ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR POSITIVE OPINION AND AMENDMENT OF THE LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Scientific conclusions

Overall summary of the scientific evaluation of Priligy and associated names (see Annex I)

Priligy is a pharmacologic treatment approved for men with Premature Ejaculation (PE). It has been granted marketing authorisation in 25 countries worldwide, including 7 countries in the European Union which were part of a decentralised procedure with Sweden acting as reference Member State. The countries involved in the first wave were Austria, Germany, Spain, Finland, Italy, Portugal. The approved indication in the EU is for the treatment of PE in men 18 to 64 years of age.

Subsequently, Janssen Cilag submitted an application for mutual recognition of Priligy, 30 mg and 60 mg film-coated tablets in the following Member States: Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Greece, France, Hungary, Ireland, Iceland, Lithuania, Luxembourg, Latvia, Malta, Netherlands, Norway, Poland, Romania, Slovenia, Slovakia and the United Kingdom.

The active substance of Priligy is dapoxetine hydrochloride that belongs to the class of selective serotonin reuptake inhibitors (SSRIs), originally developed as a potential treatment of pain, obesity and depression. Following reports of ejaculatory delay in patients taking dapoxetine for major depressive disorder and based on the rapid onset and elimination profile of the substance it was later developed as a PE treatment on an as needed (p.r.n) basis.

In the Phase III studies that were conducted, a dose-response was observed with respect to efficacy (≥ 12% more responders on 30 mg compared to placebo and an additional 5-10% responders on 60 mg compared to 30 mg) as well as safety (0.05, 0.06 and 0.23% cases of syncope with loss of consciousness for placebo, 30 mg and 60 mg, respectively).

During the mutual recognition procedure some Members States considered that the benefit-risk balance for the 60 mg dose was not positive. Considering that PE is not a life-threatening disease, the added benefit of 60 mg compared to 30 mg (5-10% more responders) was considered too modest to outweigh the potentially increased risk for severe cases of syncope. As an agreement could not be reached the procedure was subsequently referred to CHMP.

- **Efficacy issues**

Efficacy and safety were documented in four Phase III studies of 12-24 weeks duration comparing dapoxetine 30 mg p.r.n and 60 mg p.r.n with placebo. One study of 9 weeks duration was also conducted to evaluate the withdrawal effects of dapoxetine 60 mg p.r.n. and 60 mg q.d (once daily) as well as another open-label 9-month extension study (see summary table below). The key efficacy endpoints were Intravaginal Ejaculation Latency Time (IELT) and percentage of responders based on Control Over Ejaculation and Personal Distress (at least a 2-category increase in Control Over Ejaculation and at least a 1-category decrease in Personal Distress).

Study	Design and dosage	Number of subjects
R096769-PRE-3001	Double-blind, randomised, placebo-controlled 24-week study evaluating dapoxetine 30 mg and 60 mg p.r.n.	Placebo: 385 Dapoxetine 30 mg: 388 Dapoxetine 60 mg: 389
R096769-PRE-3003	Double-blind, randomised, placebo-controlled 12-week study evaluating dapoxetine 30 mg and 60 mg p.r.n.	Placebo: 357 Dapoxetine 30 mg: 354 Dapoxetine 60 mg: 356
C-2002-012	Double-blind, randomised, placebo-controlled 12-week study evaluating dapoxetine 30 mg and 60 mg p.r.n.	Placebo: 440 Dapoxetine 30 mg: 429 Dapoxetine 60 mg: 425
C-2002-013	Double-blind, randomised, placebo-controlled 12-week study evaluating dapoxetine 30 mg and 60 mg p.r.n.	Placebo: 430 Dapoxetine 30 mg: 445 Dapoxetine 60 mg: 445
R096769-PRE-3002	Double-blind, randomised, placebo-controlled 9-week study evaluating dapoxetine 60 mg p.r.n. and 60 mg q.d.	Placebo: 245 Dapoxetine 60 mg p.r.n.: 491 Dapoxetine 60 mg q.d.: 502
C-2002-014	Multicenter, open-label, 9-month extension study (enrolling subjects from studies C-2002-012 and C-2002-013)	Dapoxetine 60 mg: 1774 Dose reduction to 30mg: 194

The objecting Member States noted that the 60 mg dose yields only mild clinical benefit over the 30 mg dose and asked the MAH to justify that the increase in response for the 60 mg is statistically significant and clinically meaningful. The data submitted by the company are presented below.

