Despite the fact that duloxetine is not renally eliminated, there was a substantial effect on duloxetine pharmacokinetics with a doubled exposure of duloxetine and a 2 to 9-fold increase for the two major metabolites.
Based on these considerations no dose adjustment is necessary for patients with mild or moderate renal dysfunction, and as such that is noted in the SPC.
Age: pharmacokinetic differences have been identified between younger and elderly females (≥65 years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose.
Gender: gender has an effect on the pharmacokinetics of duloxetine, with females having approximately twice as high exposure compared with males. However, many pharmacokinetic studies were performed in males and the results may, thus, not be immediately extrapolated to females. It is agreed that the isoenzymes involved in the metabolism of duloxetine, i.e. CYPs 1A2 and 2D6 are not *sex-specific*. Bearing this in mind, it cannot be excluded that a different effect of duloxetine on a CYP1A2 substrate would be observed in females as compared to males. A study investigating the effect of duloxetine on the pharmacokinetics of a CYP1A2 substrate, e.g. theophylline, is to be performed also in females.

- Interaction studies

In vitro data show that CYP2D6 has been shown to be non-inducible and that duloxetine may inhibit CYP3A, CYP1A2, or CYP2C9 at concentrations substantially higher than those anticipated in the clinical setting. It is unlikely that enzyme induction would occur clinically.
In vivo drug-drug interaction studies have been carried out with CYP2D6 substrates (desipramine and tolterodine), CYP2D6 inhibitors (paroxetine), CYP1A2 substrates (theophylline), CYP1A2 inhibitors (fluvoxamine), and other drugs and substances likely to be co-administered with duloxetine (lorazepam, temazepam, ethanol and antacids). Duloxetine has shown to be a moderate CYP2D6 inhibitor (3-fold increase in the overall exposure to desipramine and 2-fold increase to tolterodine). Similarly, paroxetine (CYP2D6 inhibitor) increases duloxetine overall exposure by 60 %. Fluvoxamine, a potent CYP1A2 inhibitor, increases the exposure of duloxetine (more than 5-fold)No significant interactions with benzodiazepines and antacids have been found. The SPC clearly reflect these findings.
Additional data for CYP2C19 was submitted for this application. It is agreed that these isoforms represent a small part of the metabolism of commonly prescribed drug. However, CYP2C8 is an isoenzyme that has recently gained more interest because of the occurrence of clinically important interactions due to inhibition of this enzyme, e.g. by gemfibrozil. An *in vitro* study investigating the effect of duloxetine on the metabolism of a CYP2C8 substrate is to be performed.

- Conclusion on human pharmacokinetics

Duloxetine is a drug with highly variable pharmacokinetics and many factors affect the systemic exposure. From the presented data, gender, age, renal and hepatic function, smoking status, CYP2D6 status and drug-drug interactions are all factors affecting the plasma levels of duloxetine. Interindividual differences in plasma concentrations of α1-acid glycoprotein (AAGP) may also contribute to the variability.
Based on the large inter-individual pharmacokinetic variability and the frequency of adverse events, the most common reason for discontinuation of treatment in clinical studies, the possibility to reduce the dose to 20 mg b.i.d. after 4 weeks in case of troublesome adverse events has been introduced.

Pharmacodynamics

Six studies were designed to evaluate pharmacodynamics in healthy volunteers. Four of them were aimed to assess pharmacodynamic effects and safety during treatment with increasing doses of duloxetine and the other two evaluated pharmacodynamic interactions with ethanol and lorazepam.
In addition the results of Study SBAB assessing the biomechanical effects of 80-mg dose of duloxetine for four weeks versus placebo on bladder and urethral function, was used to elucidate the mechanism of action.

- Mechanism of action

In vitro, duloxetine is a potent inhibitor of both 5-HT and NE reuptake and a relatively weak inhibitor of dopamine reuptake. Duloxetine has a low affinity for muscarinic acetylcholine, histamine-1, α -1-NE, 5-HT_{1A} , 5-HT_{1B}, 5HT_{1D}, D_2 and opioid receptors. The molecule was active in urinary models indicative of enhancement of serotonin and norepinephrine neurotransmision with improvement of capacity of the urinary bladder and increased urinary sphincter activity. Indirect evidence of similar activity in humans has been obtained. Changes in whole-blood 5-HT concentration following chronic administration of 20-mg or larger daily doses of duloxetine suggest that duloxetine interferes with 5-HT reuptake in humans. Measurement of 48-hour urinary excretion of NE and its metabolites showed that regimens of duloxetine 80 mg once daily or duloxetine 60 mg twice daily were associated with a significant decrease in whole body NE turnover.

Study SBAB assessed the biomechanical effects of 80-mg dose of duloxetine for four weeks versus placebo on bladder and urethral function. Sixty-five (65) women with pure genuine stress incontinence were enrolled in the study. However, only 10 patients on Ariclaim and 11 on placebo were possible to evaluate. After four weeks duloxetine-treated patients experienced a significantly greater median percent reduction of IEF than placebo patients (57.2% compared with 26.3%, p = .024) . However, the decrease in the absolute number of episodes per week was not statistically significant (mean of 11.8 with duloxetine compared with 9.1 with placebo).

Urethral function during the filling phase of the micturition and bladder function and sphincter resistance during emptying phase was measured. Although women exhibited a severe urinary incontinence (mean baseline > 21 episodes/week) and pharmacodynamic changes could be expected in a more clear way than in a less severe population, noneof the pre-specified analyses comparing duloxetine with placebo revealed statistically significant differences for any of the five biomechanical measures of urethral function measured in the study. Post-hoc analysis of Valsalva leak-point pressure data and an examination of quantitative striated sphincter electromyographic data in the small number of subjects who completed this study did provide some limited evidence to the view that duloxetine to some degree exerts an effect on the urethra.

The data provided by the Study SBAB assessing the biomechanical effects of 80-mg dose of duloxetine do not allow valid conclusions regarding its mechanism of action. This is reflected in the SPC. The unreliability of the PD data does not necessarily preclude a positive benefit/risk conclusion, but this would mostly depend on pure efficacy and safety data. However, a proper knowledge of the mechanism of action of a drug intended for chronic use and with other potential therapeutic indications is considered relevant. Therefore, the Applicant is to perform additional studies in order to further elucidate the mechanism of action of duloxetine in patients with SUI. This is a relevant issue, mainly due to the novel mechanism of action attributed to duloxetine without any other product of reference available for this condition at present.

- Primary and Secondary pharmacology

In the first human study with duloxetine (Study HMAA), a 90% inhibition of ex vivo platelet serotonin uptake was found 2 to 3 hours after the 60-mg doses of up to 60 mg of an immediate-release formulation of duloxetine.
In Study HMAB, 6 subjects received single doses up to 80 mg. Inhibition of ex vivo platelet serotonin uptake were found with all doses tested. Eight hours after dosing, 10 mg produced 35% to 61% inhibition, 20 mg produced 49% to 75% inhibition, 40 mg produced 64% to 92% inhibition, 60 mg produced 70% to 88% inhibition, and 80 mg produced 84% to 92% inhibition.
Other studies aimed to demonstrate significant increase in bladder capacity when comparing doloxetine with placebo. Increase in urethral closure preassures was also evaluated in the same manner. The different founded however was not statistically significant, an the magnitude of such effects is of uncertain relevance when trying to predict a relevant therapeutic effect.

Potential secondary pharmacologic reactions of duloxetine at the clinical dose were noted in the anaesthetised dog model and included increases in pulmonary pressure, pulmonary vascular resistance, and respiratory rate. These effects are attributable to the known actions of norepinephrine and

serotonin and are not likely to pose a clinical risk. There were also no substantive cardiovascular liabilities identified.
As other drugs that inhibit monoamine reuptake, duloxetine significantly increases systolic and diastolic blood pressure (less than 2 mmHg) and heart rate (2 to 3 beats per minute). This can be considered as a class effect and no major safety concern seems to derive from this observation. The effects of duloxetine on QT interval have been assessed in about 160 subjects. There is no signal indicating that duloxetine might prolong the QT interval regardless of the correction method used.

Clinical efficacy

The clinical program was developed to assess the efficacy and safety of Duloxetine in female patients with SUI. One Phase II study (study SAAW) and three Phase III studies (studies SBAT, SBAV and SBAX) were conducted. In addition, Phase III studies were extended evaluating safety with long-term exposure to form studies SBAU, SBAW and SBBM respectively. Study SBAY is a stand alone open-label safety study. These studies are summarised in the following table.

Study # (Country)	Phase	Design	Treatment Groups	Duration of Treatment	Number Of Patients			
					Safety	IEF	I-QOL	PGI-I
(USA)	II	ra, db, pc, fd, pg, mc	Placebo D 20 mg D 40 mg D 80 mg	12 weeks	138 138 137 140	96 % 88 %	96% 93%	96% 93%
(USA, Canada)	III	ra, db, pc, fd, pg, mc, str	Placebo D 80 mg.	12 weeks	247 247	98 % 86 %	99% 97%	98% 97%
(USA, Canada)	III	ra, db, pc, fd, pg, mc, str	Placebo D 80 mg	12 weeks	339 344	95 % 83 %	98% 97%	98% 97%
(Australia, USA, SAf, SAm, EU)	III	ra, db, pc, fd, pg, mc, str	Placebo D 80 mg	12 weeks	231 227	99 % 88 %	99% 97%	99% 97%
(EU, Canada)	III	nr, o, nc, fd, mc	D 80 mg	Ongoing	363 [a]			
(USA, Canada)	III	nr, o, nc, fd, mc	D 80 mg	Ongoing	493[a]			

Study # Country)	Phase	Design	Treatment Groups	Duration of Treatment	Number Of Patients			
					Safety	IEF	I-QOL	PGI-I
(Australia, SAf, SAm, EU)	III	nr, o, nc, fd, mc	D 80 mg	Ongoing	334 [a]			
(USA)	III	nr, o, nc, fd, mc	D 80 mg	Ongoing	662 [a]			

db: double-blind; fd: fixed dose; mc: multi-centre; nc: non-controlled; o. open, pc: placebo-controlled; pg: parallel group; ra: randomised; nr: not randomised; str: stratified; SAf: South Africa, SAm: South America; EU: Europe; D: Duloxetine; ITT: intent-to-treat; a: As of 14 June 2002

An overall total of 2850 patients were included in the above referenced program (SAAW + SBAT + SBAV + SBAX + SBAY) and constitute the efficacy population for this indication. Of those, 1913 subjects were randomised to duloxetine 40 mg twice daily or placebo in Studies SAAW, SBAT, SBAV, and SBAX(958 to duloxetine and 955 to placebo).

