMs. If it is known that the patient is a CYP2D6 EM, a maximum dose of 30mg 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 CYP3A inhibitor.

IV.3 Pharmacodynamics

Mode of action
Dapoxetine is an SSRI originally developed as a potential treatment of pain, obesity and depression. Due to its short-acting pharmacokinetic properties it was later developed as a p.r.n. treatment of PE in men. The ejaculation delaying effect of SSRIs is a common and well established side effect during long-term treatment. A substantial body of evidence has also emerged for the use of daily SSRI as an effective treatment of PE.

Ejaculation is controlled by sympathetic innervation to the genital organs, and, in normal functioning, there is considerable voluntary inhibitory control over this phase of the sexual response. The exact mechanism of ejaculatory delay is poorly understood. It is not confirmed that the effect is linked to the inhibition of serotonin reuptake. However, acute i.v. administration of dapoxetine to male rats modulated the ejaculatory reflex, causing an increase in pudendal motoneuron reflex discharge (PMRD) latency and a reduction in PMRD duration. These results provide a possible explanation of the mode of action by which on demand dapoxetine delays ejaculation in men with PE.

Effects on human platelets
The effect of dapoxetine on serotonin uptake in human platelets was studied in a Phase 1 trial following single (5, 10, or 20 mg) and repeated (10 and 14 days of 5 mg bid, 10 mg bid, or 20 mg daily) doses. Dapoxetine inhibited uptake of serotonin into human platelets *ex vivo* in a dose-dependent manner. The 5 and 10-mg bid regimens inhibited *ex vivo* platelet serotonin uptake for 12 hours. The 20-mg q.d. regimen showed greater inhibition than the 5- or 10-mg doses, but uptake had returned to control levels by 24 hours. The dose-related inhibition of serotonin uptake in human platelets confirms the pharmacological profile of dapoxetine as an SSRI.

Drug-drug interactions
No clinically harmful pharmacodynamic drug-drug interactions have been identified in the Phase 1 studies. However, a SPC warning is included concerning concomitant use of other SSRIs. So far, only PK interaction with fluoxetine has been evaluated. The possibility of the

development of a serotonin syndrome with concomitant use of dapoxetine and other SSRIs have been considered and relevant SPC changes have been added.

In addition, warnings of possible pharmacodynamic interactions between dapoxetine and other CNS active drugs, like ethanol and recreational drugs, and possible reduced orthostatic tolerance with concomitant administration of PDE5Is and alpha adrenergic blocking agents, have also been added to the SPC.

Cardiac effects
Combined pharmacodynamic results of dapoxetine single (60 – 160 mg) or multiple doses (80 – 120 mg) showed no clinically relevant effects on systolic and diastolic blood pressures. No clinically relevant effects on heart rate or mean arterial pressure were found. However, several incidences of syncope occurred in the clinical trials, particularly at the higher dose of dapoxetine (60 mg). Warnings of this AE have been included in the SPC and preventive as well as follow up measures have been added in the SPC and RMP.

No clinically significant differences in vital signs were found during treadmill exercise.

Electrocardiographic Studies
Two Phase 1 studies were conducted to evaluate the ECG PD of dapoxetine 60, 120, and 240 mg.
Uncorrected and heart-rate corrected intervals (QT and QTc (using several methods)) were calculated. ECGs were also evaluated for the presence of arrhythmia, ST segment changes, and P-, T-, and U-wave morphology, as well as other indications of potential myocardial ischemia. Dapoxetine at doses of 60, 120 mg or 240 mg did not prolong the QTc interval as measured by a variety of correction methods, and the ECG morphology and rhythm observed with dapoxetine were comparable to those of placebo.

A third Phase-1 study was conducted with 60 mg dapoxetine in CYP2D6 poor and extensive metabolizers. Single oral dapoxetine doses of 60 mg did not have clinically significant ECG effects and did not prolong the QTc interval as assessed using a variety of correction methods.

There were no differences in the ECG effects in poor and extensive metabolizers.

IV.4 Clinical efficacy

The efficacy of dapoxetine has been studied in an extensive clinical program including two phase II studies, four main phase III studies, one study evaluating withdrawal effects of dapoxetine, and one open label extension study.