In the Phase III studies, the treatment benefit was measured in subjects who met the prespecified composite endpoint requiring functional benefit (i.e., improved control over ejaculation) as well as emotional benefit (i.e., decreased levels of distress) related to the latency of their ejaculation. The mean average IELT at study end for responders in studies R096769-PRE-3001 and R096769-PRE-3003 approached 6 minutes compared to approximately 1 minute at baseline irrespective of treatment group (subjects were randomly assigned to fixed-dose treatment with either dapoxetine 30 mg or 60 mg).

For this composite endpoint, the analysis of the pooled dataset demonstrated that the percentage of subjects who were responders in the dapoxetine 60 mg group was 40.2% versus 30.8% in the 30 mg group and 18.1% in those receiving placebo at Week 9-12. The placebo-subtracted percentage difference was 22.1% with dapoxetine 60 mg and 12.8% with dapoxetine 30 mg.

In the analysis of the pooled data for the CGIC (Clinical Global Impression of Change) PRO (Patient Reported Outcome) measure the percentage of subjects reporting the two highest CGIG ratings of "better" or "much better" was 39.0% in the dapoxetine 60 mg group, 30.7% in the dapoxetine 30 mg group and 14.8% in the placebo group at Week 12. For all subjects with improvement in their PE condition (i.e. CGIC rating of at least "slightly better") the percentage of subjects that reported an

improvement at Week 9-12 was 71.7% for dapoxetine 60 mg, 62.1% for dapoxetine 30 mg and 36.0% in the placebo group. The corresponding placebo-subtracted difference was 35.6% with dapoxetine 60 mg and 26.0% with dapoxetine 30 mg.

The 4 PRO measures reflected inability to control ejaculation, distress related to the timing of ejaculation, satisfaction with sexual intercourse, and relationship difficulty. The distribution of responses to these PRO measures in men who met the composite endpoint was compared to that of men without PE who participated in the EU Observational study (R096769-PRE-3004).

More specifically, among responders to treatment (i.e., those subjects that reported at least a 2-category increase in Control Over Ejaculation and at least a 1-category decrease in Personal Distress) in Study R096769-PRE-3001, regarding:

- Control Over Ejaculation, 98.9% of responders reported "very poor" or "poor" control at baseline but 67.4% reported "good" or "very good" control at study end, compared with 78.4% of men without PE who reported "good" or "very good" control in the EU observational study (R096769-PRE-3004);
- Personal Distress, 77.9% of responders reported "extremely" or "quite a bit" of distress at baseline but 80.1% reported "not at all" or "a little bit" of distress at study end, compared with 91.9% of men without PE who reported "not at all" or "a little bit" of distress in the EU observational study (R096769-PRE-3004);
- Satisfaction With Sexual Intercourse, 64.4 % of responders reported "very poor" or "poor" satisfaction at baseline but 71.9% reported "good" or "very good" satisfaction at study end, compared with 91.6% of men without PE who reported "good" or "very good" satisfaction in the EU observational study (R096769-PRE-3004);
- Interpersonal Difficulty, 33.7% of responders reported "extremely" or "quite a bit" of interpersonal difficulty at baseline but 79.1% reported "not at all" or "a little bit" of interpersonal difficulty at study end, compared with 98.4% of men without PE who reported "not at all" or "a little bit" of interpersonal difficulty in the EU observational study (R096769-PRE-3004).

