SCIENTIFIC DISCUSSION

1. Introduction

Eli Lilly Netherlands B.V. has submitted a Marketing Authorisation Application through the Centralised Procedure, for the medicinal product CYMBALTA, containing duloxetine hydrochloride, for the treatment of major depressive episodes.

This is a complete and independent marketing authorisation application, as stated in Art. 8 (3) of Directive 2001/83/EC, as amended. The provided data cover all aspects of the clinical characterization of safety and efficacy of duloxetine. The Applicant has submitted the results of non-clinical and clinical studies carried out for the application.

Major Depressive disorder is reported to be the most common mood disorder, with a lifetime prevalence of about 15% and as high as 25% in women. Despite the availability of effective treatments, many persons with depressive disorders are disabled, and risk of suicide is considerable. It tends to be chronic and both relapse and recurrence are seen frequently.
The diagnosis of major depression is based primarily on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria. The criteria state that at least five of the following symptoms must be present during the same period to receive a diagnosis of major depression: depressed mood, markedly diminished interest or pleasure in almost all activities (one of these two must be present necessary), significant weight loss/gain, insomnia/hypersomnia, psychomotor agitation/retardation, fatigue, feelings of worthlessness (guilt), impaired concentration and recurrent thoughts of death or suicide (American Psychiatric Association, 1994). The symptoms should be present most of the day, nearly daily, for a minimum of two weeks.

A number of options are currently available for the treatment of MDD, including psychological therapies such as cognitive behavioural therapy and psychoanalytic psychotherapy, antidepressant medications, and electro-convulsive therapy.

Initial treatment objectives in the treatment of depression include:

1) Symptom remission (acute phase)
2) Prevention of a relapse (continuation phase)
3) Prevention of recurrences, or new episodes in patients with recurrent depressions (maintenance phase).

For the *acute phase treatment*, according to literature a minimum of 6, and preferably 8 weeks of treatment is necessary to determine the full extent of symptom reduction attainable, although most patients would show a partial response during the initial weeks of treatment. Accordingly, the CPMP "Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Depression" establishes as acceptable a duration of 8 to 12 weeks for the first period of treatment in clinical trials.

The *continuation phase of treatment*, which purpose is to prevent deterioration of the index episode (relapse), is usually set at about 6 months, to correspond to the average duration of an episode of depression. In clinical practice this may change according to patient characteristics (duration and number of prior episodes...).

Maintenance phase of treatment aims at preventing new episodes (recurrence). This phase of treatment is appropriate for patients with three or more episodes of depression, and could last several years. This part of treatment is not compulsory for registration unless specifically claimed, according to the CPMP "Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Depression".

The presumed mechanism of action of the majority of antidepressants in the treatment of MDD is thought to be via inhibition of neuronal reuptake of monoamines (mainly serotonin and

norepinephrine), with a resultant increase in monoamine neurotransmission in the central nervous system (CNS).

The major classes of drugs used to treat depression are the tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine and sertraline), heterocyclics (e.g., bupropion), monoamine oxidase (MAO) inhibitors, and a few other compounds such as venlafaxine, which inhibits specifically the reuptake of both serotonin and norepinephrine. No single antidepressant medication is clearly more effective than another and no single medication results in remission for all patients. In many occasions the choice of the medication is made looking at the side effect profile.

The cyclic antidepressants are less commonly used as first-line antidepressants with the development of the SSRIs and other newer antidepressants. This is mainly due to the less benign side-effect profile of the cyclic antidepressants. These drugs interact with a wide variety of brain receptor types, providing the basis for both their antidepressant efficacy and their side-effect profiles. At therapeutic doses, the cyclic antidepressants tend to have dose-related side effects such as anticholinergic and orthostatic effects, as well as sedation, weight gain, and sexual dysfunction. Overdose of cyclic antidepressants can cause potentially lethal arrhythmias, anticholinergic toxicity and seizures. Nevertheless, many patients use these drugs safely, and their antidepressant efficacy equals that of antidepressants from other classes.

The selective serotonin reuptake inhibitors (SSRIs) all share the property of blocking the action of the presynaptic serotonin reuptake pump, thereby increasing the amount of serotonin available in the synapse and increasing postsynaptic serotonin receptor occupancy. As the side-effect profile is better than the TCAs they have become widely used in clinical practice, especially in mild to moderate depression. Jitteriness, restlessness, agitation, headache, gastrointestinal symptoms (diarrhea and nausea), and insomnia are common side effects with SSRIs. A significant percentage of patients develop sexual side effects after several weeks or months of SSRI therapy, especially a decreased ability to have an orgasm.

MAO inhibitors still have a role in the treatment of depression. However, they are not used as first line drugs because of their potential to precipitate enhanced sympathetic activity and severe hypertension with the concomitant ingestion of tyramine containing foods (e.g., fermented cheeses, beer, champagne, some other wines, soy sauce, avocados, bananas, overripe or spoiled food, and any fermented, smoked, or aged fish or meat). The hypertensive reaction is dose-dependent and can be exacerbated if the patient is also taking a sympathomimetic drug.

Venlafaxine is a relatively recent developed treatment. It is a potent inhibitor of serotonin and norepinephrine reuptake, and a mild inhibitor of dopamine reuptake. It has some similarities to the TCAs in its effects upon neurotransmitter systems. However, in contrast to the TCAs, it has no interactions with histaminic, muscarinic, or adrenergic receptors and therefore tends to have a more benign side-effect profile. The most common side effects of venlafaxine are nausea, dizziness, insomnia, sedation, and constipation. It can also induce sweating in some patients. Dose-related sustained hypertension has been reported, which can be significant in some patients

Duloxetine is classified as a serotonin norepinephrine reuptake inhibitor (SNRI).
The claimed mechanism of action of Duloxetine is based on the specific inhibition of both serotonin and norepinephrine reuptake, while it weakly inhibits dopamine reuptake and has no significant affinity for histaminergic, dopaminergic, cholinergic or adrenergic receptors.
CYMBALTA® 30 and 60 mg capsules contain enteric-coated pellets of the active substance duloxetine hydrochloride (+)-(S)-N-methyl-γ-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride) equivalent to 30 and 60 mg of duloxetine.
The recommended posology is 60 mg once daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day can be uptritated in evenly divided doses. Based on this posology, a combined package leaflet including both strengths has been adopted.
Duloxetine has been already approved for the treatment of Stress Urinary Incontinence (SUI)

The development programme of duloxetine was initiated in the mid-1980s. The toxicology and toxicokinetic studies were performed in accordance with Good Laboratory Practise (GLP) regulations and, except for the oldest studies, met Organisation of Economic Cooperation and Development (OECD) and Japanese Ministry of Health, Labour, and Welfare (MHLW) standards. Applicable ICH and CPMP guidance documents were also referred to during the development of the compound.

All clinical studies with duloxetine have been conducted in accordance with GCP and agreed ethical principles.

2. Part II: Chemical, pharmaceutical and biological aspects

Introduction

The product is presented in the form of hard gastro-resistant capsules containing enteric-coated pellets, and it contains duloxetine hydrochloride equivalent to 30 mg and 60 mg of duloxetine base as active substance. Other ingredients are sucrose, hydroxypropyl methylcellulose, sugar, talc, gelatine, colorants, etc.
The capsules are packaged in Polyvinylchloride (PVC), Polyethylene (PE), and Polychlorotrifluoroethylene (PCTFE) blisters sealed with an aluminium foil.

Active Substance

Duloxetine hydrochloride is an active substance not described in any Pharmacopoeia.
Duloxetine hydrochloride which has the chemical name (+)-(S)-N-methyl-γ-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride is a white to practically white solid, and is slightly soluble in water; its solubility is not pH dependent.
The chemical structure of duloxetine hydrochloride is well characterised. It is an optically active molecule, which presents 1 asymmetric carbon, therefore two enantiomers are possible. The S enantiomer has been selected based on both *in vitro* and *in vivo* studies. The optical purity of the drug substance is controlled by selecting the correct chiral starting materials. According to the manufacturing process described, the S-enantiomer is routinely obtained and the R-enantiomer is considered as a specified impurity.

- Manufacture

Duloxetine hydrochloride is synthesized by two manufacturing process. Both processes are equivalent. Batch analysis data provided allow for the conclusion that the analytical profiles are similar between batches.
Adequate In-Process Controls are applied during the manufacture of duloxetine active substance. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and are satisfactory.

- Specification

The active substance specification includes tests for physical characterisitics of the active substance , identity, assay , process and product related impurities, as well as additional pharmacopoeia testing requirements consistent with this active drug substance.
The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance.
Batch analysis data of a number of batches of active substance are provided. The results are within the specifications and consistent from batch to batch.