A total of 1190 of the placebo controlled studies patients were included in uncontrolled studies (SBAU + SBAW + SBBM) and treated with Duloxetine.

All clinical studies were performed according to Good Clinical Practice (GCP).

- Dose response study

After an initial study failing to show differences between Duloxetine (20, 30 and 40 mg), the dose finding data package of this dossier is based on one single placebo controlled trial (Study SAAW). Study SAAW was a randomised, parallel, double blind, placebo controlled trial, where 3 doses of Duloxetine (20, 40 and 80 mg) were tested. After a 4-week pre-treatment phase that included a 2-week blinded placebo lead-in, patients were given either placebo or one of the 3 dose levels of Duloxetine (10 mg BID, 20 mg BID or 40 mg BID). The follow-up period on double blind therapy lasted 12 weeks. Patients on Duloxetine 80 mg were dose escalated over two weeks at the initiation of therapy and also de-escalated over two weeks at the end of the 12-week treatment period. As compared with phase III pivotal studies, study SAAW included a population with a slightly lower incontinence episode frequency (IEF) threshold at entry. Study SAAW excluded subjects over 65 years of age and those with prior continence surgery.

The primary efficacy variable was weekly incontinence episode frequency at week 12 based on the ITT population, using the LOCF method. The number of incontinent episodes per 24 hours is a subject-recorded count of the number of incontinent episodes during a 7-day period, obtained from the subject diary. A number of secondary measures were also assessed, including disease-specific tests: cough stress test (CST) and stress pad test (SPT), assessment of the severity of the disease: stress incontinence visual analog scale (SIVAS) and incontinence severity index (ISI), and different measures of QoL and daily life activities. In addition, the Patient Global Impression-Improvement (PGI-I), and the Clinical Global Impression Improvement (CGI-I) at Weeks 4 and 8, and Week 12 were also assessed.

A responder analysis was also carried out for different variables including the main efficacy endpoint. For this purpose, a responder was defined as a patient who had at least a 50% decrease in IEF from baseline to endpoint.

All efficacy evaluations were performed according to an intent-to-treat analysis, defined as patients who were randomized to duloxetine or placebo and who had baseline efficacy data and any post-baseline efficacy data. Questionnaire responses were treated as continuous variables. Analysis of variance (ANOVA) models were used to evaluate continuous efficacy variables. The ANOVA model included terms for treatment, site (as a fixed effect), and treatment-by-site interaction. Pairwise comparisons were analysed with the least squares means (LSMEANS) from the appropriate ANOVA model. Categorical variables were analysed using Pearson's Chi-square tests. All statistical tests were performed as two-sided, at a .050 significance level except where noted. The analysis of covariance (ANCOVA) models was also used to evaluate efficacy on original and transformed scale.

In order to assess prospectively the accuracy of history, examination, simple bladder filling and stress pad test for the diagnosis of genuine stress incontinence (GSI), provocative subtracted electronic cystometry (PSEC) was performed on 90 women at eight sites. This urodynamic test was employed to determine the proportion of subjects in the study population with GSI, as well as identifying a subset of the patients with GSI who have intrinsic sphincteric deficiency (ISD). Urodynamic traces were centrally read.

Five hundred fifty three patients were enrolled to provide power of 80% to detect a 20% difference in the IEF, assuming a placebo response reduction of 30%.

Duloxetine at 40 and 80 mg/day doses was superior to placebo in decreasing the IEF per week. Statistically significant differences were observed for the percent change from baseline to endpoint in IEF per week for the Duloxetine 40 (adjusted p=.049; unadjusted p=.018) and 80-mg/day (unadjusted p=.045) groups as compared to placebo. The adjusted analysis did not show statistically significant differences between Duloxetine 80 mg and placebo (p = .114). Duloxetine at 40 and 80 mg/day doses was also superior to placebo in decreasing IEF per week when all baseline and post-baseline diaries were pooled. The median percent change from baseline to endpoint in IEF per week was 40% for the placebo group, compared with 59% and 58% for the Duloxetine 40 and 80 mg/day groups, respectively. An analysis of PGI-I ratings and I-QOL questionnaire scores revealed a significant improvement only for the duloxetine 80-mg/day group compared with the placebo group.. An analysis of data from subjects who completed the 12-week study did not demonstrate statistically significant differences in the percent change from baseline to endpoint for IEF per week between the placebo group and any of the duloxetine groups.

	Duloxetine 20	**Duloxetine 40**	**Duloxetine 80**	**Placebo**
Randomized N	138	137	140	138
Median IEF change[a]	-44.4% (.625)[b]	-58.6% (.018)[b]	-57.9% (.045)[b]	-40.0%
Median IEF change[c]	-54.0% (.057)[d]	-59.2% (.002)[d]	-63.7% (<.001)[d]	-40.7%
PGI-I rating[e]	31.1% (.440)[f]	36.9% (.185)[f]	43.8% (.004)[f]	27.3%
Mean I-QOL change	+5.3 (.614)[d]	+7.8 (.165)[d]	+9.3 (.026)[d]	+5.8
Mean number voids/day change[c]	-1.0 (.051)[d]	-1.2 (.003)[d]	-1.4 (<.001)[d]	-0.6

[a] Using last visit diary analysis. [b] Significance (p) versus placebo using ANOVA with treatment and site as effects but without controlling for multiple analyses; when controlled for multiple analyses p=.114 for Duloxetine 80 mg.

[c] Using pooled diary analysis. [d] Significance (p) versus placebo using ANOVA with treatment and site as effects.

[e] Percent in "Very Much Better" or "Much Better" categories at endpoint. [f] Significance (p) versus placebo using Cochran-Mantel-Haenszel Test

The responder analysis on the basis of IEF (defined as a reduction ≥ 50% in the number of episodes from baseline) was significantly higher in the Duloxetine 80 mg (60%) group as compared to placebo (47%). 59% of patients on Duloxetine 40 mg were considered as responders (p = .067 vs placebo).

It was considered that, higher plasma concentrations are associated with significantly greater clinical response. Analyses of change in I-QOL scores also demonstrated a significantly greater improvement when the Duloxetine plasma concentrations were higher than the median value (34.8 ng/mL). A significant correlation was observed between Css values and the change in the I-QOL scores (rho = 0.187, p<0.04), indicating that an increase in I-QOL scores is observed when Duloxetine plasma concentrations are higher. A responder analysis for both IEF and I-QOL demonstrated that subjects whose C'ss values were above the median were significantly more likely respond to Duloxetine therapy in terms of both IEF and QoL (defining response as a ≥ 50% decrease in IEF and an increase in I-QOL of at least 30% of the largest possible increase) than those subjects with C'ss value averages below the median. In the applicant's view, the PopPK characteristics of Duloxetine support the conclusion that an individual is more likely to maintain a plasma concentration of Duloxetine above a specific critical threshold if she takes 80 mg/day than if she takes only 20 or 40 mg/day. Further, characteristic values for the half-life (averaging approximately 12 hours) and time to peak concentration (averaging approximately 6 hours) predict that concentrations above this threshold level are more likely to be maintained in the early as well as the late hours of the day when administration is twice daily rather than only once daily.

The safety profile of Duloxetine exhibited in this study is fully consistent with the known safety profile of other agents that inhibit monoamine reuptake. Nausea was the most common AE and was experienced by 13% of women at the 80-mg/day dose. Twelve of 18 women who experienced nausea at the 80-mg/day dose continued medication despite this adverse event. Fatigue, and insomnia were the most clinically relevant dose-dependent AEs; however, these events were not considered to have long-term safety consequences. The Applicant considered that the safety and tolerability of the 40 and 80 mg/day doses are comparable and are not a determining factor for limiting the dose. Based on the overall analysis of the safety and efficacy data, the 80 mg/day dose of Duloxetine was the selected dose for being further assessed.

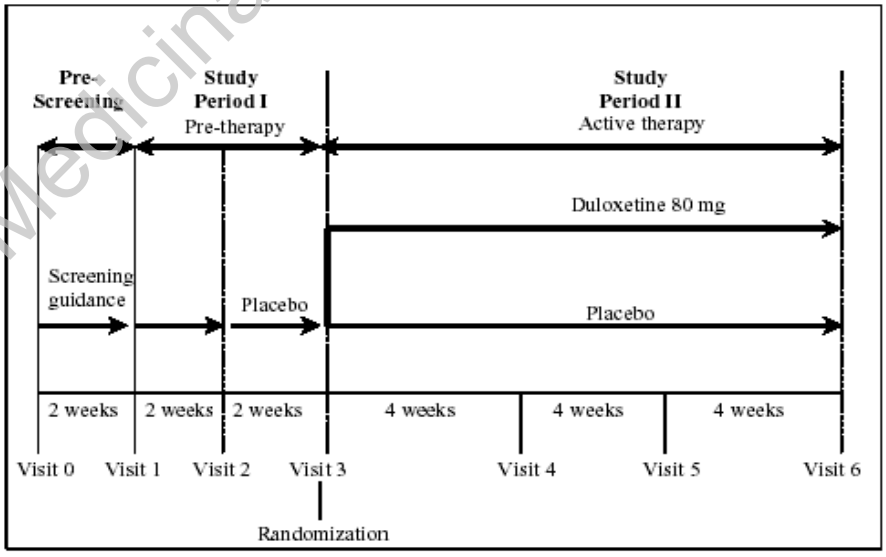
Study SAAW enrolled a slightly different population than one supposed to be the real target population. Thus, as compared with phase III pivotal studies, study SAAW included patients with a lower incontinence episode frequency (IEF) threshold at entry and excluded subjects over 65 years of age. These selection criteria, although should not have a major impact when extrapolating the efficacy results to the intended target population, might have been a relevant conditioning factor for the high placebo response rate observed in this study. The observed placebo response with regard the primary outcome of the study (IEF) was about 40%, when the expected reduction rate was 25%. This fact has resulted in a clearly underpowered study, where the p values for the finally selected dose are just neighbouring the statistical significance threshold.