The Phase III studies were originally designed to compare the effect of dapoxetine 30 and 60 mg to that of placebo, and not to each other (i.e., 30 mg versus 60 mg). Because of that, the MAH conducted exploratory analyses to compare the effect of dapoxetine 60 mg to that of dapoxetine 30 mg.

At Week 24 in the E.U. efficacy and safety study (R096769-PRE-3001), the statistical significance of the effect for dapoxetine 60 mg compared to dapoxetine 30 mg for the key efficacy parameters of median average IELT, the composite endpoint, and the subject-rated CGIC measure thresholds of at least "better" and at least "slightly better" can be observed in Table 1.

Table 1: Dapoxetine 30 mg versus 60 mg Treatment Comparisons: R096769-PRE-3001 Summary at Endpoint (TRT WK 24)

(Dapoxetine - SCE: ITT Analysis Set)

	Diff-30mg-vs-60mg	---95%-CI---	P-value
Mean Average IELT(Minutes)	0.4	-0.12, 1	0.1226
Median Average IELT (Minutes)	0.43	0.17, 0.69	0.0010
Composite Endpoint (C2D1) (%)	11.8	5.01, 18.52	0.0011
CGIC at Least Slightly Better (%)	14.8	7.86, 21.7	<0.0001
CGIC at Least Better (%)	8.6	1.58, 15.55	0.0253

C2D1=Control +2/Distress -1; CGIC=Clinical Global Impression of Change; CI=confidence interval; Diff=difference; IELT=intravaginal ejaculatory latency time; ITT=intent-to-treat; SCE=Summary of Clinical Efficacy; TRT WK=treatment week

In the analyses of the pooled Phase III study data, the statistical significance of the effect for dapoxetine 60 mg compared to dapoxetine 30 mg for the key efficacy parameters of mean average IELT, median average IELT, and both subject-rated CGIC measure thresholds of at least "better" and at least "slightly better" can be observed in Table 2.

Table 2: Dapoxetine 30 mg versus 60 mg Treatment Comparisons: Pooled Phase 3 Studies at Endpoint (TRT WK12)

(Dapoxetine - SCE: ITT Analysis Set)

	Diff-30mg-vs-60mg	---95%-CI---	P-value
Mean Average IELT (Minutes)	0.5	0.24, 0.72	<0.0001
Median Average IELT (Minutes)	0.28	0.16, 0.40	<0.0001
Composite Endpoint (C2D1) (%)	4.7	-0.22, 9.71	0.0676
CGIC at Least Slightly Better (%)	9.4	5.97, 12.74	<0.0001
CGIC at Least Better (%)	7.6	4.17, 11.01	<0.0001

C2D1=Control +2/Distress -1; CGIC=Clinical Global Impression of Change; CI=confidence interval; Diff=difference; IELT=intravaginal ejaculatory latency time; ITT=intent-to-treat; SCE=Summary of Clinical Efficacy; TRT WK=treatment week
Studies pooled: C-2002-012 C-2002-013 PRE-3001 and PRE-3003

Although the Phase III studies were not intended to detect a statistically significant difference between the 30 mg and 60 mg dose, a dose response was observed in all studies for all endpoints.

Given that IELT data is not expected to be normally distributed, the geometric mean IELT has been proposed as a more appropriate summary statistic than the mean IELT. In the analysis of log-transformed data, the geometric mean average IELT at Week 24 in Study R096769-PRE-3001 was 2.3 minutes for dapoxetine 60 mg and 1.8 minutes for dapoxetine 30 mg ($p<0.001$) (Table 3). Similar results for the geometric mean average IELT at Week 12 were seen in each Phase III study in which IELT was measured.