Design of the four main pivotal studies: All studies were multi-centre, randomised, double-blind, placebo controlled parallel group studies. After a screening and baseline assessment period eligible subjects were randomised to placebo, dapoxetine 30mg p.r.n. or 60 mg p.r.n. Randomisation was stratified based on baseline IELT (≤1 min; >1min, see Efficacy measurements below). In three studies (C-2002-012, C-2002-013 and PRE-3003) the duration of the double-blind treatment was twelve weeks while it was 24 weeks in the fourth study (PRE-3001).

Efficacy measurements: The primary endpoint was the average IELT of the intercourses during the last four weeks at Week 12 (Week 24 in study R096769-PRE-3001). IELT (Intra-

vaginal Ejaculation Latency Time, i.e. time from penetration to ejaculation) was measured by a partner-operated stopwatch. Ejaculation before penetration was recorded as "0". The subjects were encouraged to have at least six intercourses per moths during the twelve weeks double-blind phase.

Important secondary endpoints were based on a number of subject and partner (in study C-2002-012, C-2002-013 and PRE-3001) patient-reported outcome (PRO) measures, in particular Control over ejaculation, Satisfaction with sexual intercourse and Personal distress (**Table 2**). A responder was defined as at least a 2-category increase in Control over ejaculation and at least a 1-category decrease in Personal distress.

PRO measures were evaluated at 9 weeks in the study (PRE-3002) designed to evaluate withdrawal effects.

Table 2 *Key subject and partner PRO measures*

Measure	Question Text	Scores and Response Options
Control Over Ejaculation	**Subject:** Over the past month, was your control over ejaculation during sexual intercourse: **Partner:** Over the past month, was your partner's control over ejaculation during sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Satisfaction With Sexual Intercourse	**Subject and Partner:** Over the past month, was your satisfaction with sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Personal Distress	**Subject:** Over the past month, how distressed were you by how fast you ejaculated during sexual intercourse? **Partner:** Over the past month, how distressed were you by how fast your partner ejaculated during sexual intercourse?	0: Not at all 1: A little bit 2: Moderately 3: Quite a bit 4: Extremely

Study population: Subjects enrolled were required to be healthy, heterosexual males who had been in a stable, monogamous, sexual relationship for at least 6 months. In all studies the subjects should be18 years of age or older.

Subjects had to meet the DSM-IV-TR criteria for PE, and the condition should have caused moderate to marked distress and/or interpersonal difficulty over the prior 6 months. In addition to the DSM-IV-TR criteria, subjects were to have an IELT of ≤2 minutes in at least 75% of their evaluable sexual intercourse events at baseline.

Of subjects actually included 58% had an average baseline IELT≤1 minutes. Baseline responses on the PRO measures showed that 95% had poor or very poor Control over ejaculation, 57% had poor or very poor Satisfaction with Sexual intercourse, 92% had moderate or higher levels of Personal distress related to ejaculation, and 63% had moderate or higher levels of Interpersonal difficulty related to ejaculation. Most of the partners (83%) reported at baseline that subjects had poor or very poor Control over ejaculation and about half (49%) reported that they had poor or very poor Satisfaction with sexual intercourse.

Dose-response: No comprehensive dose-response studies were performed. In two separate phase II studies two doses (20 mg *vs* 40 mg and 60 mg *vs* 100 mg p.r.n., respectively) were compared to placebo. In these studies, as well as in the Phase III studies, a larger magnitude of effect was observed for the higher dose in each study. In particular for some of the key secondary endpoints some of these differences are statistically significant. Thus, overall a dose-response is considered demonstrated. The observed difference between 60 mg and 100 mg was not considered sufficiently large to outweigh the higher incidence of adverse reactions on 100 mg, and 30 mg and 60 mg were chosen for the phase III studies.

Efficacy results: The withdrawal pattern differs between treatments. In three studies the total number of discontinuations is higher on dapoxetine treatment, in particular with the 60 mg dose. In all studies discontinuations due to adverse events were more frequent on dapoxetine treatment, again in particular on the 60 mg dose.

The average IELT at baseline was 0.9 min. Roughly, this was doubled with placebo treatment, three times as long with dapoxetine 30 mg, and prolonged four times with dapoxetine 60 mg (**Table 3**).