The observed effect of Duloxetine (40 and 80 mg) on the IEF reduction from baseline is about 60%, which can be considered a modest effect when considering that placebo reduces the IEF by 40%. In addition, and despite of this 20% difference in the percentage o reduction of IEF, when translating this effect into the median absolute number of SUI episodes per week saved for each patient, Duloxetine 80 mg saves just 1 more episode per day than placebo does (D 80 mg from 7 at baseline to 3 at endpoint vs. PBO from 7 at baseline to 4 at endpoint). This and the effects on I-QOL and other subjective outcomes (PGI-I and CGI-I) could be regarded as a marginal effect.

- Main studies

Three studies (Studies SBAT, SBAV, and SBAX) with identical main protocols are the Phase 3 studies that form the basis for efficacy of duloxetine. These studies have the same duloxetine dose (40 mg twice daily), same duration of double blind treatment (12 weeks), and determined subject eligibility based on the same clinical algorithm. Additionally, all three used the same two primary efficacy endpoints and were performed in the target population.

The three studies included 1,635 women with signs of SUI. They were aimed to assess the efficacy of duloxetine 40 mg twice daily versus placebo in the treatment of women with stress urinary incontinence. All of these studies followed a randomised, placebo-controlled, multi-centre, fixed-dose, double blind, parallel-group design, and 12-week comparison study. In all studies, there was a 4-week baseline period with subjects receiving no study drug for two weeks and placebo for last two weeks. After that, patients were randomised to duloxetine 80 mg/day given as 40 mg twice daily (BID) or placebo for 12-weeks.



Methods

Study Participants

All studies enrolled women, 18 years or older, with a stress urinary incontinence of more than 3 months.

Stress urinary incontinence was defined by a clinical algorithm that included a predominant symptom of SUI, with a weekly IEF ≥7, absence of predominant symptoms of urge incontinence, normal diurnal and nocturnal frequencies, a bladder capacity of at least 400 mL, and both a positive cough stress test (CST) and stress pad test (SPT) at a bladder volume of 400 mL.
Studies SBAT, and SBAV had addenda that specified urodynamic testing after randomisation for subjects at some study centres. The primary objective of the addendum was to evaluate the ability of the main study' s inclusion and exclusion criteria to define a population of subjects with urodynamic (genuine) stress incontinence. This algorithm was 83%, and 100% specific for urodynamic stress incontinence in subsets of subjects in Studies SBAV, and SBAT, respectively, and assured that the majority of women in the trials, in fact, had SUI. The individual study reports for those studies, which included urodynamics, document that the algorithm was concordant with urodynamic (genuine) stress incontinence in 83% (Study SBAV), and 100% (Study SBAT) of subjects who had urodynamic testing.
To prevent potential imbalance at baseline in both treatment assignment and incontinence severity, a stratified randomisation was used. At Visit 3, subjects within each site were stratified based on their incontinence episode frequency severity (<14 and ≥14 IEF per week). The calculation of severity was made from all the diary records collected after Visit 1 and prior to Visit 3.
Patients with significant uncontrolled comorbidity, any condition of the genitourinary tract, recent continence surgery within 6 months), the current use of a continence device, or treatment with an antidepressant, drugs for obesity, or a medication for incontinence were excluded. Subjects who were on a stable PFMT program for at least 3 months were enrolled as long as they agreed to continue on their PFMT regimen at the same intensity throughout the study.

Treatments

Duloxetine 80 mg/day, given as 40 mg BID or placebo given BID were administered at fixed doses for 12 weeks (visit 3 to visit 6). Subjects were instructed to take their medication twice daily (morning and evening) at consistent times every day.

Outcomes/endpoints

Primary efficacy parameters

- Incontinence Episode Frequency per week (IEF): The IEF was a subject count of the number of incontinence episodes recorded real-time on paper diaries during a 7-day period.
The first primary efficacy endpoint was the percent change (as computed by [Endpoint – Baseline] / Baseline) in weekly IEF from baseline to endpoint. The diary consisted of seven 24-hour diary records. Only those 24-hour diary records that were deemed to be satisfactory were considered in the efficacy analyses. A satisfactory 24-hour diary record was an account of a calendar date on which the subject recorded the date and time of at least three voids. The 24-hour diary record that had entries on the day of a visit was not considered satisfactory because it could not contain information for a full 24-hour calendar day. At each visit, a single value was produced for each diary variable by taking the mean of all entries from satisfactory diary records (for example, for IEF, mean = total number of incontinence episodes divided by total number of satisfactory diary records) obtained since the previous visit. For IEF, seven to obtain incontinence episode frequency per week multiplied this mean. If less than three satisfactory daily 24-hour diary records were collected, the visit value was considered missing. This way of computing and analyzing the diary variables is referred to as "the last 7-day diary approach."

- Incontinence Quality of Life (I-QOL): The I-QOL is a validated, disease-specific, 22-item, self-administered questionnaire allowing subjects to evaluate in their native language the effects and

concerns relating to urinary incontinence. The 22 items in the I-QOL can be scored as an overall score or as three domain scores: Avoidance and Limiting Behaviour, Social Embarrassment, and Psychosocial Impact. I-QOL scores and subscale scores are standardized to a scale from 0 to 100, with 100 indicating the best possible condition-specific quality of life. Health status and health-related quality of life measures were used in this study to provide detailed information on the impact of urinary incontinence on subjects' day-to-day lives.
The second primary endpopint was the change in I-QOL (as computed by [Endpoint – Baseline]). Changes and percent changes were computed for all randomized subjects with at least one postbaseline and one baseline visit measurement using a last observation carried forward approach.

Secondary efficacy parameters

- Patient Global Impression of Improvement (PGI-I): PGI-I is a validated, single-item treatment outcome questionnaire, measuring a subject's self-perceived improvement since she started taking the study medication. It is measured on a 7-point scale from "Very much better" to "Very much worse".
- Mean Time Between Voids (MTBV): The MTBV is the average voiding interval derived from the same urinary diaries as defined a priori in the statistical analysis plans for the Phase 3 studies.

Sample size

The sample size provided approximately 80% (SBAT, SBAX)-90% (SBAV) power for detecting a treatment difference of 20% in the median percent change in IEF from baseline to endpoint using a two-sided, .05 level van Elteren test.
The sample size also provided approximately 94% (SBAT, SBAX)-98% (SBAV) power for detecting a treatment difference of 3.5 points in the mean change in I-QOL from baseline to endpoint using a two-sided, .05 level t-test, assuming a standard deviation of 9.9.
This calculation assumed that, 10% or fewer of the randomized subjects would drop out without providing any postbaseline measurement.

Randomisation

Randomization was controlled by a computerized voice response system at a central location for all study sites. The investigator called the voice response system at each visit in order to receive instructions for distributing study medication and/or diary data collection.

Blinding

Conventional methods have been used to ascertain blinding of patients and investigators.

Statistical methods

The primary time point for all efficacy variables was the last visit after randomization at which the variable was obtained. For IEF, this was specified "the last 7-day diary analysis" in contrast to a secondary analysis that compared all pre-randomization diaries to all post-randomization diaries, "the pooled diary analysis."
Primary statistical analyses were performed according to intent-to-treat (ITT) principles and included all subjects with a baseline and a postbaseline measurement. A secondary completer analysis was also performed to assess the impact of early discontinuations due to adverse events on the efficacy profile of duloxetine. If adverse events and clinical benefits were linked, including discontinued subjects in the ITT analysis could bias the overall results in favour of duloxetine. Therefore, a comparison of ITT and completer analyses results for important outcome variables was critical to assess this potential bias.