Table 3: Dapoxetine 30 mg versus 60 mg Treatment Comparisons in Geometric Mean Estimates at Endpoint (LPOCF)

(Dapoxetine - SCE: Intent-to-Treat Analysis Set)

	Baseline Values			Pairwise Comparisons						
	Treatment-Group	N	Geometric Mean (SD)	Reference Group	N	LS Geometric. Mean (SE)	Comparison-Group	N	LS Geometric. Mean (SE)	LS Geometric Mean Ratio (95%CI)	P-value
Week 12 LPOCF											
C-2002-012	DPX 30 MG	388	0.8 (1.95)	DPX 30 MG	390	1.9 (1.04)	DPX 60 MG	364	2.1 (1.04)	1.1 (1.01, 1.26)	0.0309
	DPX 60 MG	362	0.8 (1.92)								
C-2002-013	DPX 30 MG	410	0.8 (1.97)	DPX 30 MG	411	1.8 (1.04)	DPX 60 MG	398	2.3 (1.05)	1.3 (1.12, 1.4)	<0.0001
	DPX 60 MG	397	0.8 (1.95)								
PRE-3001	DPX 30 MG	359	0.7 (2.16)	DPX 30 MG	359	1.9 (1.05)	DPX 60 MG	354	2.2 (1.05)	1.2 (1.05, 1.36)	0.0056
	DPX 60 MG	352	0.7 (2.29)								
PRE-3003	DPX 30 MG	332	1 (1.77)	DPX 30 MG	331	2.5 (1.05)	DPX 60 MG	329	2.9 (1.05)	1.2 (1.04, 1.3)	0.0106
	DPX 60 MG	330	0.9 (1.93)								
Pooled	DPX 30 MG	1489	0.8 (1.98)	DPX 30 MG	1491	2 (1.02)	DPX 60 MG	1445	2.4 (1.02)	1.2 (1.12, 1.26)	<0.0001
	DPX 60 MG	1441	0.8 (2.04)								
Week 24 LPOCF											
PRE-3001	DPX 30 MG	359	0.7 (2.16)	DPX 30 MG	357	1.8 (1.05)	DPX 60 MG	353	2.3 (1.05)	1.3 (1.14, 1.48)	<0.0001
	DPX 60 MG	352	0.7 (2.29)								

CI=confidence interval; DPX=dapoxetine; LPOCF=last postbaseline observation carried forward; LS=least squares; N=number; SCE=Summary of Clinical Efficacy; SD=standard deviation; SE=standard error

Note: Only the positive Average intravaginal ejaculatory latency time (IELT) values can be used for the log-transformed Average IELT data.

Note: Analysis results based on the analysis of covariance (ANCOVA) model on log-transformed Average IELT data with the factors: treatment group, pooled center (or study), baseline Average IELT strata, and log-transformed baseline Average IELT as a covariate.

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Sensitivity analyses: Sensitivity analyses were conducted for the key efficacy variables, each representing more conservative assumptions than the originally planned analyses, which included the intent-to-treat (ITT) population with last postbaseline observation carried forward (LPOCF). All analyses for all endpoints confirmed the treatment benefit of dapoxetine when subjects who discontinued early, had no postbaseline data, or had no postbaseline data at Week 9-12 were considered as non-responders. Those analyses assume that all subjects with missing data, irrespective of the reason for discontinuation, experienced no benefit from treatment with dapoxetine.

On the basis of the available data the CHMP concluded that patients receiving Priligy 30 mg and 60 mg showed statistically significant response over patients receiving placebo.

Concerns were raised with regard to the added benefit of the 60 mg strength compared to the 30 mg strength.

The most important study for the European target population (R096769-PRE-3001) failed to demonstrate statistical significance for the primary endpoint (mean average IELT) in the comparison of the 30 and 60 mg doses. However the median and the geometric mean are more appropriate measures of central tendency for IELT, and for these endpoints highly significant differences between 30 and 60 mg were obtained. More important, there are statistically significantly more responders to 60 mg in different responder analyses, including the primary responder analyses.

In the pooled analyses of all Phase III studies significant differences in favour of the 60 mg doses compared to 30 mg were observed for median average IELT, and two out of three PRO measures i.e.

composite endpoint (C2D1) and CGIC at least "slightly better". This difference was not noted for mean average IELT.