- Stability

Stability studies for primary batches (manufactured by one of two alternative processes) from storage under long term ICH conditions (30°C/60%RH) up to 24 months and under stress conditions (40ºC / 75% RH) up to 6 months were provided. Supportive data was provided in terms of data from six batches manufactured by the same process as for the primary batches and for six batches manufactured

by the second process. The batches were packed in a linear low-density polyethylene liner (LLDPE) placed inside a laminated foil liner. The parameters evaluated were stability indicating. Methods are validated and stability indicating.

The re-test period proposed is acceptable taking into account the results obtained in formal stability studies and the supportive stability data.

Finished Product

- Pharmaceutical Development

Duloxetine hydrochloride is an acid-labile substance, therefore, the product development has been focus to develop an enteric-coated dosage form in order to prevent degradation of the active substance in the acidic environment of the stomach. Hard gastro-resistant capsules with enteric-coated pellets were selected after development of some prototype formulations to be the optimal market formulation.

The excipients in the capsule content are: hypromellose, hydroxypropyl methylcellulose acetate succinate sugar spheres, sucrose, talc, ammonium hydroxide, triethyl citrate, and titanium dioxide (E 170) and in the capsule shell are: gelatin, sodium lauryl sulfate, colorants and ink. All of them are included in compendial monographs.
Analytical certificates of excipients are included. Specifications and analytical certificates for the capsules and the printing ink cover are presented.
TSE certificates of suitability for gelatin included in capsule shell are presented.
Duloxetine capsules are packaged in Polyvinylchloride (PVC), Polyethylene (PE), and Polychlorotrifluoroethylene (PCTFE) blisters sealed with an aluminum foil. The choice of materials for the container is adequate to the type of product and moreover supported by the stability studies performed.

- Manufacture of the Product

The product is manufactured in accordance with conventional processes for this pharmaceutical form.
The manufacturing process has been adequately validated by a number of studies for the major steps of the manufacturing process in three batches produced for stability studies and clinical trials.
The batch analysis data show that the hard capsules can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

- Product Specification

The specification includes tests by validated methods for physical appearance, identity, assay product and process impurities, as well as additional pharmacopoeia testing requirements consistent with this dosage form

The test and limits of the release and shelf life specification for the finished product are appropriate to control the quality of this medicinal product for the intended purpose.
Batch data are provided for pilot and production batches and indicate satisfactory uniformity as well as compliance with the specification.

- Stability of the Product

36 months data generated under ICH conditions are presented in the primary stability study. The parameters evaluated were stability indicating. A supplementary stability study was also conducted to address the effect of the capsule shell colours in stability.
Photostability testing was conducted according to the ICH guideline for photostability testing of new active substances and medicinal products. The results indicate that the drug substance in the capsule formulation is chemically stable with respect to light.
Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

3. Part III: Toxico-pharmacological aspects

Introduction

Duloxetine is a combined serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI), which weakly inhibits dopamine reuptake and has no significant affinity for histaminergic, dopaminergic, cholinergic or adrenergic receptors. The proposed indication for duloxetine is major depression disorder(MDD).

Duloxetine contains a formulation in the form of capsules for oral administration, containing enteric-coated pellets of duloxetine hydrochloride, designed to prevent degradation of the drug in the acidic environment of the stomach (delayed-release formulation). The excipients included in the formulation are general recognised as safe (GRAS) compounds, with the exception of hydroxypropylmethylcellulose acetate succinate (HPMCAS), and are widely used in oral pharmaceutical preparations.
Studies carried out to assess general pharmacodynamics and toxicology of hydroxypropyl methylcellulose acetate succinate indicate that it is poorly absorbed and is excreted predominantly in the faeces, with no significant toxic effects and therefore, does not appear to pose a toxicological liability as an enteric coating for duloxetine capsule.

The Applicant has submitted extensive documentation concerning nonclinical pharmacology and toxicology of duloxetine, as well as for related substances and impurities, and excipients included in the formulation. The initial development of duloxetine involved the maleate salt, but later experiments utilised the hydrochloride salt, which is the proposed salt for marketing.

The development programme of duloxetine was long, with initial toxicology studies being conducted in the mid-1980s. The first directive concerning the application of the Good Laboratory Practices (GLPs) in non-clinical studies carried out with chemical and pharmaceutical products dates 1987 (87/18/EEC) and therefore, several non-clinical studies were not carried out specifically under GLP standards. Studies previously conducted included in this dossier were carried out following previously established analytic procedures, with an extensively description of the material and methods used, and reviewed by the scientific committee where these studies were published, that guarantee their quality. The rest of the studies were performed in accordance with Good Laboratory Practise standards.

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

A range of pharmacodynamic studies was performed with duloxetine concerning primary pharmacodynamics. Duloxetine is a combined serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI). Reuptake by nerve endings is thought to be a primary mechanism for removing monoamines from the synapse and terminating their effects at pre- and post-synaptic receptors. Therefore, blockade of reuptake may increase synaptic levels of monoamines and enhance monoaminergic neurotransmission.

- *In vitro* **studies**

In vitro, duloxetine inhibits the uptake of 5-HT and NE. It weakly inhibits dopamine reuptake and has no significant affinity for histaminergic, dopaminergic, cholinergic or adrenergic receptors. Furthermore, duloxetine has relatively weak affinity in vitro for other neuronal receptors and binding

sites. None of the various hydroxy-substituted compounds had appreciable affinity for the 5-HT, NE and dopamine transporters. The R (-) enantiomer of duloxetine, was also a potent inhibitor of 5-HT and NE reuptake.

Studies evaluating the pharmacodynamic potential of the possible metabolites and/or degradation products of duloxetine were performed. The 5- and 6-hydroxy analogues of duloxetine had relatively high affinity for human 5-HT and NE transporters in vitro with K_i values ranging from 1 to 18.4 nM. The 6-Hydroxy-5-methoxy duloxetine metabolite had high affinity for human 5-HT transporters, whereas 5-hydroxy-6-methoxy duloxetine and the dihydrodiol isomers had low affinity for 5-HT and NE transporters. The 4-, 5-, and 6-hydroxy analogs of duloxetine, the dihydrodiol isomers, 5-hydroxy-6-methoxy duloxetine, 6-hydroxy-5-methoxy duloxetine and the conjugated compounds did not have appreciable affinity for neuronal receptors.
Conjugates of the various hydroxy-substituted compounds had greatly reduced affinity for the 5-HT and NE transporters. None of the compounds had appreciable affinity for human dopamine transporters.

- *In vivo* **studies**

As previously discussed, the effectiveness of duloxetine in the treatment of MDD is linked to its inhibition of presynaptic neuron reuptake of serotonin and norepinephrine in the central nervous system, resulting in elevated levels of serotonin and norepinephrine in the synaptic cleft, enhancing monoaminergic neurotransmission.
No specific animal models for MDD are available. Hence, the *in vivo* pharmacodynamic studies provide indirect evidence for the potential clinical efficacy of duloxetine. However, a forced swimming test, a behavioural test in rodents, is thought to predict the clinical activity of antidepressants.

Duloxetine was investigated in several animal models measuring activities in noradrenergic and serotonergic neural systems and in 'animal models' for depression. Duloxetine's activity in the behavioural assays indicates enhancement of 5-HT and NE neurotransmission, and activity in antidepressant models were in general agreement with the values obtained for blockade of ex vivo binding and increases in extracellular monoamines. Furthermore, it was investigated whether duloxetine produced an anticholinergic action.
Duloxetine dose-dependently reduced tetrabenazine-induced ptosis in mice (ED_{50} of 4.0 mg/kg) and in rats (ED_{50} of 14.0 mg/kg). Reserpine-induced hypothermia was significantly reduced by duloxetine with an ED_{50} of 12.1 mg/kg. When duloxetine (12.5-100 mg/kg p.o.) and 5-hydroxytryptophan (80 and 100 mg/kg i.p.) were administered simultaneously to mice and rats, head movement behaviour and tremor were observed. Duloxetine (ED_{50} of 27.6 mg/kg) reduced the immobility in the forced swimming test in mice. A dose-dependent (10-40 mg/kg) reduction in immobility by increasing the frequency of climbing behaviour was observed in the forced swimming test in rats. A weak anticholinergic action was demonstrated at 25-50 mg/kg of duloxetine but not at 100 and 200 mg/kg.

- Secondary pharmacodynamics

Duloxetine demonstrated activity in nonclinical models of pain and effects on lower urinary tract function, as a consequence of its mechanism of action, via an enhancement of serotonin and norepinephrine neurotransmission. Duloxetine suppressed food consumption in mice and rats, and suppressed alcohol consumption in selectively inbred high-alcohol-drinking rats, in a dose dependent manner.