Table 3 *Average IELT at Week 12 (LPOCF) in Phase 3 Placebo-Controlled Studies by Study and Pooled Results. Week 24 results for Study PRE-3001.*

		Endpoint		Difference vs Placebo
	Treatment Group	N Mean (SD)	LS Mean (SE)	in LS Means (95% CI)
Week 12 LPOCF				
C-2002-012	PLACEBO	406 1.7 (2.09)	1.6 (0.17)	—
	DPX 30 MG PRN	390 2.9 (3.59)	2.8 (0.17)	1.3 (0.83, 1.71)***
	DPX 60 MG PRN	364 3.4 (3.97)	3.3 (0.18)	1.7 (1.30, 2.19)***
C-2002-013	PLACEBO	381 1.8 (2.33)	2.0 (0.17)	—
	DPX 30 MG PRN	411 2.7 (3.39)	2.9 (0.16)	0.9 (0.43, 1.27)***
	DPX 60 MG PRN	399 3.3 (3.40)	3.5 (0.17)	1.4 (1.02, 1.86)***
PRE-3001	PLACEBO	339 1.9 (3.11)	1.6 (0.24)	—
	DPX 30 MG PRN	363 3.2 (4.61)	2.9 (0.23)	1.3 (0.73, 1.86)***
	DPX 60 MG PRN	355 3.5 (4.04)	3.3 (0.23)	1.7 (1.12, 2.26)***
PRE-3003	PLACEBO	342 2.4 (2.05)	2.3 (0.20)	—
	DPX 30 MG PRN	333 3.9 (3.95)	3.7 (0.20)	1.4 (0.87, 1.87)***
	DPX 60 MG PRN	331 4.2 (3.97)	4.1 (0.20)	1.8 (1.27, 2.28)***
Pooled	PLACEBO	1468 1.9 (2.43)	2.0 (0.09)	—
	DPX 30 MG PRN	1497 3.1 (3.91)	3.1 (0.09)	1.2 (0.93, 1.41)***
	DPX 60 MG PRN	1449 3.6 (3.85)	3.6 (0.09)	1.6 (1.41, 1.89)***
Week 24 LPOCF				
PRE-3001	PLACEBO	339 1.9 (2.89)	1.7 (0.23)	—
	DPX 30 MG PRN	363 3.1 (4.88)	2.9 (0.23)	1.2 (0.59, 1.72)***
	DPX 60 MG PRN	355 3.5 (3.80)	3.3 (0.23)	1.6 (1.02, 2.16)***

*** p-Value <0.001 for comparison between DPX and placebo based on the ANCOVA model.
LS Mean, LS Mean difference (2-sided 95%C.I.): Based on ANCOVA model with treatment, pooled center (or study for pooled analysis), and stratum as factors and baseline value as a covariate.

The relevance of these mean differences is substantiated in the responder analyses (**Table 4**, the Personal distress component of the responder definition was not included in study C-2002-012 and C-2002-013). In pooled analyses there were 13 %-units (including only studies with a

direct placebo comparison) and 22 %-units more responders on dapoxetine 30 mg and 60 mg, respectively, than in the placebo group.

Table 4 *Response Rates for the Composite of at Least a Two-Category Increase in Control Over Ejaculation and at Least a One-Category Decrease in Personal Distress at Week 9-12 (LPOCF) in Phase 3 Placebo-Controlled Studies by Study and Pooled Results. Week 24 results for Study PRE-3001.*

	Treatment Group	n/N (%)	Difference. vs Placebo in % Responders (95% C.I.)[a]
Week 9-12 LPOCF			
PRE-3001	PLACEBO	42/346 (12.1%)	—
	DPX 30 MG PRN	98/359 (27.3%)	15.2 (9.41, 20.91)***
	DPX 60 MG PRN	120/353 (34%)	21.9 (15.83, 27.88)***
PRE-3002	PLACEBO	48/221 (21.7%)	—
	DPX 60 MG PRN	205/431 (47.6%)	25.8 (18.65, 33.04)***
PRE-3003	PLACEBO	74/341 (21.7%)	—
	DPX 30 MG PRN	114/329 (34.7%)	12.9 (6.20, 19.70)***
	DPX 60 MG PRN	125/336 (37.2%)	15.5 (8.73, 22.27)***
Pooled	PLACEBO	164/908 (18.1%)	—
	DPX 30 MG PRN	212/688 (30.8%)	12.8 (8.49, 17.01)***
	DPX 60 MG PRN	450/1120 (40.2%)	22.1 (18.31, 25.93)***
Week 24 LPOCF			
PRE-3001	PLACEBO	45/346 (13%)	—
	DPX 30 MG PRN	91/359 (25.3%)	12.3 (6.61, 18.07)***
	DPX 60 MG PRN	131/353 (37.1%)	24.1 (17.94, 30.27)***

[a] Based on CMH test controlling for baseline IELT strata and pooled center (except that IELT stratum was not controlled for Study PRE-3002 or for the pooled analysis).