Thus, although a statistically significant result was not observed in every analysis it must be concluded from the overall pattern that a statistically significant efficacy difference between 30 and 60 mg has been established.

It can also be concluded that up to about 10% more patients responds to 60 mg compared to 30 mg.

It was concluded that Priligy 30 mg shows greater efficacy versus placebo. Regarding the 60 mg strength a more or less pronounced dose-response is observed in all analyses. A statistically significant efficacy difference in favour of 60 mg compared to 30 mg has been established. On the average the effects appears modest. However, in different responder analyses there is a consistent pattern of $\geq$12% more responders on 30 mg compared to placebo and an additional 5-10% more responders on 60 mg. It is acknowledged that these results are conservative estimates obtained with the Baseline Observation Carried Forward (BOCF) approach for imputation of missing values, i. e. subjects discontinuing prior to end of study are counted as non-responders.

- **Safety issues**

The objecting Member States pointed out that the increase in response noted for the 60mg strength compared to the 30 mg strength in the clinical studies is counteracted by the dose related increase in adverse events, especially the occurrence of syncope associated with loss of consciousness, bradycardia and asystole.

The majority of adverse events reported in Phase III clinical studies, (including nausea, diarrhoea, dizziness, headache, insomnia, and fatigue, which are typical of the SSRI class of drugs), were generally acute symptomatic events that were typically self-limited, mild or moderate in severity, brief in duration, and temporally related to dosing.

Of the most commonly reported dose-dependent adverse events, more than half were reported within the first 4 weeks of the double-blind treatment period of the Phase III studies, and as early as the first dose, and emerged and resolved in a predictable timeframe around the time of anticipated C_{max} of dapoxetine (Table 4).

Table 4: Treatment-Emergent Adverse Events (≥2%) With Onset Days Within 4 Weeks on the Study in Phase III Placebo-Controlled Studies (Dapoxetine SCS: Intent-to-Treat Analysis Set)

System Organ Class Preferred Term	PLACEBO (N=1857) n (%)[a]	DPX 30 MG PRN (N=1616) n (%)[a]	DPX 60 MG PRN (N=2106) n (%)[a]	DPX 60 MG QD (N=502) n (%)[a]	Total DPX (N=4224) n (%)[a]
Total number of subjects with adverse events	**342 (18.4)**	**487 (30.1)**	**987 (46.9)**	**276 (55.0)**	**1750 (41.4)**
Gastrointestinal disorders	**70 (3.8)**	**205 (12.7)**	**541 (25.7)**	**124 (24.7)**	**870 (20.6)**
Nausea	21 (1.1)	130 (8.0)	371 (17.6)	72 (14.3)	573 (13.6)
Diarrhoea	16 (0.9)	40 (2.5)	104 (4.9)	32 (6.4)	176 (4.2)
Dry mouth	7 (0.4)	16 (1.0)	45 (2.1)	12 (2.4)	73 (1.7)
Nervous system disorders	**95 (5.1)**	**178 (11.0)**	**391 (18.6)**	**99 (19.7)**	**668 (15.8)**
Dizziness	28 (1.5)	69 (4.3)	188 (8.9)	55 (11.0)	312 (7.4)
Headache	45 (2.4)	58 (3.6)	124 (5.9)	32 (6.4)	214 (5.1)
Somnolence	7 (0.4)	39 (2.4)	76 (3.6)	13 (2.6)	128 (3.0)
Psychiatric disorders	**31 (1.7)**	**54 (3.3)**	**144 (6.8)**	**56 (11.2)**	**254 (6.0)**
Insomnia	11 (0.6)	20 (1.2)	55 (2.6)	25 (5.0)	100 (2.4)
General disorders and administration site conditions	**26 (1.4)**	**51 (3.2)**	**102 (4.8)**	**48 (9.6)**	**201 (4.8)**
Fatigue	13 (0.7)	21 (1.3)	56 (2.7)	29 (5.8)	106 (2.5)
Vascular disorders	**21 (1.1)**	**21 (1.3)**	**58 (2.8)**	**36 (7.2)**	**115 (2.7)**
Orthostatic hypotension	10 (0.5)	6 (0.4)	23 (1.1)	24 (4.8)	53 (1.3)