- Safety pharmacology

The potential of duloxetine to alter cardiovascular, central nervous system (CNS), smooth muscle, renal, immune, and gastrointestinal motility functions, as well as its potential for substance abuse was examined as part of the safety pharmacology dossier provided by the Applicant.

Cardiovascular effects: *in vitro*, duloxetine had no effect on the function of the smooth and cardiac muscles at concentrations of 10^{-6} M and lower, while antagonistic effects were observed at concentrations of 10^{-5} and above. Duloxetine did not affect smooth or cardiac muscle function of rat and guinea pig at concentrations of 1 nM to 1 μM.
Cardiac ion channel results, together with QT measurements from dogs and humans would not indicate an arrhythmogenic risk with the use of duloxetine.

Central nervous system effects: Duloxetine would not be predicted to substantively affect CNS. It did not adversely affect CNS function of mice after single oral doses 3 mg/kg. At higher doses (10 and 30 mg/kg) an increase in hexobarbital-induced time sleep was observed, indicating that duloxetine may produce CNS depression or interfere with hexobarbital metabolism. Moreover, an increase in seizure threshold in electroshock-induced convulsions was observed at the highest dose. Comparable changes have been obtained following multiple dosing (5 days). Mydriasis has been reported in association with duloxetine treatment.

Gastrointestinal, renal and immunological effects: there were no important effects on gastrointestinal motility or immune functions in mice. Regarding renal function, no effects on urine volume were observed in rats based on the studies provided by the Applicant. However, a slight elevation of serum potassium levels and an increase in sodium excretion were observed with 10 and 20 mg/kg doses.

Potential for abuse: the abuse potential of duloxetine was evaluated in monkeys and rats; duloxetine demonstrated the above mentioned CNS effects in rats, but not in rhesus monkeys up to 64 mg/kg doses. Duloxetine also did not demonstrate cross physical dependence potential with barbital or physical dependence-producing potential. As such, duloxetine would not be expected to pose a risk for substance abuse.

Based upon the results of these studies, therapeutically relevant doses of duloxetine would not be predicted to substantively affect CNS, smooth muscle, renal, immune, or gastrointestinal functions, neither would be expected to pose a risk for substance abuse. Potential secondary pharmacologic reactions at clinical doses would be limited to potential increases in pulmonary pressure, pulmonary vascular resistance, and respiratory rate. However, these effects are attributable to the known actions of norepinephrine and serotonin (Brunner and Gross 1979; Garattini and Valzelli 1965; Weiner 1985), and were only observed in anaesthetised animals.

- Summary of salient findings

The rationale for the development and application for marketing approval of the duloxetine formulation is well established. In vitro, duloxetine was an inhibitor of both serotonin and norepinephrine reuptake and a relatively weak inhibitor of dopamine reuptake. In addition, no significant affinity for histaminergic, dopaminergic, cholinergic or adrenergic receptors was evidenced.
The effectiveness of duloxetine in the treatment of MDD is linked to its inhibition of presynaptic neuron reuptake of serotonin and norepinephrine in the central nervous system, resulting in elevated levels of serotonin and norepinephrine in the synaptic cleft, enhancing monoaminergic neurotransmission. Although no specific animal models for MDD are available, the in vivo pharmacodynamic studies provide indirect evidence for the potential clinical efficacy of duloxetine.
At therapeutic range, duloxetine is not expected to pose a risk on CNS, smooth muscle, renal, immune, or gastrointestinal functions. Substance abuse is unlikely.
The extent and scope of the documentation provided in this application are appropriate to support the non-clinical-pharmacology profile of duloxetine
All the non-clinical-pharmacology information provided is supported by relevant bibliographical references.

Pharmacokinetics

The Applicant has conducted a number of studies concerning the absorption, distribution, metabolism, and excretion of duloxetine in mice, rats, and dogs. Only limited metabolism and excretion were

evaluated in the monkey, since the dog had been chosen as the nonrodent specie for use in the toxicology programme. Radiolabeled drug was administered in the pharmacokinetic, metabolism, excretion, and tissue distribution studies. The plasma protein binding of ^{14}C-duloxetine has been determined in mouse, rat, dog, and human plasma. Additional studies have investigated the placental transfer of ^{14}C-duloxetine in rats and the excretion of ^{14}C-duloxetine into milk of lactating rats.

- Absorption- Bioavailability

The Applicant has conducted a number of studies concerning absorption of duloxetine in several animal species. Duloxetine was well absorbed in these species after gavage or dietary administration
After oral administration, duloxetine is well absorbed and extensively metabolised, t_{max} being approx. 1.5 hours in mice and rats. Absorption was found to be greatest from the duodenum and least from the stomach. Additionally, pharmacokinetics of duloxetine were similar in fed and fasted male rats.
Bioavailability was determined to be 21% in rats and 5% in dogs, probably due to extensive metabolism in the latter.
No consistent gender differences in exposure occurred in dogs, although female rats tended to have higher exposure than male rats and male mice had greater values than female mice, but only at the highest doses tested. Even though the AUC values increased with increasing doses in mice, rats and dogs, these increases were not always proportional at the higher doses. Additionally, there was no evidence of accumulation with increasing duration of exposure.

- Distribution

With respect to the distribution of duloxetine, several studies using quantitative whole-body autoradiography (QWBA) and tissue dissection studies techniques were performed. Duloxetine was highly bound to proteins in plasma, the mean percent bound to human plasma proteins at a duloxetine concentration of 150.2 ng/mL being 95.9%
Duloxetine was present in high concentrations in the stomach and intestinal contents at 3 to 12 hours postdose. Kidney, liver, and lung contained the highest tissue concentrations.
Duloxetine and/or its metabolites were distributed into breast milk of rats, and does undergo placental transfer. Therefore, embryonic tissues were exposed to duloxetine and its metabolites during the period of organogenesis in the embryo-foetal toxicity studies. Although there was no embryo-foetotoxicity effect observed, delay in postnatal development was reported.
In conclusion, duloxetine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. While breast-feeding, the use of duloxetine, is not recommended.

- Metabolism

The Applicant has performed a number of studies concerning metabolism of duloxetine in mice, rats, dogs and monkeys. After oral administration, duloxetine was well absorbed, but extensively metabolised regardless of the salt form. Overall, the liver was determined to be the primary organ responsible for the metabolism of duloxetine. In all animal species, the major biotransformation pathways involve several oxidations, especially in the naphthyl ring followed by further oxidation and conjugation or formation of a dihydrodiol. Additional reactions involved cleavage at the ether linkage to form thienyl derivatives and naphthol.
Some differences related to the metabolic profile and exposure exist between animals species and humans.
Duloxetine was a mixed cytochrome P-450 inducer in all species tested, at higher doses CYP1A and CYP2B were induced), but there was no significant induction of CYP1A2 or CYP3A in cultured human hepatocytes. Both CYP2D6 and CYP1A2 participate in the biotransformation of 4-hydroxy and 5-hydroxy duloxetine, suggesting that the clearance of duloxetine would be related to the levels and activities of both of these enzymes.

- Excretion

Several excretion studies were performed by the Applicant in mouse, rat, dog and human.
The excretion profile was similar after either oral or intravenous administration to rats and dogs, which indicates that duloxetine was well absorbed and that elimination was not affected by the route of administration. Duloxetine was cleared rapidly primarily by metabolism in all species tested, and one or more of its metabolites has an extended elimination phase.

Mice, rats, and dogs excreted the majority of a single oral dose of ^{14}C-duloxetine in the faeces, whereas humans excreted a larger amount of the dose in urine. Further, approximately 66% of the radioactivity excreted in the bile is reabsorbed in rats, indicating that enterohepatic circulation of metabolites likely contributes to the extended elimination phase of radioactivity in the animal species.

- Pharmacokinetic drug interactions

Duloxetine is a moderate inhibitor of CYP2D6, and therefore, caution is advisable if administering duloxetine together with other CYP2D6 inhibitors. Concomitant use of duloxetine with drugs undergoing CYP2D6 metabolism may result in higher concentrations of the latter. There was no significant induction of CYP1A2 or CYP3A in cultured human hepatocytes. Concomitant use of duloxetine with potent inhibitors of CYP1A2, like fluvoxamine, ciprofloxacin or enoxacine, will result in higher concentrations of duloxetine and therefore co-administration is contraindicated.
Duloxetine is contraindicated in patients taking monoamine oxidase inhibitors (MAOI). It should not be used within at least 14 days of discontinuing treatment with MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping duloxetine before starting MAOI.