*** p-Value <0.001 for comparison between DPX dose and placebo.

These results have been confirmed in several alternative responder analyses, including one where all discontinuing patients are counted as non-responders. Thus, there is no indication of a bias in favour of active treatment due to the differential withdrawal pattern and the LPOCF approach for missing values.

Partner self-reported outcome measures were collected in three studies. Significant effects in favour of both doses of dapoxetine supporting the above results were found for all PRO items (illustrated in **Table 5** with partner satisfaction).

Table 5 *Response Rates for at Least a One-Category Increase in Partner Satisfaction With Sexual Intercourse at Week 12 (LPOCF) in Phase 3 Placebo-Controlled Studies by Study and Pooled Results*

	Treatment Group	n/N (%)	Difference. vs Placebo in % Responders (95% C.I.)[a]
Week 12 LPOCF			
C-2002-012	PLACEBO	109/385 (28.3%)	—
	DPX 30 MG PRN	183/378 (48.4%)	20.1 (13.35, 26.86) ***
	DPX 60 MG PRN	174/352 (49.4%)	21.1 (14.23, 28.01) ***
C-2002-013	PLACEBO	99/375 (26.4%)	
	DPX 30 MG PRN	175/403 (43.4%)	17.0 (10.44, 23.61) ***
	DPX 60 MG PRN	176/386 (45.6%)	19.2 (12.52, 25.87) ***
PRE-3001	PLACEBO	113/320 (35.3%)	
	DPX 30 MG PRN	155/328 (47.3%)	11.9 (4.42, 19.47) **
	DPX 60 MG PRN	177/322 (55.0%)	19.7 (12.11, 27.20) ***
Pooled	PLACEBO	321/1080 (29.7%)	
	DPX 30 MG PRN	513/1109 (46.3%)	16.5 (12.53, 20.54) ***
	DPX 60 MG PRN	527/1060 (49.7%)	20.0 (15.93, 24.06) ***

[a] Based on CMH test controlling for baseline IELT strata and pooled center (except that IELT stratum was not controlled for the pooled analysis).

** p-Value <0.01;

*** p-Value <0.001; for comparison between DPX dose and placebo.

Clinical Global Impression of Change

There was a significantly greater percentage of subjects who responded in the CGI-C that their PE was at least slightly better at Week 9-12 (LPOCF) in the dapoxetine 30-mg (62.1%) and 60-mg groups (71.7%) than in the placebo group (36.0%) ($p<0.001$ for both comparisons), Table 6.

Table 6. *Response Rates For at Least a 'Slightly Better' Rating in Clinical Global Impression of Change at Week 9-12 (LPOCF) in the Phase 3 Placebo-Controlled Studies by Study and Pooled Results*

Studies	Treatment Group	n/N (%)	Difference. vs Placebo in % Responders (95% C.I.)[a]
Week 9-12 LPOCF			
C-2002-012	PLACEBO	97/396 (24.5)	
	DPX 30 MG PRN	235/389 (60.4)	35.9 (29.47, 42.36) ***
	DPX 60 MG PRN	243/366 (66.4)	41.9 (35.47, 48.33) ***
C-2002-013	PLACEBO	103/376 (27.4)	
	DPX 30 MG PRN	232/410 (56.6)	29.2 (22.61, 35.77) ***
	DPX 60 MG PRN	272/401 (67.8)	40.4 (34.02, 46.86) ***
PRE-3001	PLACEBO	113/347 (32.6)	
	DPX 30 MG PRN	221/359 (61.6)	29.0 (21.95, 36.04) ***
	DPX 60 MG PRN	258/352 (73.3)	40.7 (33.97, 47.49) ***
PRE-3002	PLACEBO	113/222 (50.9)	
	DPX 60 MG PRN	314/433 (72.5)	21.6 (13.81, 29.42) ***
PRE-3003	PLACEBO	180/341 (52.8)	
	DPX 30 MG PRN	235/329 (71.4)	18.6 (11.44, 25.85) ***
	DPX 60 MG PRN	267/337 (79.2)	26.4 (19.60, 33.29) ***
Pooled	PLACEBO	606/1682 (36.0)	
	DPX 30 MG PRN	923/1487 (62.1)	26.0 (22.67, 29.41) ***
	DPX 60 MG PRN	1354/1889 (71.7)	35.6 (32.58, 38.71) ***

[a] Based on CMH test controlling for baseline IELT strata and pooled center (except that IELT stratum was not controlled for Study PRE-3002 or for the pooled analysis)
*** p-Value <0.001 for comparison between DPX dose and placebo.