For the three Phase 3 trials, the primary analyses for median percent changes in IEF and mean changes in I-QOL score compared duloxetine 40 mg twice daily with placebo using with the following two models:
- Because the normality assumption was not satisfied (Shapiro-Wilks, □.01), van Elteren test (van Elteren 1960; a type of stratified Wilcoxon test) was used for analysis of percent change in IEF between the last prerandomisation and last postrandomisation visit diaries with baseline incontinence

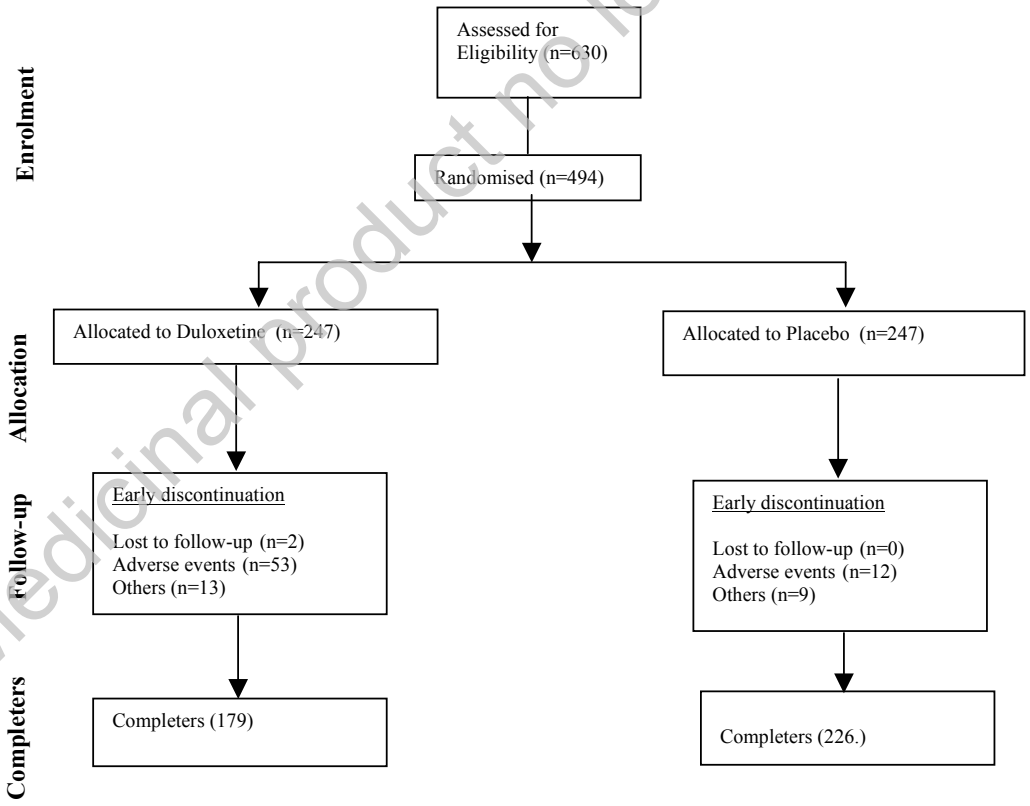
severity strata (<14 and ≥14 IEF per week from Visit 1 to randomisation visit) as the stratification variables.

- Changes in I-QOL total scores were analysed using an analysis of covariance (ANCOVA) model. The dependent variables were the change scores, and the model included terms for baseline scores, treatment, baseline incontinence severity strata, and study.

The van Elteren test was also used to analyse other IEF analyses including absolute change scores and pooled analyses (comparing all prerandomisation to all postrandomisation diaries). ANCOVA was also used to analyse changes in I-QOL subscales and mean time between void. Treatment differences in PGI-I responses were tested using the Cochran-Mantel-Haenszel statistic.
Efficacy was also analysed by grouping subjects into responders and nonresponders based on relative improvement from baseline in IEF and I-QOL. For IEF, a responder was defined a priori as a subject who had at least a 50% decrease from baseline to endpoint. An I-QOL responder was defined a priori as a subject who improved by at least 30% of the greatest possible improvement in score from baseline to endpoint. The validation of the PGI-I scale with I-QOL improvements suggests that the definition is reasonable. In this validation, subjects who rated themselves "A Little Better" had a 6.4-point increase in their I-QOL scores, while those who rated themselves "Much Better" had a 13.0-point increase. These increases are comparable to the 10.8-point increase that would represent 30% of the maximum possible increase in I-QOL score in the overall integrated database
Results

Study SBAT

Participant flow



Recruitment

The recruitment period for study SBAT comprised from December 7 th 2000 to March 4th 2002

Conduct of the study

The studies were conducted according to GCP principles and the ethical principles as stated in the Declaration of Helsinki.

Baseline data

No significant baseline differences between groups in the individual studies were found for IEF, I-QOL, urine loss in Stress Pad Test, Patient Global Impression - Severity, number of micturitions per day, and nocturia.

The groups seem to be representative regarding age, BMI and menopausal status. More than half of the non-menstruating patients used HRT, which is a high figure. The significant difference in age in study SBAT is probably of no clinical importance. The importance of the lower alcohol consumption in the duloxetine groups is difficult to judge. The dominance of Caucasian women limits the possibility to conclude on efficacy in other ethnic groups.

Summary of demographic and other baseline characteristics : % or mean (range)

	SBAT		SBAV		SBAX	
	Placebo	Duloxetine	Placebo	Duloxetine	Placebo	Duloxetine
Age (years)	54 (28-82)	52 * (24-76)	53 (24-83)	52 (23-81)	53 (27-77)	54 (30-79)
BMI	27 (18-47)	27 (18-56)	29 (18-61)	29 (18-76)	28 (18-48)	28 (19-50)
Caucasian	97.6	98.8	90.9	88.7	93.5	95.2
Menstruating	31	34	40	39	34	33
On HRT	33	32	44	45	35	38
On PFMT	19	19	18	17	12	6
Previous surgery	8	8	11	10	16	17
Consuming alcohol	85	77*	60	50 *	66	39
Alcohol Units/week	4 (0-20)	3 (0-20)*	1.9 (0-15)	1.6 (0-18)	1.4 (0-34)	1.4 (0-14)

* difference between groups, $p<0.05$

Numbers analysed

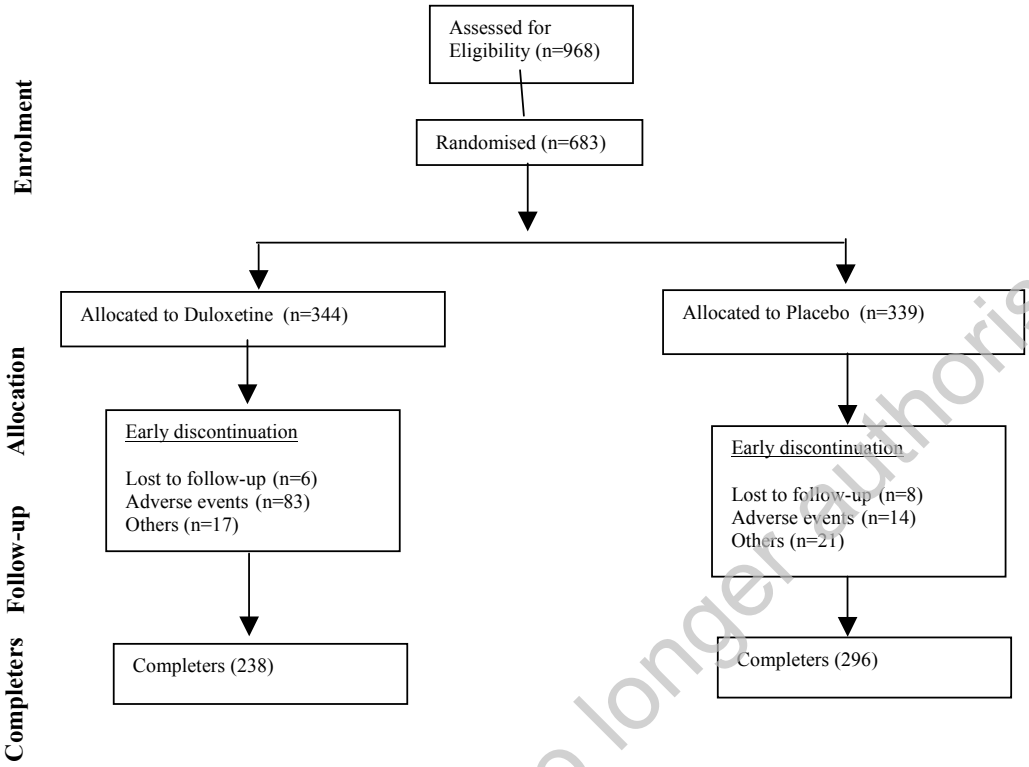
Study SBAT enrolled 494 patients (247 to placebo and 247 to duloxetine), of which, at 12-weeks, 8.5% (21 patients) discontinued in placebo group and 27.5% (68 patients) in duloxetine. Insufficient therapeutic effect led to a premature discontinuation in 0.8% of placebo group and 2.4% in duloxetine. Adverse events led to a premature discontinuation in 4.9% of the placebo group and 21.5% in duloxetine group. For the IEF analysis, 35 subjects were excluded from the duloxetine group and 5 from the placebo group because they had no post-baseline results for IEF. For the I-QOL analysis, 7 subjects were excluded from the duloxetine group and 2 from the placebo group because they had no post-baseline results for I-QOL.

Outcomes and estimation

The primary objective for IEF but not for I-QOL was met. At 12 weeks (primary analysis) Duloxetine was significantly superior to placebo in decreasing the IEF per week (p=.002). The median decrease was 50.0% in the duloxetine group and 29.3% in the placebo group. However, there was no significant difference between duloxetine and placebo in I-QOL score improvements (5.5 vs. 4.1) When the responder rate was analysed significantly more subjects in the duloxetine than in the placebo group were classified as IEF responders (51.9% vs 33.5%) and I-QOL responders (37.1% vs 27.8%)

Study SBAV

Participant flow



Numbers analysed

Study SBAV enrolled 683 subjects randomly assigned to duloxetine 80 mg/day (n = 344), or placebo (n = 339). Considering causes for discontinuation, adverse events led to discontinuation in 4.1% of patients in placebo group, and 24.1% in duloxetine group. Discontinuation due to insufficient therapeutic effect occurred in 2.4% in placebo group and 0.6% in duloxetine. Premature discontinuation was 30.8% in duloxetine placebo group and 12.7% with placebo. For the IEF analysis, there were 608 patients eligible for the ITT population (without taking into account discontinuations) with 322 in the placebo group and 286 in the duloxetine group. For the I-QOL analysis, 11 subjects were excluded from the duloxetine group and 7 from the placebo group.