DPX=dapoxetine; N/n=number; PRN=as needed; QD=daily; SCS=Summary of Clinical Safety

[a] Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Studies included: C-2002-012, C-2002-013, R096769-PRE-3001, -PRE-3002, and -PRE-3003.

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Cross reference: SCS, Table 22. Refer to Part II for a complete copy of the SCS.

Of the 6,081 subjects randomly assigned to treatment in the Phase III studies, 41 subjects reported serious adverse events (25 subjects were treated with dapoxetine, 16 subjects received placebo). For these serious adverse events no imbalance between the 30 mg and 60-mg doses of dapoxetine relative to placebo was obsereved: placebo, 0.9%; dapoxetine 30 mg p.r.n., 0.6%; and dapoxetine 60 mg p.r.n., 0.5%).

SSRI class-related adverse effects were not apparent with dapoxetine treatment when evaluated with specific instruments in studies that assessed treatment with dapoxetine 60 mg p.r.n. and 60 mg q.d. for up to 24 and 9 weeks, respectively. These include many of the safety concerns associated with marketed antidepressant SSRIs, such as treatment-emergent suicidality, clinically important mood-related adverse events (including depression and anxiety), akathisia, SSRI discontinuation syndrome, and sexual function adverse effects, which were measured using broadly accepted and validated rating scales, including the Montgomery-Asberg Depression Rating Scale (MADRS) and Beck Depression Inventory-II (BDI-II) (mood), Hamilton Anxiety Scale (HAM-A) (anxiety), Barnes Akathisia Scale (BARS) (akathisia), discontinuation-emergent signs and symptoms (DESS) (withdrawal syndrome), and International Index of Erectile Function (IIEF) (sexual function effects) and methods (Columbia Classification Algorithm of Suicide Assessment [C-CASA] for suicidality).

Syncope

During the Phase III studies of dapoxetine, Holter monitoring detected bradycardia and asystole (including 1 case of 28-second asystole) associated with the occurrence of syncope. These findings suggest that syncope associated with the administration of dapoxetine is vasovagal in etiology. Vasovagal syncope represents a transient, self-limited loss of consciousness, from which subsequent recovery is spontaneous, complete, and usually prompt, without reported serious associated injury. Typical syncope episodes are brief and usually last no longer than 20 seconds. Of the adverse events coding to the MedDRA preferred terms of "syncope" or "syncope vasovagal" (i.e., cases of interest)

reported across the dapoxetine clinical development program, 7 subjects were wearing a Holter monitor at the time of the syncopal event. Ventricular tachycardia (VT) or other serious dysrhythmias were not observed in any of these 7 subjects during the events.

A total of 30 syncope cases (cases of interest) were observed during the clinical studies. Half of them were considered as medically confirmed (adjudicated syncope).

All events of syncope observed in the Phase III clinical development program summarized in the MAA occurred before implementation of activities intended to minimize the occurrence of syncope, including the administration of patient instructions and the exclusion of orthostatic manoeuvres from the study designs, suggesting that syncope could be managed through patient and clinician instruction/education. After the sponsor implemented risk minimization measures during the course of the two then-ongoing Phase III studies (R096769-PRE-3001 and R096769-PRE-3003), no further episodes of syncope were reported in those studies. Some of the required procedures in the dapoxetine clinical development program (e.g., venipuncture and orthostatic challenge) that may have contributed to the occurrence of syncope are not expected in routine clinical practice. It was also noted that the Phase III studies utilized a fixed-dose design, in which subjects who were randomly assigned to treatment with dapoxetine 60 mg were initiated on a 60-mg dose rather than the 30-mg dose, which is recommended in the Summary of Product Characteristics (SmPC). Therefore, unlike the post-approval setting where all patients initiate treatment with the 30-mg dose of dapoxetine, subjects enrolled into the Phase III studies did not experience the effect of the lower dose first, with the option to increase to the higher dose only if the lower dose was well tolerated. The dose-titration recommendation in the SmPC is intended to mitigate the risk to those patients who are exposed to the 60 mg dose of dapoxetine and thereby reduce the possibility that a patient may experience more severe adverse events, including syncope, in routine clinical practice.