Subgroup results: In subgroup analyses based on baseline IELT (≤1 min; >1 min), baseline satisfaction category, age, race and region no statistically significant or clinically conspicuous interactions were found.

Efficacy comparison with continuous treatment: In the study evaluating withdrawal effects the subjects were initially randomised to placebo, dapoxetine 60 mg p.r.n. or dapoxetine 60 mg qd. Prior to the withdrawal randomisation at nine weeks PRO measures were recorded. Both dapoxetine treatments were superior to placebo. There were no relevant differences between the active treatments, although the minor numerical differences favoured the p.r.n. treatment for most items.

Maintenance of effect: Sixty-eight % (1774 subjects) of the patients initially enrolled in study C-2002-012 and C-2002-013 were included in an open label extension study (C-2002-014) with nine month treatment with dapoxetine 60 mg p.r.n. Fifty-four % completed nine months of open label treatment. Early discontinuation was due to lack of effect (12.8%), adverse event (6.7%), personal reason (7.3%), withdrawal of consent (6.6%), lost to follow up (9.9%), and other (3.5%).

In intention to treat analyses (all premature discontinuations counted as "failures") the effect was maintained fairly well during open label treatment (**Table 7**). Similar results were seen for the other PRO items. Although these results are based on a selected patient population and uncontrolled data, they provide some support for maintenance of effect.

Table 7 *Percentage of patients with Fair/Good/Very good control of ejaculation during open label treatment with dapoxetine 60 mg p.r.n. ITT results.*

Initial treatment	**Number entering open label treatment**	**Percent with ≥ fair control over ejaculation**	
		Month 1	**Month 9**
Placebo	615	22	43
Dapoxetine 30 mg	607	47	44
Dapoxetine 60 mg	552	57	51

IV.5 Clinical safety

Clinical safety

General safety
A total of 4,536 patients were exposed to dapoxetine ranging from 20 – 100 mg in the Phase 2 and 3 placebo-controlled studies. Most patients (4,236) were exposed to the proposed dose range 30 – 60 mg. The majority (4,034) received dapoxetine p.r.n. but 502 received it q.d., the latter all 60 mg/day. The patients were instructed to take a minimum of 6 doses per month. The mean duration of exposure in the five phase 3 studies ranged from 51 – 88 days and the mean number of doses from 24 – 49 with a substantial variation between subjects.

The AEs were generally well-known from and consistent with available SSRIs. Further, in consistency with the SSRI class of drugs most AEs were dose-related. Of all subjects randomized to receive dapoxetine in the Phase 3 placebo-controlled studies, 287 patients (6.8 %; range 3.5% - 10.0 %) discontinued their treatment due to adverse events. The frequently most reported events resulting in discontinuation were nausea (0.9 %– 3.4%) and dizziness (0.7 % - 2.0 %). Like most common AEs related to SSRIs and dapoxetine, these symptoms were non-serious, dose-related, and usually reported soon after starting treatment (i.e., on or before the first follow up visit occurring at 4 weeks.)

A possible effect on mood and suicidality as well as neurocognitive AEs have been analysed without raising any major safety concerns. The SSRI withdrawal syndrome seems to be less common than in available SSRIs, probably due to the short half-life of DPX. A negative effect on sexual function commonly observed as a side-effect in other SSRIs is in the case of DPX used therapeutically.

The general safety profile for dapoxetine is thus similar to that of other SSRIs with one major exception: orthostatic hypotension and syncope.

Orthostatic hypotension and syncope
Cardiovascular system AEs were identified early in the DPX developing program based on the observation of syncope. Dizziness was the most commonly appearing AE related to the cardiovascular system followed by orthostatic hypotension. The cardiovascular AEs exhibited evidence of dose-dependency.