Outcomes and estimation

Duloxetine was significantly superior to placebo in decreasing the IEF per week (p<.001). The median decrease was 50.0% in the duloxetine group and 27.5% in the placebo group. I-QOL score increases were significantly greater in duloxetine subjects than in placebo subjects, with mean improvements of 11.01 points in the duloxetine group compared with 6.80 points in the placebo group (p<.001). Significantly more subjects in the duloxetine group than in the placebo group were classified as responders by IEF (51.4% vs 33.5%) and I-QOL (47.7% vs. 35.5%) criteria.

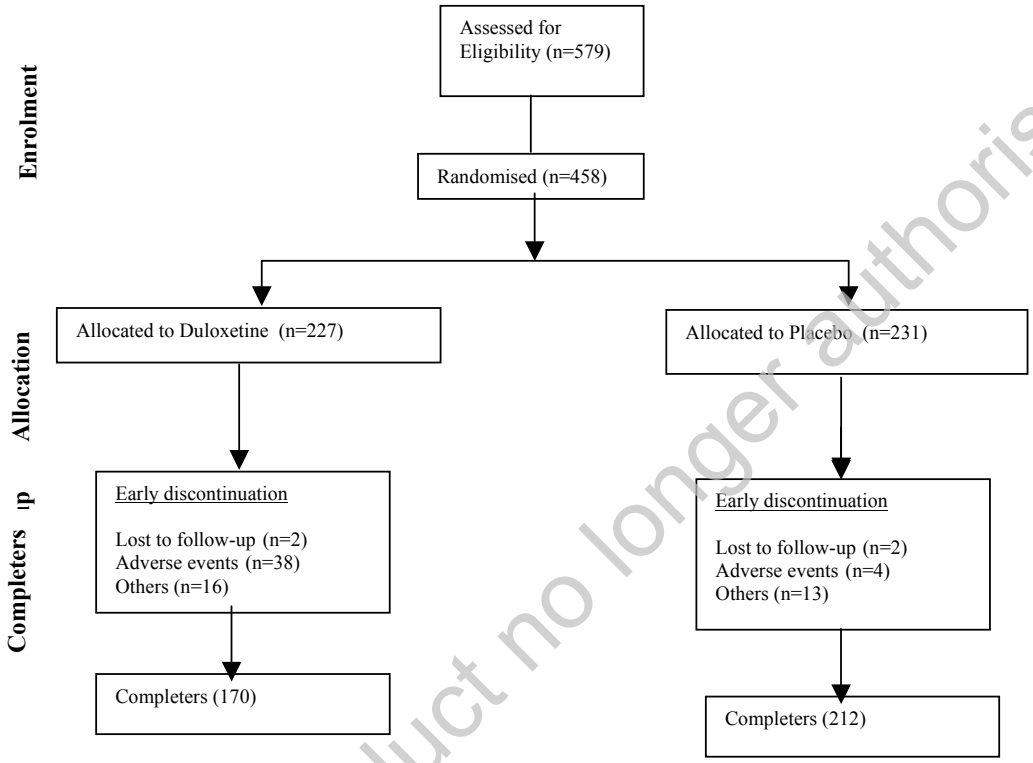
Ancillary analyses

In this study subjects were systematically evaluated for depression according the Beck Depression Inventory–II (BDI-II) at the last baseline visit and at the last treatment visit. Subjects receiving treatment with antidepressants were excluded from the study. Mean BDI-II scores did not differ at baseline between duloxetine- and placebo-treated subjects. Only 23 of 649 (3.5%) subjects had appreciable symptoms of depression based on a BDI-II score of 17 or greater at baseline. This small subset of subjects had somewhat lower I-QOL scores and a somewhat greater number of incontinence episodes at baseline than subjects with lower BDI-II scores. However, the higher BDI-II score

subgroup did not demonstrate neither a significant reduction in median IEF (duloxetine-placebo difference 10.7%, p = .42) nor a significant improvement in total mean I-QOL scores (duloxetine-placebo difference 2.36, p = .69), while the lower BDI-II score subgroup did (duloxetine-placebo difference 22.3%, p< .001 and 4.62, p<.001, respectively).

Study SBAX

Participant flow



Numbers analysed

In study SBAX 458 subjects were enrolled and randomly assigned to duloxetine 80 mg/day (n =227), or placebo (n =231). Of this, at 12-weeks, 8.2% (19 patients) discontinued in placebo group and 26% (56 patients) discontinued in the duloxetine group. While no premature discontinuation was due to lack of efficacy, adverse events led to a premature discontinuation in 1.7% of the placebo group and 17.2% in the duloxetine group. For the IEF analysis, 27 subjects were excluded from the duloxetine group and 2 from the placebo group because they had no postbaseline results. For the I-QOL analysis, 7 subjects were excluded from the duloxetine group and 2 from the placebo group because they had no postbaseline results.

Outcomes and estimation

Duloxetine was superior to placebo in decreasing the IEF per week (p=. 050) using the last 7-day diary approach.. The median decrease was 53.6% in the duloxetine group and 40.0% in the placebo group. I-QOL score increases were significantly greater for subjects taking duloxetine than for subjects taking placebo, with mean improvements of 10.34 points in the duloxetine group compared with 6.42 points in the placebo group (p=. 007).

- Analysis performed across trials (pooled analyses and meta-analysis)

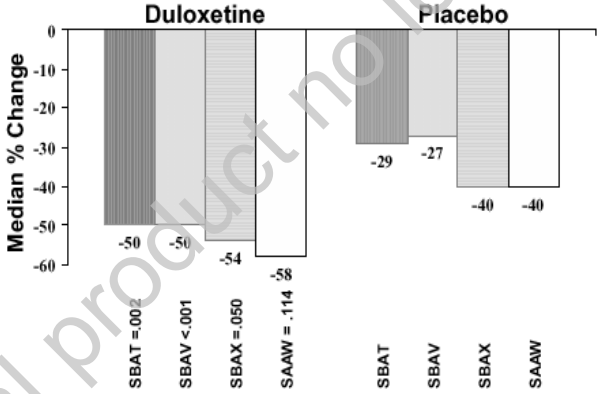
The Applicant has carried out a pooled analysis including data derived from four studies (Studies SBAT, SBAX, SBAV, and SAAW) with the same duloxetine dose (40 mg twice daily) and duration of treatment (12 weeks), and that determined subject eligibility based on the same clinical algorithm (except that that Study SAAW had a slightly lower IEF threshold at entry and excluded women over

age 65 years and those with prior continence surgery). Most of the subjects (except in study SAAW) rated their disease severity as moderate or severe.
A total of 1913 subjects were randomised in Studies SAAW, SBAT, SBAV, and SBAX. Of these subjects, 538 (28.1%) were enrolled in Western Europe, 978 (51.1%) in North America, and 397 (20.8%) in Africa, South America, and Australia.

Condition-Specific Baseline Severity

	Weekly IEF[a]		Total I-QOL score[a]		PGI-S[b]	
Study	Placebo	Duloxetine	Placebo	Duloxetine	Placebo	Duloxetine
SBAV	19.0	18.2	64.3	62.0	66.8	68.4
SBAT	17.2	17.3	64.4	66.6	71.0	69.5
SBAX	18.3	18.5	58.3	58.9	73.1	72.7
SAAW	9.3	10.4	72.8	71.5	41.3	45.3
Meta-analysis	17.0	16.9	64.1	63.8	65.6	66.2

The percent decrease in IEF in the duloxetine 40 mg twice daily group was significantly greater than in the placebo group (duloxetine median 52% [95% confidence interval, 47% to 56%], placebo median 33% [95% confidence interval, 29% to 36%], p<.001) in the ITT analysis. Results on the completer analysis at week 12 are similar to those for the ITT population. There was a greater median decrease in percent change for the duloxetine group at every visit, compared with the placebo group. The following figure shows the results by study.

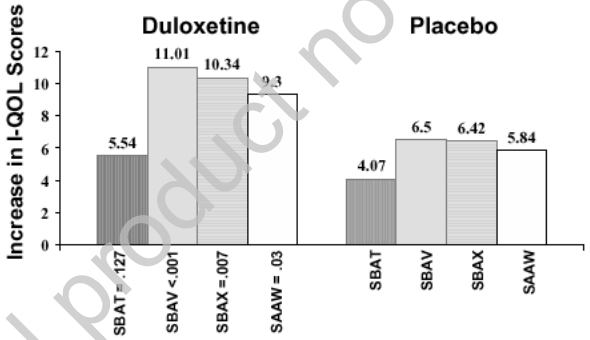


There were significantly more IEF responders (50% or greater reduction in IEF) in the duloxetine group (53%) than in the placebo group (38%, p<.001) and more than twice as many duloxetine subjects than placebo subjects (228 duloxetine, 108 placebo, p<.0001) were responders at every visit after randomisation. While the number of continuing responders decreased at each visit, the majority of initial duloxetine responders (228/448, 51%) were responders at every visit and 73% (327/448) were responders at a minimum of 2 of the 3 visits in the ITT analysis. Overall, 33.4% of duloxetine-treated subjects were classified as responders at every visit.
When the results were analysed by the predefined severity strata for incontinence, there was no significant response for duloxetine compared with placebo among women with IEF <14 per week (i.e. mild SUI) in 1 of the 3 studies (see table below). However, the clinical relevance of the reduction was marginal.