Syncope occurrence during Post-authorisation

Evidence on the safety profile of Priligy in clinical practice is available from 2 complementary data sources, including

- spontaneously reported adverse events summarized in 5 Periodic Safety Update Reports (PSURs) from 17 December 2008 to 17 June 2011, and
- data from a large post-marketing safety surveillance study (R096769-PRE-4001).

Nine events of syncope were reported in the post-approval setting. Four of these events were associated with the 30 mg dose and the other five were associated with the 60 mg dose. They are all included in the 5 PSURs mentioned above. Five of these events were medically confirmed and four events were unconfirmed. These events were transient in nature and resolved spontaneously, without any reported accidental injury or long-term sequelae. The 9 events occurred in the context of an estimated exposure between 1,967,483 and 3,934,965 treatment courses, representing an estimated 850,000 patients exposed from the time that Priligy became commercially available until 17 June 2011. No event of syncope has been spontaneously reported in association with the administration of Priligy since February 2011.

In the post-marketing safety surveillance study (R096769-PRE-4001) 4,002 patients have been treated with Priligy and 1,696 patients have been treated with an alternate form of treatment (669 of which were treated with oral medication) for PE as of the data cut-off of 30 June 2011, representing data collected over approximately 24 months since regulatory approval through the Decentralized Procedure (DCP). Data from this study substantiate that the majority of patients are initiated on dapoxetine at

the 30 mg dose, as recommended in the SmPC. The severity of the adverse events has generally been reported as mild or perhaps moderate, resulting in limited discontinuation from the study by patients.

Seventeen patients in the study have reported a serious adverse event (11 patients taking Priligy, 6 patients taking alternate care/non Priligy), all of which were considered to be "not related to treatment" by the treating health care provider.

In this study, no events of "syncope" or "syncope vasovagal" have been reported in any patient prescribed with Priligy. Syncope has been reported in 1 patient taking alternate care/non-Priligy treatment.

Patients who were prescribed with Priligy in study R096769-PRE-4001 were given a survey at the last observational visit to provide feedback on the understandability and helpfulness of the Priligy Patient Brochure and/or Patient Information Leaflet (PIL). Based on data collected to date, responses to the survey questions indicated that the majority (>98%) of patients who received the Patient Brochure and PIL understood the content and felt that the information regarding Priligy dosing, Priligy safety, and PE was adequate.

The CHMP having reviewed the above available data on safety noted the following:

After occurrence of infrequent cases of syncope in the early phases of the clinical development program Holter monitoring was introduced in the phase III program. A total of 30 syncope cases (cases of interest) were observed during the clinical studies. Half of them were considered as medically confirmed (adjudicated syncope). Of these the strict medical definition requiring loss of consciousness was fulfilled for 8 cases, including one case with sinus arrest (with an associated 28-second period of asystole). It should be noted that 3 of the 6 cases of syncope with loss of consciousness on 60 mg occurred in Study R096769-PRE-3002 in which all subjects underwent orthostatic manoeuvres, and comparing only 60 mg and placebo randomised in a 4:1 ratio, potentially introducing a bias against the 60 mg dose.