There were 30 cases of syncope in subjects exposed to dapoxetine. These 30 cases are from a cohort of 5929 exposed subjects, which means that about 0.5% of the subjects were affected. The incidence for 30 mg and 60 mg were 0.36% and 0.45%, respectively, compared to 0.08% for placebo. Of the 30 cases, seven (7) had a Holter ECG running at the time of syncope, and judging from the results of the Holter ECG all of these seven cases showed sign of a cardio-inhibitory response, such as sinus bradycardia, prolonged R- R interval, and in one case a sinus arrest for 28 seconds. A few subjects fell during syncope and suffered minor injuries.

A total of 15 subjects in the dapoxetine clinical development program met the strict definition of syncope as defined by a loss of consciousness. In the Phase 3 studies, 0.05%, 0.06%, and 0.23% of subjects treated with placebo, dapoxetine 30 mg, and dapoxetine 60 mg, respectively, experienced syncope with loss of consciousness, showing a similar incidence of syncope between the placebo and dapoxetine 30-mg groups.

A vaso-vagal reaction is the most probable explanation for the cases of syncope. A small number of patients showed more pronounced and serious reactions. These reactions were

probably also vagaly mediated but affected cardiac rhythm more profoundly. As these cases were few, it is therefore concluded that appropriate contraindications for patients suffering from significant cardiac diseases such as severe heart failure, AV conduction abnormalities or sick sinus syndrome not treated with a permanent pacemaker and severe ischemic heart disease should be sufficient to address these safety concerns.

An orthostatic test should be performed before initiation of treatment and the physician should take a careful medical history focusing on past orthostatic events. As there is a clear relation between dose and orthostatic reactions, the starting dose for all patients should be 30 mg and a dose increase should only be undertaken if the patient has had no orthostatic events on the 30 mg dose. These recommendations are included in the SPC.

Additional safety measures included in the risk management plan to reduce the risk of syncope consist of a targeted education material for physicians, pharmacists and patients. In order to evaluate the utility of the orthostatic test to minimize the risk of syncope a post approval observational study is planned. Furthermore, the labelling of the package has been specially designed to make the patients aware of certain safety characteristics of the drug such as syncope. The RMP and the risk minimization measures are considered adequate.

IV.6 Discussion on the clinical aspects

Statistically and clinically significant benefits of dapoxetine 30 mg p.r.n. and 60 mg p.r.n. in terms of prolonged average IELT have been shown in an adequate PE population. In pooled analysis of twelve week data IELT increased from 0.9 minutes at baseline to 3.1 and 3.6 minutes for 30 and 60 mg, respectively, compared to 1.9 minutes for placebo. The clinical relevance has been further demonstrated in terms of non-trivial responder differences *versus* placebo, with a responder definition based on patient reported outcome measures of apparent validity. At least a 2-category increase in control over ejaculation and at least a 1-category decrease in personal distress was achieved by 18%, 31% and 40% of the patients treated with placebo, 30 mg and 60 mg, respectively. The positive effects were also recognised by the partner. At least a 1-category increase in Partner satisfaction with sexual intercourse was reported by 30%, 46% and 50% in the placebo, 30 mg and 60 mg group, respectively.

The robustness of these efficacy results are demonstrated in additional analyses with alternative assumption about missing values. There is a lack of convincing data on maintenance of effect beyond 24 weeks. However, at any time it should be left to the patient to judge whether he still benefits from treatment.

Risks
To a large extent the clinical safety pattern for dapoxetine is as expected for an SSRI. Most adverse events are mostly of mild to moderate severity and self limiting but the occurrence of syncope (potentially leading to accidental injuries) in about 0.5% of exposed cases causes concerns for the safety of the drug.

In the clinical studies the orthostatic reactions were more pronounced for the 60 mg dose. With a starting dose of 30 mg and additional precautionary measures, the risk for orthostatic reactions and other effects on cardiac performance can be minimised. These kinds of reactions are particularly important to avoid in the elderly and especially in those patients that have a previous history of significant cardiac disease.

Dapoxetine has an equally active metabolite, DED. The metabolite contributes to maximum 1/3 of the effect of a dapoxetine dose. There are situations and populations where the exposures of these two substances are increased. This has been handled with restrictions in the SPC: potent CYP3A4 inhibitors are contraindicated as well as moderate and severely impaired hepatic function. The dose is restricted to 30 mg in patients treated with moderate CYP3A4 inhibitors and caution is advised. The exposure of "active moiety"(unbound exposure of pharmacological equivalents) is somewhat increased in CYP2D6 poor metabolizers. However, with the measures taken by the applicant to minimize the risk of syncope, including the restrictions regarding use together with CYP3A4 inhibitors, which is mainly due to the expected increased exposure in CYP2D6 poor metabolizers treated with these drugs, there is no need to include genotyping before using dapoxetine.