IEF/week, pooled diary approach, by baseline incontinence severity (<14, ≥14)

Study	Baseline IEF	Treatment (n)	Baseline, mean (SD)	Endpoint, mean (SD)	Percent change, median	p-value
SBAT	<14	Placebo (113) Duloxetine (107)	9.6 (2.5) 9.4 (2.5)	6.7 (4.3) 5.8 (4.9)	-33.3-49.3	.036
	≥14	Placebo (129) Duloxetine (106)	27.2 (12.0) 27.5 (11.5)	20.1 (14.1) 14.0 (10.3)	-29.1-54.4	<.001
SBAV	<14	Placebo Duloxetine	9.3 (2.4) 9.4 (2.5)	6.7 (4.6) 4.2 (3.3)	-36.8-60.3	<.001
	≥14	Placebo Duloxetine	27.9 (14.3) 27.7 (13.5))	20.0 (14.3) 12.8 (10.4)	-26.3-56.8	<.001
SBAX	<14	Placebo Duloxetine	9.2 ((2.6) 9.9 (2.3)	6.0 (5.1) 5.1 (4.0)	-52.2-56.4	.155
	≥14	Placebo Duloxetine	29.0 (15.2) 28.5 (15.1)	18.3 (13.5) 13.7 (12.7)	-35.9-54.7	<.001

In the combined database, the duloxetine 40 mg twice-daily group showed significantly greater improvement in I-QOL total scores compared with the placebo group in the ITT analysis (9.2 versus 5.9, p<. 001) and the completer analysis (10.4 versus 6.1, p<. 001). The following figure shows the results by study. As with the IEF analysis, the effect on I-QOL was less pronounced and not significant in patients with a baseline IEF <14.



- Discussion on clinical efficacy

The selection criteria applied in phase III clinical trials identify patients with SUI on the basis of clinical findings (signs and symptoms). A subset of patients underwent urodynamic evaluations indicating that most of enrolled patients were truly suffering from SUI. Exclusion criteria intend to avoid the inclusion of patients with urge incontinence.

Patients enrolled in phase III correspond to a moderate/severe SUI population (according to the PGI rating). Only 16% of the patients were having concurrent pelvic muscle floor training (PFMT), which is considered the first step in the treatment of SUI. However the ever-use and current-use PFMT rates were similar to those reported in the general population, supporting the generalizability of the study populations.

Design of pivotal studies as parallel double blind against placebo, measurement of efficacy at 12 weeks and efficacy parameters are considered appropriated and are, in fact, in agreement with the recommendations made by the CHMP Note for Guidance on the Clinical Investigation of Medicinal Products for the treatment of Urinary Incontinence (CHMP/EWP/18/01)

The Applicant has selected the percentage reduction from baseline in IEF as the primary endpoint, using a quantitative assessment of a disease-specific QoL scale as a supportive primary endpoint. As secondary variables, PGI, CGI (among other variables) and an analysis of responders on the basis of pre-defined cut-off points for the different variables have been also provided. This strategy is not entirely in line with the CHMP Note for Guidance, suggesting that main therapeutic trials should focus the use of measurements of subjective improvement, as the PGI or the CGI. However, and provided that consistency in the drug effect on these variables is proven, the Applicant approach was considered acceptable when taking on board that the mentioned CHMP Note for Guidance came into operation on December 2002 and the present dossier was filed on November 2002.

Overall, although not statistically significant in all trials, duloxetine has shown a consistently greater effect on IEF and QoL than placebo. The magnitude of the relative effect on IEF is about a 50% reduction with considerable placebo response ranging from 27% to 40%. However, and as already highlighted for the dose-finding study, the absolute median reduction in incontinence episode frequency per week was only 1.5, 3.0, and 3.9 for the phase 3 trials compared with placebo. The clinical relevance of such magnitude can be questioned. I-QOL assessment as well as the PGI and the CGI show a consistent effect of duloxetine over placebo.

Only 16% of patients were receiving PFMT during the study and no information is provided on the quality of and compliance with it. PFMT is considered the first therapeutic approach for women with SUI. Published data indicate that this non-pharmacological approach can improve symptoms in around half of patients. In this regard, the clinical development program does not reveal whether duloxetine therapy provides any additional effect to an adequately standardised PFMT.

Study SBAF provides additional information about the role of duloxetine in the moderate-severe SUI therapeutic program where PFMT is considered a first stage step. The primary objective of this study was to compare combined therapy (duloxetine + PFMT) versus no treatment (placebo + imitation PFMT) and to compare combined therapy versus PFMT. Combined therapy showed the greatest IEF reduction than each monotherapy (duloxetine or PFMT) or placebo. Duloxetine alone showed greater reduction than PFMT. Thus, in the assessors' view, study SBAF would support use of the combined treatment. It could be questioned, however, if the study period of 3 months was long enough to allow the maximum effect of PFMT to be demonstrated. The results would therefore support a recommendation to use the combined treatment. This is reflected in the SPC.

In this type of disease, the clinical relevance of the observed improvement assessed by mean of quantitative (continuous or discrete) variables is of difficult interpretation, and a responder analysis in a prospectively defined way is considered of paramount importance. Upon request, an analysis of the number of "dry" days during treatment in relation to pre-treatment was made to contribute to the interpretation of clinical effects.

When patients were analysed according their incontinence severity at baseline (< 14 IEF/week and ≥ 14 IEF/week) the improvement was less pronounced for the less severe strata of patients without a clear translation into a quality of life benefit. A new analysis of the previously submitted efficacy data was provided according to the number of dry days (from 7 to 0) at the end of the study. Cure rates (i.e. dry 7 days) are really scarce for both stratum (more severe: duloxetine 5.4%, placebo 2.9%; less severe: duloxetine 15.7%, placebo: 12.5%). For the less severe subjects differences between duloxetine and placebo treated patients hardly achieved 6% across the complete distribution of dry days. Thus, the clinical meaningfulness of duloxetine in women with less severe SUI is still questionable.

When a new definition (post-hoc) of cure or improvement was applied (4 or more dry days/week) 58.6% of patients on duloxetine and 52.5% on placebo responded (p=.09; chi-square) within the less severe stratum. Among patients with more than 14 episodes per week the response rate on the basis of the same variable was 27% for duloxetine and 14.7% for placebo.

Although previous surgery, in a pooled data analysis, did not appear to have an impact on duloxetine efficacy with regard to reduction of IEF, the weight of this analysis is considered limited, and this is reflected in the SPC.

Study SBBA compared the of duloxetine80 mg/day with placebo on quality of life in a naturalistic protocol resembling general conditions of clinical practice. The study failed to show any positive effect of duloxetine over placebo on quality of life. No information regarding the number of incontinence episodes at baseline has been provided nor on the reduction in IEF achieved at the end of the treatment. However, less restrictive inclusion criteria considered for this study (≥ 1 incontinence

episode per week) would allow recruiting a population close to the less severe end of the disease. Those negative results seem to confirm the negligible effect of duloxetine in mild SUI patients.
On the other hand, when severely affected patients are enrolled (Study SBAM) significantly greater reduction in IEF was achieved in duloxetine treated patients compared with those in placebo group. This was also reflected in I-QOL improvement. The SPC, therefore, clearly reflects the limited usefulness of duloxetine in patients with mild SUI.
It is important to assess the efficacy beyond 3 months. The negative results of the study SBBA, which failed to show positive effect of duloxetine over placebo over a treatment period of 36 weeks in an ordinary clinical setting, throws serious doubts as to the clinical meaningfulness of the product in general long-term use. Thus, the long-term (>3 months) results still remain weak and, considering that SUI is a sustained problem for the majority of women, the lack of documented long-term effects is reflected in the SPC.

Clinical safety

The integrated safety data were classified into three databases based on duloxetine dosage and treatment indications.
The primary safety database includes data on duloxetine- and placebo-treated women from all completed double blind SUI studies in which subjects were randomly assigned to a dose of 40 mg twice daily throughout the trial. The three Phase 3 randomised clinical trials (Studies SBAT, SBAV, and SBAX), one Phase 2 randomised clinical trial (Study SAAW), the three open-label extensions to the three Phase 3 trials (Studies SBAU, SBAW, and SBBM), and one stand-alone open-label safety study (Study SBAY) comprise the primary safety database.
The secondary safety database includes data from all subjects (women and men) from all completed double-blind depression and pain studies in which subjects were randomly assigned to a dose of at least 40 mg twice-daily duloxetine or to placebo. Also included are data from the final locked database of the long-term, open-label depression study.
The tertiary safety database consists of data from clinical pharmacology studies, all completed urinary incontinence and depression studies in which subjects were randomised to a dose of less than duloxetine 40 mg twice daily or placebo, Japanese studies, and all ongoing duloxetine studies except those in the primary safety database.
Safety data (adverse events, vital signs, and clinical laboratory tests) were monitored throughout the studies. Adverse events were elicited by open-ended, nondirected questioning of the subject, clinical observation, and source document review. The adverse events terms initially recorded by site personnel were mapped to Medical Dictionary for Regulatory Activities (MedDRA) terms. The study site investigator based on his or her clinical judgement assigned causality for SAEs and deaths.

- Patient exposure

A total of 4127 duloxetine subjects, representing approximately 1842 subject-years of exposure to duloxetine, were included in the primary and secondary safety databases up to the data cut-off date of 14 June 2002.
There were 2301 subjects in the primary safety database ranging from 20 to 87 years of age; all were women, and 93% were Caucasian. They had approximately 956 subject-years of exposure, with 190 of those subject-years of exposure occurring in the placebo-controlled trials in patients with SUI (958 duloxetine-treated and 955 placebo-treated patients). Of all the subjects in the primary safety database, 818 had more than 6 months of exposure to duloxetine, and 191 had more than 12 months of exposure.

- Adverse events

Treatment-emergent adverse events (TEAEs) from double-blind trials in the primary safety database for which the incidence in the duloxetine treatment group was ≥5.0% and significantly greater than the incidence in the placebo group were nausea (23.2% vs 3.7%), dry mouth (13.4% vs 1.5%), fatigue (12.7% vs 3.8%), insomnia (12.6% vs 1.9%), constipation (11.0% vs 2.3), headache (9.7% vs 6.6%), dizziness (excluding vertigo) (9.5% vs 2.6%), somnolence (6.8% vs 0.1%), and diarrhoea (5.1% vs 2.7%).
Adverse events reported with a significantly greater frequency in the duloxetine group compared with placebo for which the incidence was <5% and ≥1% were vomiting, increased sweating, anorexia,

dyspepsia, tremor, lethargy, decreased appetite, sleep disorder, anxiety, decreased libido, anorgasmia, pruritus, blurred vision, weakness, nervousness, and thirst. Adverse events reported with a significantly greater frequency in the duloxetine group compared with placebo for which the incidence was < 1% was nocturia, rigors, asthenia, mydriasis, lost of libido, and yawning.