- Summary of pharmacokinetic parameters

The Applicant has appropriately described the non-clinical pharmacokinetics properties for duloxetine. A number of studies concerning the absorption, distribution, metabolism, and excretion of duloxetine in mice, rats, and dogs have been performed.
Rats might be suggested to be the most appropriate species for toxicology studies since major biotransformation pathways for duloxetine, in female rats as in man, were similar. However, mice and dogs are also valuable since exposure to specific human circulating metabolites could be seen in their plasma.
Duloxetine was well absorbed in the mentioned species, and absorption was maximum at the duodenum. It did not show evidence of accumulation when duration of exposure increased.
Duloxetine presented high protein binding across all species. Although it is not widely distributed it crosses the blood-brain barrier, undergoes placental transfer and is excreted into milk.
Duloxetine is extensively metabolised, primarily by the liver.
The main pharmacokinetics features are summarised in the following table:

Table 1. Summary of pharmacokinetics for duloxetine

Absorption	Well absorbed. After oral administration: t_{max} = 1.5 hrs in mice, rats, dogs and monkeys t_{max} =6 hrs in humans; with food t_{max} delayed to 10 hrs (variable)
Bioavailability	Rat approximately 21%. Dog approximately 5%. Human approximately 50% (32%-80%)
Dose proportionality	Linear kinetics was seen in mice and rats. In dogs, linear kinetics was observed at low daily doses (< 30 mg/kg). Non-linear at and above daily doses of 30 mg/kg in dog. Non-linear kinetics in humans
Terminal plasma half-life	Mouse: 2.1 hrs, radioactivity half life: 27 hrs Rat: 1.5 hrs, radioactivity half life: 122 hrs Dog: 4 hrs, radioactivity half life: 93 hrs Monkey: 3.5 hrs, radioactivity half life: 91 hrs Human: 12.1 hrs, radioactivity half life: 120 hrs
Distribution	High protein binding (93.6%-97.3% in all species). Not widely distributed but crosses the blood-brain barrier. Distribution over placenta and excreted into milk.
Metabolism	Rapid and extensive metabolism. Some differences related to the metabolic profile and exposure exist between animals species and humans.
Excretion	Mice, rats and dogs: main route via faeces (46%-77%). Monkey: main route via urine (58%) Human: main route via urine (72%) Biliary excretion in rats, dogs.

Toxicology

Duloxetine hydrochloride has been evaluated in a variety of toxicology studies in laboratory animals and in vitro test systems. Studies included single-dose toxicity in mice, rats, and dogs; repeated-dose toxicity in mice, rats, and dogs; in vitro and in vivo genotoxicity; carcinogenic potential in mice and rats; and reproductive and developmental toxicity in rats and rabbits.
All toxicity studies were performed according to GLP.

- Single dose toxicity

Single-dose toxicity studies were conducted with duloxetine hydrochloride and duloxetine maleate in mice, rats and dogs using oral administration, the intended clinical route. In general, the toxicologic effects seen in the three species were extensions of the pharmacology of duloxetine. The primary

findings following oral administration were related to central nervous system (CNS) effects (i.e., tremors, convulsions, emesis, mydriasis, salivation, and hyper-responsiveness).
The median lethal doses in mice were approximately 300-400 mg/kg, and in rats 500-600 mg/kg (males) and 300-500 mg/kg (female). In dogs, no deaths occurred at the maximum tested dose of 100 mg/kg.

- Repeat dose toxicity

Repeat-dose toxicity studies were conducted with duloxetine hydrochloride and duloxetine maleate in mice, rats and dogs using dietary (mice and rats) or gavage (dogs) administration. Altogether eight studies were performed.
Based on the results provided by the Applicant, the most relevant adverse events, target organ-related to duloxetine administration in all species tested was the liver, with signs occurring at or below the clinical exposure in all animal species investigated. The changes observed in this target organ did not appear to be indicative of toxicity, and they could have been a consequence of hepatic induction. Major findings were increased liver weights, moderate induction of hepatic enzymes (CYP1A1 and CYP2B) and slight to moderate centrilobular hypertrophy. Slight lipofuscin pigmentation was also noted in male mice.
In conclusion, the mainly adverse events related to duloxetine prolongued administration involve the liver, which could be consistent with the fact that duloxetine accumulates in this organ. Based on toxicologic effects from the repeat-dose studies, and taking into account the steady-state AUC values from the interspecies comparison study, several hepatic issues are observed across species at levels equal to or below therapeutic exposure multiple in humans.

- Genotoxicity *in vitro* and *in vivo*

Duloxetine maleate and duloxetine hydrochloride were not mutagenic when tested at appropriate doses in a battery of genotoxicity in vitro and in vivo studies that included all relevant positive controls. All studies were performed with duloxetine hydrochloride or maleate according to GLP.
There was no evidence of induced mutation by treatment with duloxetine maleate and duloxetine hydrochloride when tested.
Taking into account the results of these studies, duloxetine can be considered as a non-genotoxic substance.

- Carcinogenicity (with toxicokinetics)

The oncogenic/carcinogenic potential of duloxetine hydrochloride was evaluated in both mice and rats. The studies were performed according to GLP.
A dose dependent increase in the percentage of cells with diplochromosomes was seen in the in vitro chromosomal aberration test in CHO cells. Hepatocytes with more than one nucleus are a common histological finding. However, hepatocytes with more than 2-3 nuclei are rare.
Multinucleated cells were seen in the liver in the rat carcinogenicity study. The underlying mechanism is unknown. The multinucleated hepatocytes were observed as a dose-related effect in the rat carcinogenicity study without any sign of other pathological changes observed in the hepatocytes. No genotoxicity or hepatic tumourigenesis were observed. No multinucleated hepatocytes were seen in either the mouse or dog, which indicates a species-specific effect in the rat. However, the clinical relevance of this finding is unknown. To properly reflect this information, the following text is included in section 5.3 of the SPC: " Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown."

- Reproductive and developmental studies

Fertility studies were conducted by the Applicant to test reproductive performance in both male and female rats. Duloxetine had no effect on male fertility and effects in females were only evident at doses that caused maternal toxicity. Furthermore, foetal viability and morphology were not adversely

affected by treatment. In a pre/postnatal toxicity study in rat, duloxetine induced adverse behavioural effects in the offspring at systemic exposures levels below maximum clinical exposure (AUC).
In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. As a consequence of this, the SPC states that duloxetine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus, while women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy.

- Local tolerance

Fischer 344 rats given daily 30-minute intravenous infusions at doses of 1, 5, or 10 mg/kg had findings of excessive irritation at the injection sites. Systemic toxicity was not observed in rats given 1 mg/kg/day for 15 days. Similarly, daily 30-minute intravenous infusions to beagle dogs at doses of 1, 2.5, or 5 mg/kg had no evidence of systemic toxicity. However, local irritation at the injection sites precluded dosing of the 5-mg/kg/day group for longer than 10 days.

- Other toxicity studies

The potential for immunogenicity and hypersensitivity-eliciting antigenicity of duloxetine was evaluated in a number of studies in guinea pigs and mice. Duloxetine was not immunogenic and does not possess hypersensitivity-eliciting antigenicity in any of the studies performed. These results indicate that the risk of duloxetine causing adverse allergic reactions is negligible.

The abuse potential of duloxetine was evaluated in monkeys and rats. Duloxetine did not demonstrate cross physical dependence potential with barbital or physical dependence-producing potential, or any reinforcing effects. The results from studies specifically designed to examine abuse potential indicate that duloxetine would not be expected to pose a risk for substance abuse.

The enteric coating, HPMCAS, has no evidence of absorption; further, HPMCAS has been widely used in medicinal products for oral use in several countries and therefore would not pose any toxicological concern.

Ecotoxicity/environmental risk assessment

An environmental risk assessment was submitted. Although duloxetine would be regarded as a medium risk for aquatic organisms, a low potential for bioaccumulation is observed. Further, duloxetine is extensively metabolised to metabolites that lack pharmacological activity, and therefore substantive excretion of duloxetine from humans is not expected; thus, duloxetine would not pose an environmental concern.

Discussion on the non-clinical aspects

Extensive documentation concerning nonclinical pharmacology and toxicology of duloxetine has been submitted, as well as for related substances and impurities, and excipients included in the formulation.
The data presented by the Applicant has been adequately supported by relevant literature references.
The rationale for the development and application for marketing approval of the duloxetine formulation is well established. *In vitro*, duloxetine was an inhibitor of both serotonin and norepinephrine reuptake, as other antidepressant compounds described in the literature. Blockade of the reuptake of these two monoamines increases the concentration in the synaptic cleft, thereby facilitating neurotransmission via serotonergic and adreneric receptors. Several *in vivo* pharmacodynamic studies showed that duloxetine has a profile similar to that seen for other substances approved for this indication.
Safety pharmacology studies on the cardiovascular system, central nervous system, gastrointestinal system, immune system and the kidney have been performed. At therapeutic range, duloxetine is not expected to pose a risk on CNS, smooth muscle, renal, immune, or gastrointestinal functions, and

substance abuse is unlikely. The extent and scope of the documentation provided in this application are appropriate to support the non-clinical-pharmacology profile of duloxetine.
Duloxetine is well absorbed in all studied species, and is extensively metabolised, especially in the liver.
For the treatment of pregnant women with MDD duloxetine should only be used if the potential benefits outweight the potential risk to the foetus.
Duloxetine was not shown to be genotoxic or carcinogenic in the studies performed, but multinucleated cells were seen in the liver in the rat carcinogenicity study a species-specific effect, the clinical relevance of this finding being unknown. These findings are reflected in the SPC.