Nine spontaneously reported events of syncope in the post-approval setting are included in the PSURs summarizing safety from 17 December 2008 to 17 June 2011, of which 5 events are medically confirmed and 4 events are unconfirmed. Each of these events was transient in nature and resolved spontaneously, without any reported accidental injury or long-term sequelae. The 9 events occurred in the context of an estimated exposure between 1,967,483 and 3,934,965 treatment courses, representing an estimated 850,000 patients exposed from the time that Priligy became commercially available to 17 June 2011.

The available evidence shows that the risk minimisation measures put in place have been effective in the management of syncope events:

- Some of the risk minimisation measures (e.g. patient instructions, exclusion of orthostatic manoeuvres) were introduced already during the course of Phase III program with no further episodes of syncope reported in the clinical program following that.
- Against a background of a post-marketing exposure estimated to 850,000 patients only 9 events of syncope have been spontaneously reported, 5 of which are medically confirmed and 4 of which are unconfirmed. All of these events were of short duration and spontaneously resolved.
- Interim data (4,002 patients treated with Priligy) from the observational post-marketing safety study (R096769-PRE-4001) show:
  - No events of syncope have been reported.
  - 92% of patients were prescribed treatment according to the SmPC, i.e. initiation of treatment with 30 mg.
  - More than 98% of the patients prescribed Priligy found that the Patient Brochure and PIL were understandable, and felt that the information regarding Priligy dosing and Priligy safety was helpful.

Overall discussion and benefit / risk assessment

Regarding efficacy on the basis of the available data the CHMP concluded that patients receiving Priligy 30 mg and 60 mg showed statistically significant response over patients receiving placebo. With regard to the added benefits of the 60mg strength, the mean (or median) difference in IELT between the 30 and 60 mg dose appears marginal. However, in conservative responder analyses based on IELT data as well as on patient and partner reported outcome measures an additional 5-10% responders to 60 mg compared to 30 mg.

Regarding safety the main events reported during clinical trials were nausea, diarrhoea, dizziness, headache, insomnia, and fatigue, which are typical of the SSRI class of drugs. The main safety concern was related to the occurrence of syncope in particular for the 60mg strength. However, the initially observed excess risk for syncope with the 60 mg was found manageable with the risk minimisation measures introduced during the phase III program. With additional wording in the Product Information it was concluded and agreed in the initial decentralised procedure that benefit-risk was positive for the 60 mg dose. This conclusion has been further strengthen with no cases of syncope in the post-marketing safety study and an estimated post-marketing exposure of 850,000 patients with only 5 medically confirmed spontaneous reports of syncope, all of short duration and spontaneously resolved.

In conclusion, a non-negligible improvement can be achieved with 60 mg for some patients with insufficient response to 30 mg. The potentially increased risk for syncope has been proven manageable with the risk minimization measures put in place. Therefore, the CHMP concluded that the benefit-risk of Priligy 30 mg and 60 mg is considered positive.

Grounds for positive opinion and amendment of the labelling and package leaflet

- The Committee considered the notification of the referral triggered by Sweden under Article 29(4) of Council Directive 2001/83/EC.
- The Committee reviewed all available data submitted by the marketing authorisation holder, in particular to support the efficacy of Priligy 60 mg film-coated tablets versus Priligy 30 mg film-coated tablets.

- The Committee reviewed all available data submitted by the marketing authorisation holder on the safety of Priligy in particular for the 60 mg film-coated tablets and the reported cases of syncope.
- The Committee considered that a non-negligible improvement can be achieved with the 60 mg strength for some patients with insufficient response to the 30 mg strength and that the potentially increased risk for syncope has been proven manageable with the adequate risk minimization measures.

Therefore, the CHMP was of the opinion that the benefit/risk ratio of Priligy 30 mg and 60 mg film-coated tablets is considered to be favourable.

The CHMP issued a positive opinion recommending the granting of the marketing authorisation for Priligy 30mg and 60 mg film-coated tablets for which the summary of product characteristics remains as per the final version achieved during the Coordination group procedure. The amended labelling and package leaflet of the reference Member State are set out in Annex III.