The most common adverse events, except diarrhoea, typically began within the first month of treatment, many within the first 2 days. Most common adverse events resolved in the majority of subjects within 7 to 30 days. Insomnia, dry mouth and constipation tended to be more persistent than other common adverse events.

Treatment-Emergent Adverse Events in Order of Decreasing Frequency Within Duloxetine Treatment Group
MedDRA Preferred Terms
Integrated Controlled Studies – Primary Safety Database, All Randomised Subjects

(7) (8) TEA Events	***Placebo*** (n = 955) n (%)	(n = 958) n (%)	Fisher exact test	CMH test
Nausea	35 (3.7)	222 (23.2)	< .001	< 0.001
Dry mouth	14 (1.5)	128 (13.4)	< .001	< 0.001
Fatigue	36 (3.8)	122 (12.7)	< .001	< 0.001
Insomnia	18 (1.9)	121 (12.6)	< .001	< 0.001
Constipation	22 (2.3)	105 (11.0)	< .001	< 0.001
Headache NOS	63 (6.6)	93 (9.7)	.015	.012
Dizziness (excl. vertigo)	25 (2.6)	91 (9.5)	< .001	< 0.001
Somnolence	1 (0.1)	65 (6.8)	< .001	< 0.001
Diarrhoea NOS	26 (2.7)	49 (5.1)	.009	.007
Vomiting NOS	15 (1.6)	46 (4.8)	< .001	< 0.001
Sweating increased	8 (0.8)	43 (4.5)	< .001	< 0.001
Nasopharyngitis	47 (4.9)	41 (4.3)	.515	.503
Anorexia	2 (0.2)	37 (3.9)	< 0.001	< 0.001
Influenza	25 (2.6)	31 (3.2)	.498	.409
Dyspepsia	12 (1.3)	29 (3.0)	.011	.008
Tremor	0 (0.0)	26 (2.7)	< 0.001	< 0.001
Lethargy	3 (0.3)	25 (2.6)	< 0.001	< 0.001
Appetite decreased NOS	2 (0.2)	22 (2.3)	< 0.001	< 0.001
Sleep disorder NOS	8 (0.8)	21 (2.2)	.023	.014
Sinusitis NOS	21 (2.2)	20 (2.1)	.876	.859
Urinary tract infection NOS	18 (1.9)	19 (2.0)	1.00	.874
Anxiety NEC	7 (0.7)	18 (1.9)	.042	.027
Back pain	17 (1.8)	18 (1.9)	1.00	.876
Hot flushes NOS	10 (1.0)	17 (1.8)	.244	.178
Hypertension NOS	17 (1.8)	17 (1.8)	1.00	.991
Palpitations	8 (0.8)	16 (1.7)	.149	.099
Arthralgia	11 (1.2)	15 (1.6)	.554	.440
Cough	16 (1.7)	14 (1.5)	.718	.709
Libido decreased	3 (0.3)	14 (1.5)	.012	.007
Anorgasmia	0 (0.0)	13 (1.4)	< 0.001	< 0.001
Depression NOS	11 (1.2)	13 (1.4)	.838	.687

Pruritus NOS	3 (0.3)	13 (1.4)	.021	.012
Abdominal pain upper	11 (1.2)	12 (1.3)	1.00	.831
Abdominal pain NOS	18 (1.9)	12 (1.3)	.277	.270
Vertigo	8 (0.8)	12 (1.3)	.501	.367
Vision blurred	1 (0.1)	12 (1.3)	.003	.002
Weakness	3 (0.3)	12 (1.3)	.034	.019
Nervousness	0 (0.0)	11 (1.1)	< 0.001	< 0.001
Pharyngolaryngeal pain	16 (1.7)	11 (1.1)	.341	.323
Upper respiratory tract infection NOS	16 (1.6)	11 (1.1)	.341	.315
Bronchitis	18 (1.9)	10 (1.0)	.133	.125
Flatulence	18 (1.9)	10 (1.0)	.300	.199
Myalgia	5 (0.5)	10 (1.0)	.300	.194
Pyrexia	5 (0.5)	10 (1.0)	.178	.110
Rash NOS	6 (0.6)	10 (1.0)	.453	.319
Thirst	1 (0.1)	10 (1.0)	.011	.007
Migraine NOS	10 (1.0)	9 (0.9)	.823	.805

* P-value is from Cochran-Mantel-Haenzel Test stratified by study

- Serious adverse event/deaths/other significant events

One death (a 70-year-old Caucasian woman, previously diagnosed of hypertension and hypercholesterolemia who had been taking duloxetine for 52 days and suffered a multifocal embolic cerebrovascular accident resulting in coma and death) was reported from the primary safety database. This event was judged by the investigator to be unrelated to study drug. After the database cut-off date of 14 June 2002, a second death occurred in this primary safety database. A 59-year-old woman assigned to duloxetine, died from a pulmonary oat cell metastatic carcinoma. In the opinion of the investigator, it is unlikely it were related to study drug. An autopsy for this subject is pending and further information has been requested.
Two deaths were reported for the controlled studies in the secondary safety database (1 duloxetine, 1 placebo): A 77-year-old Caucasian man randomised to duloxetine 40 mg twice daily, who experienced a cardiopulmonary arrest that resulted in death 4 days after his last dose of duloxetine and was considered not related, and a 73-year-old Caucasian man randomised to placebo treatment who experienced an accidental drowning resulting in death. Six deaths (4 duloxetine, 1 placebo, 1 blinded treatment) were reported in the tertiary safety database before or after data cut-off date, none of them being attributable to study drug or procedures.

When both double blind and open-label studies in the primary safety database were reviewed, 70 subjects (3.2%) had reported a total of 105 SAEs. The majority of SAE in the duloxetine-treated group were not attributed to the study drug by the investigators who were blinded.
The incidence of SAEs that may be related to duloxetine was low. The incidence of SAEs did not differ significantly from placebo.
A recently reported SAR of a completed suicide in a healthy female volunteer without SUI on placebo after being tapered from a high dose of duloxetine reinforces the need for a detailed description of suicides occurring during the clinical development of duloxetine and during its post-marketing experience outside the EU. The risk of discontinuation symptoms are clearly stated in the SPC
Another case of suicide attempt in a 43 year-old female patient in an open label phase III study was reported during the Decision-making phase. The view of the Committee was that Ariclaim is expected to be prescribed and used by physicians and patients that might be not fully informed of the potential association between antidepressant drugs and suicidal behaviour.
As a consequence, the CHMP considered that the SPC and the PL for all medicinal products containing duloxetine should include information, warning prescribers and patients of this potential risk. This warning was considered especially important for Ariclaim, as it is expected to be used in a population, which might be unaware of this problem.
Appropriate warning information has been included in the SPC and PL. Additionally, a post-marketing surveillance program for all medicinal products containing duloxetine will be carried out.

- Laboratory findings

Numerically small but significant increases were observed in the mean values for aspartate transaminase, alanine transaminase, and alkaline phosphotase in the duloxetine-treated group compared with the placebo group. Significantly more duloxetine-treated subjects had elevations of ALT and AST above the Covance reference range than placebo-treated subjects. No significant difference was observed between duloxetine- and placebo-treated subjects in the incidence of hepatic enzyme elevations ≥3 times and ≥10 times the upper limit of normal using the Covance reference ranges. No case of previously defined as severe hepatic injury was reported in duloxetine treated subjects.
A mean increase of 5.8 U/L in CPK was observed for duloxetine-treated subjects, compared with 0.1 U/L for the subjects assigned to placebo. Elevated CPK levels were observed at any time after randomisation in 28 duloxetine-treated compared with 27 placebo-treated subjects. A single subject with baseline CPK level within the normal range had a CPK elevation of 4430 U/L 98 days after starting duloxetine. The CPK level drawn one month later was 98.
The blood preassure (BP) increases with duloxetine were small though consistent across all studies in the primary and secondary databases and averaged <2 mmHg. There was no significant difference in the incidence of sustained hypertension (sustained increases of either systolic or diastolic pressures) between the duloxetine-treated (0.2%) and placebo-treated (0.7%) groups in the placebo-controlled trials. The mean increases in systolic and diastolic BPs observed for subjects with pre-existing hypertension assigned to duloxetine were smaller than those observed for subjects assigned to placebo.
Effects of duloxetine on ECG parameters were assessed. Clinical pharmacological studies involving a total of approximately 160 subjects who had received a single 60-mg dose, showed a shorter QTc intervals and a small (4 msec) decrease in the PR interval.
Overall, the QT interval corrected for heart rate (QTc) analysis revealed no arrhythmogenic tendencies with duloxetine. A statistically significant increase in heart rate accompanied by the expected decrease in both PR and RR intervals was observed with duloxetine, consistent with its clinically mild peripheral noradrenergic pharmacologic action. (in both primary controlled and uncontrolled studies)

- Safety in special populations

Safety data were analysed according to subgroups based on age, race, and pre-existing hypertension. There were no clinically relevant interactions in the incidence of adverse events, changes in laboratory values, or in vital signs observed for duloxetine treatment for the age or race subgroups. Significantly more ESRD subjects reported adverse events occurring on or after the only dose of the study drug (8 ESRD subjects reported 17 adverse events), compared with healthy subjects (1 subject reported five adverse events). Subjects with cirrhosis Child Pugh class B experienced more adverse events although there were no serious events in any subject. Each of the 6 cirrhotic subjects reported a total of 35 adverse events (25 possible or probably related) versus no adverse events reported in seven healthy subjects. Nineteen pregnancies exposed to duloxetine at various doses were reported from all three-safety databases. All exposures were in the first trimester. Eleven had pregnancies that delivered in the third trimester, of whom 9 delivered apparently normal babies at term, and 2 delivered after premature rupture of membranes and/or preterm labour, with neither infant surviving.