4. Part IV: Clinical aspects

Introduction

The pharmacokinetic and pharmacodynamic characteristics of duloxetine have been assessed in healthy subjects, special populations, and patients with either major depressive disorder (MDD) or stress urinary incontinence (SUI). The pharmacokinetic data were available from a total of 294 subjects, including healthy volunteers, subjects with end-stage renal disease (ESRD), and subjects with cirrhosis in 21 clinical pharmacology studies and at least 421 patients in four Phase 2 and Phase 3 clinical trials.

Pharmacokinetics

Duloxetine is a chiral compound. The S-enantiomer seems to be the one that has been developed by the Applicant. Since the in vitro pharmacologic activity of the two enantiomers is similar, interconversion, should it occur would be postulated to result in no or only slight changes in the in vivo therapeutic effect. Moreover, since the assay was not specific to a single enantiomer, the pharmacokinetics of duloxetine would reflect the combined data on both enantiomers.

The pharmacokinetics of duloxetine have been characterised in healthy men and women over a single-dose range of 20 mg to 60 mg and over a multiple-dose range of 40 mg/day to 160 mg/day.

For the majority of the studies, duloxetine concentrations were determined using validated high performance liquid chromatography tandem mass spectrometry (HPLC/MS/MS) methods. The assay was validated over the concentrations range of 0.5 ng/mL to 100 ng/mL with higher concentrations obtained after dilution of the samples. In some studies, the two major metabolites of duloxetine - the glucuronide conjugate of 4-hydroxy duloxetine and the sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine - were determined. The metabolite concentrations were obtained using a validated HPLC/MS/MS method over the concentration range of 1 ng/mL to 1000 ng/mL. The overall relative standard deviation (a measure of precision) and absolute relative error (a measure of accuracy) were less than 10% for both assays. Duloxetine and its two major metabolites were found to be stable in plasma stored frozen for the length of time that the study samples were stored under similar conditions.

- Absorption

Results from mass balance studies indicate a fairly high extent of absorption (>70%) of duloxetine. Duloxetine is a delayed release formulation (capsules containing enteric-coated pellets), and as a result, T_{max} occurs, at about 6 hours. The absolute oral bioavailability was estimated to a mean of 50%, but individual results ranged between 32 and 80%.

Bioequivalence between the clinical trial and the marketing formulations of duloxetine was demonstrated using a 60 mg dose. This is acceptable, since all strengths of the final formulation contain the same enteric-coated pellets. When administered with a high-fat meal, there was a 6% decrease in C_{max} and an 11% decrease in $AUC_{0-\infty}$ The absorption was delayed by food, with an increase in T_{max} of about 4 hours. A specific dose recommendation with respect to food intake is not considered warranted based on this.

- Distribution

Duloxetine has an extensive tissue distribution and is highly bound to plasma proteins. Different figures have been reported, but the degree of binding was generally above 95%. Duloxetine is bound both to albumin and to α_1-acid glycoprotein (AAGP). Since AAGP is a protein with variable plasma concentrations, within and between patients, e.g. due to disease states like infections, this could be a source of variability in the pharmacokinetics of duloxetine.
The urinary metabolites of duloxetine were moderately bound to plasma proteins and this binding was unaffected by the presence of duloxetine.
Protein binding is not affected by end-stage renal disease (ESRD) or by hepatic impairment, and is independent of duloxetine concentration.

- Elimination

Duloxetine is predominantly eliminated in the urine after undergoing extensive metabolism to numerous metabolites that are pharmacologically inactive.
Comparison of the metabolite-to-parent ratio values after IV and oral duloxetine reveal that a larger fraction of the drug is metabolised upon oral administration, likely reflecting first-pass metabolism.
The major biotransformation pathways involve oxidation in the naphthyl ring, followed by further oxidation, methylation, and conjugation. The two major circulating metabolites of duloxetine are the glucuronide conjugate of 4-hydroxy duloxetine and the sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine. The cytochrome P450 isoenzymes involved in the oxidative metabolism of duloxetine seem to be CYP1A2 and CYP2D6 based on *in vitro* and *in vivo* data. Both CYP1A2 and CYP2D6 were identified as participants in the hydroxylation at 4 and 5 positions, the two dominant routes of duloxetine metabolism. Should the activity of one of CYP1A2 and CYP2D6 be absent or decreased in a subject, the other enzyme would be available to metabolise duloxetine. No unchanged duloxetine is excreted in urine.

In vitro studies indicate that neither of these metabolites contributes to the pharmacologic activity of duloxetine.
Hepatic impairment results in a decrease in the formation of the metabolites, which leads to higher plasma concentrations of duloxetine. In contrast, renal impairment (end stage renal disease treated with chronic haemodialysis) reduces their rate of elimination as evidenced by the longer t½ values of the metabolites.

- Dose proportionality and time dependencies

Dose proportionality has been assessed in several studies over a dose range covering the proposed dosage. These analyses, suggest that higher duloxetine doses are associated with slightly lower CL/F and, correspondingly, the average steady-state concentrations at higher doses are slightly higher than would be projected for a dose-proportional increase. Nevertheless, the magnitude of the deviation from either strictly linear pharmacokinetic behaviour or dose-proportional increases across dose is small, particularly in comparison to the degree of interindividual variability in plasma concentrations. Most importantly, within any individual subject, the deviations from classical linearity or dose-proportionality appear to be very small in magnitude. Thus, the apparent slight non-linear behaviour and more-than-proportional increase in plasma concentration across the duloxetine dosage range of 40 mg/day to 120 mg/day are unlikely to be clinically important.
Steady state is generally reached within 3-5 days.

- Special populations

Hepatic impairment: a study using a single low (20 mg) dose was used to study the effect of moderate (Child-Pugh Class B) hepatic cirrhosis on the pharmacokinetics of duloxetine and the major metabolites. However, the pharmacokinetics of duloxetine and its metabolites were not studied in patients with mild or severe hepatic insufficiency. A clear effect was observed after the single dose, with an almost 5-fold increase in $AUC_{0-\infty}$ and a 3-fold longer T½ of duloxetine. The mean plasma protein binding was lower in the hepatically impaired subjects (not statistically significant, though),

indicating an even larger difference in mean unbound exposure. The subjects included had moderate cirrhosis according the Child-Pugh classification, with scores of 7 or 8. Thus, there is an effect of hepatic disease on the pharmacokinetics of duloxetine even at a quite moderate degree of severity.
The SPC specifies that duloxetine is contraindicated in patients with liver disease resulting in hepatic impairment.

Renal impairment: renal impairment results in a substantially higher plasma concentrations of the glucuronide conjugate of 4-hydroxy duloxetine and the sulphate conjugate of 5-hydroxy-6-methoxy duloxetine (9-fold and 7-fold higherAUC, respectively) and longer elimination half-life (2-fold and 1.6-fold longer, respectively) compared to healthy controls. The Applicant proposes that duloxetine 30 mg BID may be given to ESRD subjects to produce a plasma concentration-time profile similar to that in healthy subjects receiving 60 mg twice daily (BID). Alternatively, duloxetine 60 mg once daily (QD) may be administered to ESRD subjects so that the steady-state drug concentration is similar on average but this dosing regimen has a larger peak-to-trough fluctuation compared to healthy subjects on duloxetine 60 mg BID. Although the data supporting this statement come from a single-dose study, the Applicant states that, since the $t_{1/2}$ for duloxetine remain unchanged, no accumulation is likely to occur at steady state. However, in the view of the CHMP, and quite the opposite to duloxetine used for patients with stress urinary incontinence, patients with ESRD constitute a potential relevant target population for CYMBALTA. In this regard, the terminal half life for duloxetine's metabolites is significantly increased. Thus substantially higher plasma concentrations (9-fold and 7-fold higher, respectively) and longer elimination half-life (1.6-fold and 2-fold longer, respectively) were observed in ESRD subjects compared to healthy controls, suggesting a significant reduction of the renal clearance of duloxetine's conjugated metabolites in ESRD subjects. Although the Applicant states that the conjugated metabolites are not pharmacologically active and thus, only the changes in duloxetine pharmacokinetics are of clinical concern for ESRD subjects, the CHMP does not share the same view, as pharmacological inactivity does not necessarily mean lack of toxicity. In this regard, it was agreed to contraindicate severe renal impairment (creatinine clearance <30 ml/min).