As informing the patient about the precautions needed when using dapoxetine is very important, the present PIL includes information and advice on the orthostatic test, risk of syncope, interactions, use with alcohol, driving and handling machines etc. Furthermore, Priligy has a specifically designed labelling intended to remind the patient about the more important safety precautions before every intake. Priligy is presented as carton leaflets, which when opened contains three tablets on one side and on the other side information on the risk of syncope, how to perform when having symptoms related to fainting, the need to restrict alcohol intake as well as recommendations with regard to driving.

Balance
On the positive side, clinically relevant effects have been demonstrated for short term use. This effect is clearly of value for the affected subjects.

On the negative side are the dose related vaso-vagal reactions (e.g. syncope) and the vagally mediated pronounced bradycardia. The latter reactions were relatively rare but they still are causes for concern unless certain safety measures can be implemented. These measures are twofold, first a proper wording of the SPC and secondly a risk minimisation plan addressing the proper post marketing utilisation of the drug. To avoid syncope completely is probably not possible but with careful assessment of the patients before administering the drug the risk of syncope could be managed.

The risks discussed above could be addressed by orthostatic testing and careful management of the patients. Before starting treatment the physician should examine the individual patient's medical history focusing on suspected orthostatic reactions in the past and also perform an orthostatic test. This would help to identify susceptible patients and also increase the awareness of the potential problem.
The starting dose should always be 30 mg and no dose escalation to 60 mg should be performed unless the patients have had uneventful experiences on the starting dose.
The treating physician should take care in obtaining a correct history of previous orthostatic reactions, and an orthostatic test should be performed before treatment is initiated.
Furthermore, the Applicant has added a warning in section 4.4 with a cross reference to section 4.2 about the risk for syncope and orthostatic reactions. The Applicant has accepted the contraindications that were suggested previously.

The Risk Management Plan is vital for the benefit – risk balance. The Plan has been updated with additional safety measures and in the assessor's opinion the plan has a reasonable chance to considerably reduce the risks for syncope.

In the present answer to the day 180 LoI, the Applicant has submitted a plan for a post approval study aiming at studying the effects of risk minimisation activities, such as orthostatic

testing on the risk for syncope. This was done as a reaction to an additional suggestion from one of the CMS (DE).

A market for “Internet-pharmacies” providing Priligy as well as for counterfeits of the product is probable. The applicant intends to perform Internet monitoring which will be communicated in each PSUR following the approval of Priligy.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed and is acceptable.

The risk/benefit ratio is considered positive and Priligy, 30 and 60 mg film coated tablets is recommended for approval.

Area	Description
Risk Management Plan	The Marketing Authorisation Holder will report all cases of syncope within the next PSURs and in addition will provide information whether and what kind of orthostatic measurement and test (e.g. Shellong) has been performed before starting medication to ensure the efficacy of this risk minimization measure.
Quality – Drug substance	At the time when the marketing authorisation is granted, the limits for the residual of Class 2 solvents are set at the ICH limits. The Marketing Authorisation Holder will perform additional work as a follow-up measure after 20 commercial batches are manufactured and appropriate statistical calculations can be performed to support refined specifications in terms of the residual of Class 2 solvents.
Non-clinical - Environmental Risk Assessment	The Marketing Authorisation Holder will perform and submit an updated Enviromental Risk Assessment. The following studies are required by December 2009: Aerobic and anaerobic degradation (OECD 308) Activated sludge respiration inhibition test (OECD 209) Daphnia reproduction test (OECD 211) Fish early life stage test (OECD 210) Bioconcentration test (OECD 305) Ready biodegradability test (OECD 301) Should the results of these studies indicate the need for further studies (i.e terrestrial or sediment compartment risk assessment), the Marketing Authorisation Holder will also perform these further studies.
Clinical - Pharmacokinetics	The Marketing Authorisation Holder will further investigate which transporter is involved in the efflux of dapoxetine in Caco-2 cells. The full study reports of the studies MDCKII cells should be submitted preferably including assessment of transport at more than one

	dapoxetine concentration.

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance

VI. APPROVAL

The Mutual recognition/Decentralised procedure for Priligy, 30 and 60 mg film coated tablets was successfully finalised on 2008-12-17.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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