- Safety related to drug-drug interactions and other interactions

In the double-blind studies in the primary safety database, 86.5% of subjects (duloxetine 86.0%, placebo 86.9%) used one or more of approximately 1140 concomitant medications. Of these, four (ibuprofen, paracetamol, conjugated estrogens, and a multivitamin) were used by 10.3% to 12.2% of subjects. An additional seven (acetylsalicylic acid, various thyroid and reproductive hormones, various vitamins, and calcium) were used by 5% to 10% of subjects. Of the unique medications consumed, 99% did fewer than 30 subjects assigned to duloxetine, and over 96% each use each fewer than 15 subjects assigned to duloxetine used. No analysis of the relationship between concomitant medications and adverse events with duloxetine was performed due to the large number of medications and the small size of the subgroups.
For all of the individual cases of serious adverse events occurring during the duloxetine clinical trials, the responsible investigator assessed the possible causal relationship of concomitant medications administered to the specific subject.

Women using medications in several classes (antidepressants, stimulant drugs used in the treatment of obesity, monoamine oxidase inhibitors [MAOIs], and other incontinence drugs) were excluded from participating in the stress incontinence clinical trials.

- Discontinuation due to adverse events

In the controlled studies (primary safety database), the overall incidence of discontinuation due to adverse events was significantly greater for the duloxetine group (196; 20.5%) compared with the placebo group (37; 3.9%). Specific adverse events for which the discontinuation rate in duloxetine-treated subjects was ≥ 1.0% and twice the rate of placebo-treated subjects were nausea, dizziness (excluding vertigo), insomnia, fatigue, and somnolence. All were significantly more common in duloxetine-treated subjects as well as anxiety (duloxetine 0.6% vs placebo 0%). When long-term open-label extension studies were included, the overall incidence of discontinuation due to duloxetine-associated adverse events was 30.6%. The majority of discontinuations (87%) occurred in the first 4 weeks of duloxetine treatment. The overall incidence of discontinuation due to duloxetine-associated adverse events was 30.6% in the primary safety database (including the four open-label extension studies) up to the database cutoff date of 14 June 2002.

- Discontinuation symptoms

Discontinuation symptoms seen after duloxetine treatment (secondary safety database) reported with a significantly greater frequency by duloxetine-treated subjects included dizziness (excluding vertigo), headache KNOWS, nausea, paraesthesia, abnormal dreams, nightmare, irritability, somnolence, increased appetite NOS, and tension. The risk of discontinuation symptoms is clearly stated in the SPC.

- Post marketing experience

Duloxetine has not been approved for marketing in any country at this time.

- Discussion on clinical safety

The safety database from short-term trials (12 weeks) is extensive (958 exposed patients) and well reported. Data on long-term exposure have been less extensively reported as they emanate from ongoing studies. 191 patients have been exposed for 12 months in SUI studies. In addition data from the secondary safety database including studies for other indications than SUI have been presented.
Forty various AEs occurred significantly more often in the duloxetine group than in the placebo group in the pooled 12-week studies. The most common AEs were nausea (23%), dry mouth (13%), fatigue (13%), insomnia (13%), and constipation (11%). Headache, dizziness, somnolence, and diarrhoea occurred in 5-10% of the duloxetine patients. Another 16 AEs, including vomiting, anorectic disturbances, libido disturbances, sleep disorders, lethargy, and weakness occurred in 1-5% of the duloxetine patients.
The majority of AEs was mild to moderate and resolved within 30 days of treatment. Still, in many patients the most common AEs (dry mouth, fatigue, insomnia and constipation) remained for more than 30 days. Among patients reporting dizziness, nausea, insomnia and somnolence, between 12 and 22% discontinued treatment. Among the most commonly reported AEs, 10-15% were reported as severe.
In total, 20.5% of duloxetine patients discontinued treatment for AEs vs. 3.9% in the placebo group in the four pivotal 12-week studies. Including data from the ongoing open continuation studies, 30.6% of the patients had discontinued treatment at the database cut-off date.
No deaths that were judged as related to treatment were reported and the number of SAEs was low with little or no association to treatment. Two cases with severe liver disturbances were reported. Although, in both cases other predisposing factors were present and the role of duloxetine was judged as uncertain, an association could not be excluded.
Among laboratory results the only finding that may be of clinical significance was an increase in transaminases above placebo in duloxetine treated patients and also a higher number of patients with abnormal values. No effects on vital signs of clinical importance were observed. Analysis of ECGs from all patients in the pivotal SUI studies did not reveal any arrythmogenic tendencies with duloxetine

Unsurprisingly, long term exposure show a higher incidence of discontinuation (30.6% versus 20.5%) and of SAEs (3.2% versus 1.9%) compared to short-term treatment. Apart from that, the safety profile can be considered similar to that already known.
During the Phase 3 clinical development of duloxetine in SUI patient's withdrawal symptoms were not specifically considered and only one Phase 2 study looked at a tapering phase at the end of the treatment. Based on the pattern of discontinuation symptoms from studies of duloxetine for all indications, the SPC specifies dose tapering at the time of discontinuation to minimize the risk of symptoms.
As with other drugs with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Adequate warning information of the potential association of suicidal ideation and behaviour with the use of duloxetine, has been included in the Product information.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

Overall the pharmacodynamic studies showed that that duloxetine induced inhibition of 5-HT and NE reuptake. This inhibition suppressed urinary bladder muscular activity in a dose-dependent manner, and enhanced external urethral sphincter activity through centrally mediated (CNS) mechanism. Duloxetine was active in urinary models, indicative of enhancement of serotonin and norepinephrine neurotransmission, with improvement of capacity of the urinary bladder and increased urinary sphincter activity
The general pharmacology studies are appropriate to support the non-clicical-pharmacology profile of duloxetine.
From the pharmacokinetic point of view, mice, rats, and dogs were the most relevant species for non-clinical efficacy and safety studies. The non-clinical pharmacokinetics properties for duloxetine have been appropriately described. A number of studies concerning the absorption, distribution, metabolism, and excretion of duloxetine in mice, rats, and dogs have been performed. Duloxetine is well absorbed in all studied species, and is extensively metabolised, especially at the liver.
Overall, the toxicology programme revealed the liver as the target organ related to duloxetine administration in all species tested.
The dog was chosen as the non-rodent species for use in the toxicology programme.

Efficacy

The efficacy of duloxetine 40 mg given twice daily in the treatment of SUI was established in four double-blind, placebo-controlled studies, that randomised 1913 women (22 to 83 years) with SUI; of these, 958 patients were randomised to duloxetine and 955 to placebo. The primary efficacy measures were Incontinence Episode Frequency (IEF) from diaries and an incontinence specific quality of life questionnaire score (I-QOL).
Overall, although not statistically significant in all trials, duloxetine has shown a consistently greater effect on IEF and QoL than placebo. The magnitude of the relative effect on IEF is about 50% with a placebo response ranging from 27% to 40%. When patients were analysed according their incontinence severity at baseline (< 14 IEF/week and ≥ 14 IEF/week) the improvement was less pronounced for the less severe stratum of patients without a clear translation into a quality of life benefit. Hence the indication has been restricted to moderate to severe stress urinary incontinence.
The lack of documented long-term effects is also reflected in the SPC.

Safety

The primary safety database from short-term trials (12-week, placebo-controlled clinical trials in patients with SUI) included 958 duloxetine-treated patients and 955 placebo-treated patients. This represents 190 patient-years of exposure at 40 mg twice daily. Data on long-term exposure have been less extensively reported as they emanate from ongoing studies.
Duloxetine is a drug with highly variable pharmacokinetics and many factors affect the systemic exposure (gender, age, renal and hepatic function, smoking status, CYP2D6 status, drug-drug interactions)
AEs occurred significantly more often in the duloxetine group than in the placebo group in the pooled 12-week studies. The most common AEs were nausea (23%), dry mouth (13%), fatigue (13%), insomnia (13%), and constipation (11%). Headache, dizziness, somnolence, and diarrhoea occurred in 5-10% of the duloxetine patients. Others AEs, including vomiting, anorectic disturbances, libido disturbances, sleep disorders, lethargy, and weakness occurred in 1-5% of the duloxetine patients.
The majority of AEs was mild to moderate and resolved within 30 days of treatment
In total, 20.5% of duloxetine patients discontinued treatment for AEs vs. 3.9% in the placebo group in the four pivotal 12-week studies.

Benefit/risk assessment

Stress urinary incontinence is a common and chronic condition in women. While not life-threatening, it can have a significant negative impact on the psychological well-being, social functioning and overall quality of life of those it affect. At present there is no approved pharmacological treatment for this condition.
Duloxetine has shown an effect in patients with stress urinary incontinence in terms of both frequency of incontinence episodes and subjective measures as Quality of Life, Patient Global Impression and Clinical Global Impression. Data provided by the Applicant indicate that, although modest, the observed effect is clinically meaningful in patients with moderate to severe stress urinary incontinence, especially when the drug is combined with Pelvic floor muscle training. Although the long-term safety database is limited, the tolerability profile of duloxetine seems acceptable. Therefore, and considering that no pharmacological alternative is available for the treatment of stress urinary incontinence, duloxetine might play a role in alleviating the symptoms of such an uncomfortable clinical condition. A positive benefit/risk can be concluded.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of duloxetine in the treatment of women with moderate to sever Stress Urinary Incontinence was favourable and therefore recommended the granting of the marketing authorisation.