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. 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.

A population pharmacokinetic analysis on patients with MDD (233 patients) revealed significant relationship between gender, smoking and dose and duloxetine CL/F (higher by 54% in males and 52% in smokers) It could be discussed that both facts considered altogether explain about 11% of the interpatient variability. The results from Pop-PK analyses in SUI and MDD suggest that the apparent plasma clearance is lower by approximately 1% for each year of age over the investigated age range (24 to 77 years). Nevertheless, the age effect could at most explain 6% of the interpatient coefficient of variation in CL/F and is unlikely to be clinically important. However, the information of effect of age in patients with MDD is limited, as most of the patients were below 50. It has been stated that a specific dosage recommendation based only on the patient's age would be regarded as unnecessary because an age-specific dose adjustment will not have an impact on the interpatient variability or the range of prospective steady-state duloxetine concentrations for any adult age group.

- Pharmacokinetic 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. On the other hand, since CYP2C8 isoenzymes might be involved in the occurrence of clinically important interactions due its inhibition, 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, food**,** 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.
It has been discussed whether when considered isolatedly, none of these factors (except ESRD and liver cirrhosis) is expected to induce clinically relevant changes in duloxetine PK requiring dosing adjustments.

Pharmacodynamics

Six studies were designed to evaluate pharmacodynamics in healthy volunteers. Four of them were aimed to assess pharmacodynamyc effects and safety during treatment with increasing doses of duloxetine and the other two evaluated pharmacodynamic interactions with ethanol and lorazepam.
No clinical data on primary pharmacology are provided. This was considered acceptable, as there are no validated PD models for MDD.

Study Code	Design	Subject	Dosage Regimen	Objectives
SBBN	Single-blind, randomised, outpatient study	15 healthy subjects (5 M, 10 F)	DLX beginning at 40 mg/BID for the first 2w, increasing by 40 mg/d each week up to 120 mg/BID.	Safety and tolerability
BD-O001	Double-blind, randomised, placebo-controlled, crossover.	12 healthy male subjects	DLX 80 mg/d single dose DLX 120mg/d in two doses DPM 100 mg/d in 2 doses Placebo	PK and pD parameters.
HMAE	Double-blind, randomised, three-way crossover study.	12 healthy male subjects	DLX 5 mg/d 14 d DLX 20 mg/d 14 d Placebo 40 d	Profile of mood scales.
SAAN	Randomised, 4 groups, duloxetine and placebo blinded (not clomipramine)	27 healthy male subjects	DLX 20 mg/d twice daily 14 d DLX 60 mg/d twice daily 14 d CMP 100 mg/d twice daily 14d Placebo 14 d	5-HT and NE reuptake blockade
HMBA	Randomised, single-blind, three-period crossover study	16 healthy subjects (6 M, 10 F)	DLX 60 mg single dose Ethanol single dose	Ethanol pD interaction
HMBD	Randomised, two-period, crossover study.	16 healthy subjects (8 M, 8 F)	DLX 60 mg twice daily Lorazepam 2 mg twice daily	Lorazepam pD interaction

DLX: Duloxetine; CMP: Clomipramine; DPM: Desipramine

- Mechanism of action

In vitro, duloxetine was a potent inhibitor of both serotonin and norepinephrine 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.

A variety of in vivo studies have been conducted to explain the primary pharmacodynamics of duloxetine. Pharmacodynamics directly related to the molecule must be inferred for claims toward the intended clinical utility of duloxetine, as specific animal models for MDD are not available. The models described provide indirect pharmacological evidence for the potential clinical efficacy of the molecule. Duloxetine increased extracellular levels of 5-HT and NE in the rat hypothalamus in a dose-dependent manner to 450% and >1000% of baseline levels, respectively. Extracellular levels of 5-HT, NE, and DA were also increased in a dose-related manner in frontal cortex to about 240%, 300%, and 260% of baseline levels, respectively. The increase of DA in the frontal cortex may be due to blockade of the NE reuptake carrier as DA transporters are present in low levels in frontal cortex and NE transporters regulate DA levels.

- Primary and Secondary pharmacology

Study HMAE studied the influence on mood of duloxetine in 12 healthy males. In a double-blind, randomised, three-way crossover study duloxetine 5 mg QD, duloxetine 20 mg QD or placebo were administered for 14 days. The effect on mood was registered with the Profile of Moods Scale. Duloxetine appeared to have no significant effect on mood in healthy men. The findings, however, cannot be considered conclusive since the observation period was limited to two weeks, and only a limited number of male subjects were studied

When drug –induced effects on sleep were evaluated (Study BD-O001) both 80-md QD and 60-md BID multiple dosing regimens of duloxetine and 50-mg BID desipramine demonstrated a clear REM suppression and a delay in REM occurrence.

As with SSRIs, duloxetine significantly increases systolic and diastolic blood pressure (6 and 4 mmHg) and heart rate. In the view of the CHMP 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 over 1000 patients in the phase III database. There is no signal indicating that duloxetine might prolong the QT interval regardless of the correction method used.

Clinical efficacy

- Dose response studies

Results of four initial phase 2 studies (Studies F1J-EW-E001, F1J-MC-HMAG, F1J-MC-HMAH, and F1J-MC-HMAI) were provided. They assessed the efficacy of low doses of duloxetine (ranging from 5 to 30 mg QD) in the treatment of MDD. Three out of them were double-blind, randomised and placebo controlled studies and the other one was open labelled and non-controlled study. These studies failed to demonstrate a statistically significant difference of duloxetine over placebo for the primary endpoint, although showed some effect when considering some secondary endpoints. So, these initial dosages of duloxetine were considered as to be in the lower-bound of the effective range and additional "dose finding" studies were performed using higher doses (up to 160 mg per day).
The two proof of concept studies HMAQa and HMAQb (powered 65%) also examined the doses. These were identical parallel group, double-blind, forced-titration active- and placebo-controlled studies comparing duloxetine titrated from 20 mg to 60 mg BID with placebo over 8 weeks of acute treatment. A fluoxetine 20 mg QD arm was used as an internal active comparator standard.
The primary efficacy evaluation in these studies was the comparison between duloxetine 60 mg BID and placebo at endpoint using mean change analysis of the 17-item Hamilton Depression Rating Scale (HAMD17) total score. There were not statistically significant differences between fluoxetine and placebo for the mean change in HAMD17 total score in any of the studies. Duloxetine was numerically, but not statistically significantly, superior to placebo on the primary analysis. Only study

HMAQa showed statistically significant differences for some of the secondary endpoints (HAMD17 Maier subscale, CGI-Severity, CGI-Improvement, PGI-Improvement, and SF-36 Mental Component Summary and Mental Health subscales). The Applicant concluded that only Study HMAQa supports the efficacy of duloxetine 60mg BID in the treatment of patients with DSM-IV defined MDD. In the view of the CHMP, the results of these studies are inconclusive, as neither duloxetine nor fluoxetine showed a significant greater effect than placebo.
The Applicant went on studying the efficacy of different dosages of duloxetine during the Phase 3 development programme. In these studies duloxetine 20mg BID, 40 mg BID, 60 mg BID and 60 mg QD were used.
Based on the results of these studies, the Applicant recommends the use of Duloxetine 60 mg QD as the starting and the effective maintenance dose in the treatment of MDD. The main argument given by the Applicant to support this dosage was that 60 mg QD was the only dosage that demonstrated superiority over placebo in the three studies (two acute and the relapse prevention study) in which it was tested (in contrast to that seen for the remaining dosages for which superiority over placebo was only seen in a half of the studies in which were tested) and that the effect size observed was better or comparable to other duloxetine doses tested and paroxetine 20mg.However, duloxetine 60 mg QD (HMBH a and b) was not compared to any active control or to other duloxetine regimens.

- Main studies

The efficacy of duloxetine in patients with a DSM-IV diagnosis of major depressive disorder (MDD) has been evaluated in seven Phase 3 clinical studies: F1J-MC-HMATa, F1J-MC-HMATb, F1J-MC-HMAYa, F1J-MC-HMAYb, F1J-MC-HMBHa and F1J-MC-HMBHb, focusing on the treatment of acute symptoms, and study F1J-MC-HMBC, which focus on relapse prevention.

Although dosages and secondary study objectives were not identical, all of these studies apart from Study HMBC used the same primary efficacy objective (mean change from baseline on the HAMD17 total score, similar methodology and determined patient eligibility based on the same clinical algorithm.

Study HMBC employed time to relapse as the primary outcome measure, and stipulated a higher HAMD17 entry criterion than the other Phase 3 studies.

The studies explored duloxetine doses of 40 mg daily (given as 20 mg twice daily [BID]), 60 mg daily (given as 60 mg once daily [QD]), 80 mg/day (given as 40 mg BID), and 120 mg/day (given as 60 mg BID).

OVERVIEW OF MAIN CLINICAL STUDIES: MAJOR DEPRESSIVE DISORDER

Study Design	Identifier	Groups	n	Duration
Randomised, double-blind, placebo- and active-comparator controlled, parallel group, fixed dose	**HMATa**	DLX 40 mg BID DLX 20 mg BID PLACEBO PAROX 20mg QD	84 9190 89	8 weeks
Randomised, double-blind, placebo- and active-comparator-controlled, parallel group, fixed dose	**HMATb**	DLX 40 mg BID DLX 20 mg BID PLACEBO PAROX 20mg QD	91 86 89 87	8 weeks
Randomised, double-blind, Placebo- and active-comparator-controlled, parallel group, fixed dose	**HMAYa acute Phase**	DLX 60 mg BID DLX 40 mg BID PLACEBO PAROX 20mg QD	93 95 93 86	8 weeks
Randomised, double-blind, placebo- and active-comparator controlled, parallel-group, fixed-dose	**HMAYb, acute Phase**	DLX 60 mg BID DLX 40 mg BID PLACEBO PAROX 20mg QD	103 93 99 97	8 weeks
Double-blinded continuation for those patients meeting selection critera after 8+1 week HMAYa Acute Period	**HMAYa, continuation Phase**	DLX 60 mg BID DLX 40 mg BID PLACEBO PAROX 20mg QD		26 weeks
Double-blinded continuation for those patients meeting selection critera after 8+1 week HMAYb Acute Period	**HMAYb continuation Phase**	DLX 60 mg BID DLX 40 mg BID PLACEBO PAROX 20mg QD		26 weeks
Randomised, double-blind, placebo controlled, parallel group, fixed dose	**HMBHa**	DLX 60 mg QD PLACEBO	123 122	9 weeks
Randomised, double-blind, Placebo controlled, parallel group, fixed dose	**HMBHb**	DLX 60 mg QD PLACEBO	128 139	9 weeks
12-weeks unblinded responders entering randomised, double-blind, placebo controlled, parallel, fixed-dose groups	**HMBC**	DLX 1x60 mg PLACEBO	136 142	6 months postrand.
Open-label continuation study	**HMAU**	DLX 60 mg QD		52 weeks

In Studies HMATa/b, HMAYa/b and HMBHa/b investigators and patients were blinded to the time at which randomisation to active treatment occurred and were told patients might receive between 0 and 2 weeks of placebo. Patients in protocols HMAT and HMAY received 1 week of placebo lead-in, whereas patients in protocol HMBH received no placebo lead-in at all. Thus, the duration of the active therapy period was different among the studies: 8 weeks for Protocols HMAT and HMAY; 9 weeks for Protocol HMBH.

Study HMBC consisted of five phases: an initial screening phase, followed by a 12-week, open-label acute phase (for separating patients who responded to duloxetine); patients who responded to duloxetine entered the 26-week, double blind continuation phase for determination of relapse prevention; if patients relapsed, they could enter an optional rescue phase or go straight to the follow-up phase. Response criteria for entry into the continuation phase were defined as meeting the following at both Weeks 10 and 12 of acute phase treatment: HAMD17 ≤9, CGI-Severity ≤2 and not meeting DSM-IV criteria for major depressive episode. Patients who entered the continuation phase were evaluated for re-emergence (defined as a HAMD17 ≥12) and primary for relapse (an increase in

the CGI-Severity score of at least two points relative to randomisation baseline for two consecutive visits and meeting the criteria for major depressive episode for two consecutive visits (MINI)).
Study Participants

Patients, for inclusion, had to meet the DSM-IV criteria for MDD. All enrolled patients had a HAMD17 total score ≥15 (≥18 for Study HMBC) and a CGI-Severity score ≥4 at Visits 1 and 2. Diagnosis was confirmed by the Mini International Neuropsychiatric Interview (MINI), with current episode duration of ≥2 weeks. In Study HMBC, patients must have had at least one previous major depressive episode. No baseline differences between groups were observed for some demographic and pathological characteristics in any of these studies.

Patients were excluded from the Phase 3 studies if they had any current and primary psychiatric (Axis I) disorder other than MDD, including but not limited to dysthymia; any previous diagnosis of bipolar disorders, schizophrenia, or other psychotic disorders; any anxiety disorder as a primary diagnosis within the past year; the presence of a personality (Axis II) disorder which, in the judgment of the investigator, would have interfered with compliance with the study protocol; a lack of response in the current episode to two or more adequate courses of antidepressant therapy at a clinically appropriate dose for a minimum of 4 weeks; serious medical illness; electroconvulsive therapy within the past year; were using a monoamine oxidase inhibitor (MAOI) within 2 to 5 weeks prior to Visit 1 (within 14 days prior to Visit 2 for Study HMBC); were using fluoxetine within 4 to 5 weeks prior to Visit 1 (within 30 days prior to Visit 2 for Study HMBC); were judged to be at serious suicidal risk; were initiating or stopping psychotherapy within 6 weeks prior to enrolment, or were initiating psychotherapy at any time during the study. Women who were pregnant were also excluded.
Endpoints

The primary efficacy measure used in all duloxetine Phase 3 studies of MDD was the HAMD17 (mean change from baseline), with the exception of the relapse prevention Study HMBC, where the primary efficacy measure was the time to relapse.

Secondary efficacy measures were:
HAMD17 Response and Remission rates were analyzed in all principal efficacy studies. Response was defined as a ≥50% reduction in the HAMD17 total score from baseline to endpoint. Remission was defined as a HAMD17 total score ≤7 at endpoint.

HAMD17 Subscales included the Core subscale (items 1, 2, 3, 7, and 8) and the Maier subscale (items 1, 2, 7, 8, 9, and 10), which consisted of items thought to represent the "core" symptoms of depression. The Anxiety/Somatization subscale of the HAMD17 (items 10, 11, 12, 13, 15, and 17) evaluated severity of psychic and somatic manifestations of anxiety as well as agitation. The Retardation/Somatization subscale (items 1, 7, 8, and 14) evaluated dysfunction in mood, work, and sexual activity, as well as overall motor retardation. The Sleep subscale (items 4, 5, and 6) evaluated initial, middle, and late insomnia.

Montgomery and Asberg Depression Rating Scale (MADRS), used to measure severity of depressive mood symptoms.

Clinical Global Impressions of Improvement (CGI-Improvement), to measure the degree of improvement at the time of assessment.

Clinical Global Impressions of Severity (CGI-Severity),to record the severity of illness at the time of assessment.

Patient's Global Impressions of Improvement (PGI-Improvement), was completed by the patient to measure the degree of improvement at the time of assessment.

Hamilton Anxiety Rating Scale (HAMA), that measures the presence and severity of anxiety. The 14-item version of this scale was used to assess the severity of anxiety and its improvement during the course of therapy.

Beck Depression Inventory-II (BDI-II) scale was completed by the patient and rated the severity of depression and its improvement during the course of therapy.

Health outcome measures such as the Quality of Life in Depression Scale (QLDS) that measures change in subjective well-being, the Sheehan Disability Scale (SDS) , which assess a patient's degree of disability and the Short Form 36 Health Survey (SF-36).

Somatic symptom and pain measures such as the Visual Analog Scales (VAS, to assess the severity of overall pain), the Somatic Symptom Inventory (SSI) and the Symptom Questionnaire – Somatic Subscale (SQ-SS, which focuses on somatic symptoms) and the HAMD17 Item 13 (a post hoc measure of the body pain).

Statistical methods

All analyses were conducted on an intent-to-treat basis (patients had to have a baseline and at least one non-missing post-baseline measurement). Although the protocols of the Acute Phase Studies specified a repeated measure analysis as the primary methodology for efficacy analysis, an analysis of covariance (ANCOVA) for the mean change (LOCF) from baseline to endpoint was presented based in response to a recommendation given by the CPMP and thus, is considered valid since the results of the repeated measure analysis were also provided and were consistent with the new analysis. However, since the rate of discontinuation in duloxetine (as expected in studies in MDD) was considerably high (around 30% as a mean), and considering that most patients on active therapy discontinue due to AEs while lack of efficacy is the usual cause of discontinuation in the placebo arm studies, the LOCF might not be a conservative approach when imputing missing data. A sensitivity analyses was therefore requested to the Applicant. The results provided by the Applicant supported the robustness of the observed effect. The Relapse Prevention Study focused on the differences between duloxetine and placebo on time-to-relapse using a log-rank statistic.

RESULTS

Studies HMBHA and HMBHB

The primary efficacy evaluation in these studies was a comparison between the duloxetine 60mg QD and placebo treatment groups at visit 8.

For study HMBHa, a statistically significantly greater decrease on the primary efficacy measure, HAMD17 total score, was seen for duloxetine 60 mg QD (LS mean change = -9.47, p<.001) compared with placebo (LS mean change = -5.67) by mean change analysis. Repeated measures analysis produced similar results. Compared with placebo-treated patients, patients treated with duloxetine 60 mg QD also showed statistically significantly higher rates of response (duloxetine = 45%, placebo = 23%, p<.001) and remission (duloxetine = 31%, placebo = 15%, p=.003). Duloxetine 60 mg QD was also statistically significantly superior to placebo on several secondary efficacy measures.

For study HMBHb, also statistically significantly greater decrease on the primary efficacy measure, was seen for duloxetine 60 mg QD (LS mean change = -8.75, p=.048) compared with placebo (LS mean change = -7.02) by mean change analysis. Repeated measures analysis produced similar results. Compared with placebo-treated patients, patients treated with duloxetine 60 mg QD also had statistically significantly higher rates of response (duloxetine = 50%, placebo = 35%, p=.017), but not remission (duloxetine = 32%, placebo = 24%, p= .212). Also superiority for several secondary efficacy measures was demonstrated.
However these results, the observed effect is modest (especially in study "b") and not completely consistent between both trials

Studies HMATa and HMATb
The primary efficacy evaluation in these studies was a comparison between the duloxetine 20 mg BID, duloxetine 40 mg BID, and placebo treatment groups at Visit 8. The protocol also intended to

demonstrate the noninferiority of duloxetine compared with paroxetine using combined data from Studies HMATa and HMATb.
Around 80% of the patients had moderate to severe MDD in both studies

For study HMATa, there were no statistically significant differences between duloxetine 20 mg BID and placebo or between duloxetine 40 mg BID and placebo on the primary efficacy measure, HAMD17 total score, by mean change analysis**.** There was also no statistically significant difference between these treatment groups for response or remission rates. However, duloxetine 20 mg BID and 40 mg BID were statistically significantly superior to placebo on some secondary efficacy measures (HAMD17 subscales and HAMD17 Item 1, QLDS score and CGI-Severity). Repeated measures analysis produced similar results

For study HMATb, a statistically significantly greater decrease on the primary efficacy measure was seen for duloxetine 20 mg BID dosing (LS mean change = -6.08, p=.022) and for duloxetine 40 mg BID (LS mean change = -6.77, p=.003compared with placebo (LS mean change = -3.67) by mean change analysis. There was no statistically significant difference between the duloxetine 20 mg BID and placebo treatment groups for response or remission rates. Nevertheless, compared with placebo-treated patients, patients treated with duloxetine 40 mg BID also had statistically significantly higher rates of response (duloxetine = 51%, placebo = 31%, p= .009) and remission (duloxetine = 50%, placebo = 30%, p=.008). Repeated measures analysis produced similar result. In contrast to Duloxetine 20 mg BID, Duloxetine 40 mg BID was statistically significantly superior to placebo on several secondary efficacy measures (included the MADRS scale)

According to these studies, it cannot be concluded on the efficacy of Duloxetine 20 mg BID over placebo in the acute treatment of MDD. However, duloxetine 40 mg BID has a greater effect than placebo in the acute treatment of MDD.

Studies HMAYa and HMAYb
The primary efficacy evaluation in these studies was a comparison between duloxetine 60 mg BID and placebo treatment groups at Week 8. The protocol also intended to demonstrate the noninferiority of duloxetine compared with paroxetine using combined data from Studies HMAYa and HMAYb

In study HMAYa, a statistically significantly mean decrease on the primary efficacy measure, HAMD17 total score, was seen for paroxetine 20 mg QD (LS mean change =-10.83), for duloxetine 40 mg BID (LS mean change =-10.22) and for duloxetine 60 mg BID (LS mean change =-11.06) compared with placebo (LS mean change =-8.07) by mean change analysis. Repeated measures analysis produced similar results. Compared with placebo-treated patients, patients treated with duloxetine 40 mg and 60 mg BID also had statistically significantly higher rates of response (duloxetine 40 mg=65%, duloxetine 60 mg =71%, and placebo =44%) and remission (duloxetine 40 mg =46%, duloxetine 60 mg= 52%, and placebo =30%).
Duloxetine 40 mg and 60 mg BID were statistically significantly superior to placebo on several secondary efficacy measures by mean change analysis. Repeated measures analysis produced similar results

Study HMAYb did not find statistically significant differences between either of the duloxetine dosages (40 mg and 60 mg BID) compared to placebo. It was argued that an additional analysis of the treatment-by-investigator interaction to the model showed a statistically significant effect, indicating that the difference between duloxetine 60 mg BID and placebo differed significantly among investigative sites.

Study HMBC
Patients treated with duloxetine 60 mg QD had a statistically significantly longer time to relapse (primary efficacy measure) than patients treated with placebo. The estimated (Kaplan-Meier) probabilities of relapse by 182 days were 19.7% for duloxetine 60 mg QD and 38.3% for placebo (p=.004). During the 6-month continuation phase, 17.4% of duloxetine-treated patients met the criteria for relapse compared with 28.5% on placebo (p = .042). A total of 58 patients assigned to placebo in the continuation phase were given duloxetine 60 mg QD in the rescue phase , and 29 patients assigned

to duloxetine 60 mg QD in the continuation phase were given duloxetine 60 mg BID in the rescue phase. Of the 56 patients assigned to duloxetine 60 mg QD, 43 (76.8%) responded to therapy and 32 (57.1%) met remission criteria. Of the 29 patients assigned to duloxetine 60 mg BID, 18 (62.1%) responded to therapy and 11 (37.9%) met remission criteria.
In the view of the CHMP, the main outcome of this study confirms the results of the continuation phase (i.e. the assessment of the time to relapse) and, in this sense, it has been shown a statistically significantly longer time to relapse and a lower percentage of relapse (17.4% on duloxetine vs 28.5% on placebo) in those patients treated with duloxetine 60 mg QD compared to those treated with placebo.
The Applicant also concluded that patients who had responded to duloxetine 60 mg QD and relapsed while still on duloxetine 60 mg QD or after being randomised to placebo, benefited from a dosage increase to 60 mg BID (120 mg daily) or from reintroduction of duloxetine 60 mg QD therapy. However, these conclusions are based on few patients and in the CHMP's view, the evidence produced in this regard is still limited

Comparison of Efficacy Results of All Phase III Acute Studies
The following table presents the HAMD17 total score at baseline, least-squares mean change and p-value comparison with placebo for the Phase III acute studies.
HAMD17 Total Score Mean Change from Baseline to Endpoint Phase III Acute Studies.

Study	Treatment Group	N	Baseline		Change	95% CI	p-Value Comparison with Placebo
			Mean	SD	LS Mean		
HMATa	PLACEBO	89	17.79	4.73	-4.14		
	DLX 20 BID	90	17.47	5.20	-5.30	(-3.05, 0.71)	.222
	DLX 40 BID	81	17.44	5.16	-5.59	(-3.38, 0.47)	.138
	PRX 20 QD	87	17.97	5.87	-5.96	(-3.72, 0.06)	.058
HMATb	PLACEBO	88	17.19	5.11	-3.67		
	DLX 20 BID	84	18.63	5.85	-6.08	(-4.47, -0.35)	.022
	DLX 40 BID	86	18.06	4.52	-6.77	(-5.15, -1.06)	.003
	PRX 20 QD	84	17.65	5.13	-5.18	(-3.56, 0.55)	.150
HMAYa	PLACEBO	93	19.86	3.58	-8.07		
	DLX 40 BID	93	19.88	3.54	-10.22	(-3.73, -0.58)	.007
	DLX 60 BID	93	20.17	3.41	-11.06	(-4.56, -1.41)	<.001
	PRX 20 QD	85	20.26	4.14	-10.83	(-4.37, -1.15)	.001
HMAYb	PLACEBO	99	20.58	3.73	-10.13		
	DLX 40 BID	93	21.30	2.96	-11.06	(-2.53, 0.67)	.253
	DLX 60 BID	102	21.38	4.46	-11.64	(-3.06, 0.02)	.054
	PRX 20 QD	97	21.03	3.38	-10.61	(-2.07, 1.11)	.552
HMBHa	PLACEBO	115	21.09	3.71	-5.67		
	DLX 60 QD	121	21.50	4.10	-9.47	(-5.55, -2.05)	<.001
HMBHb	PLACEBO	136	20.49	3.42	-7.02		
	DLX 60 QD	123	20.28	3.32	-8.75	(-3.45, -0.02)	.048

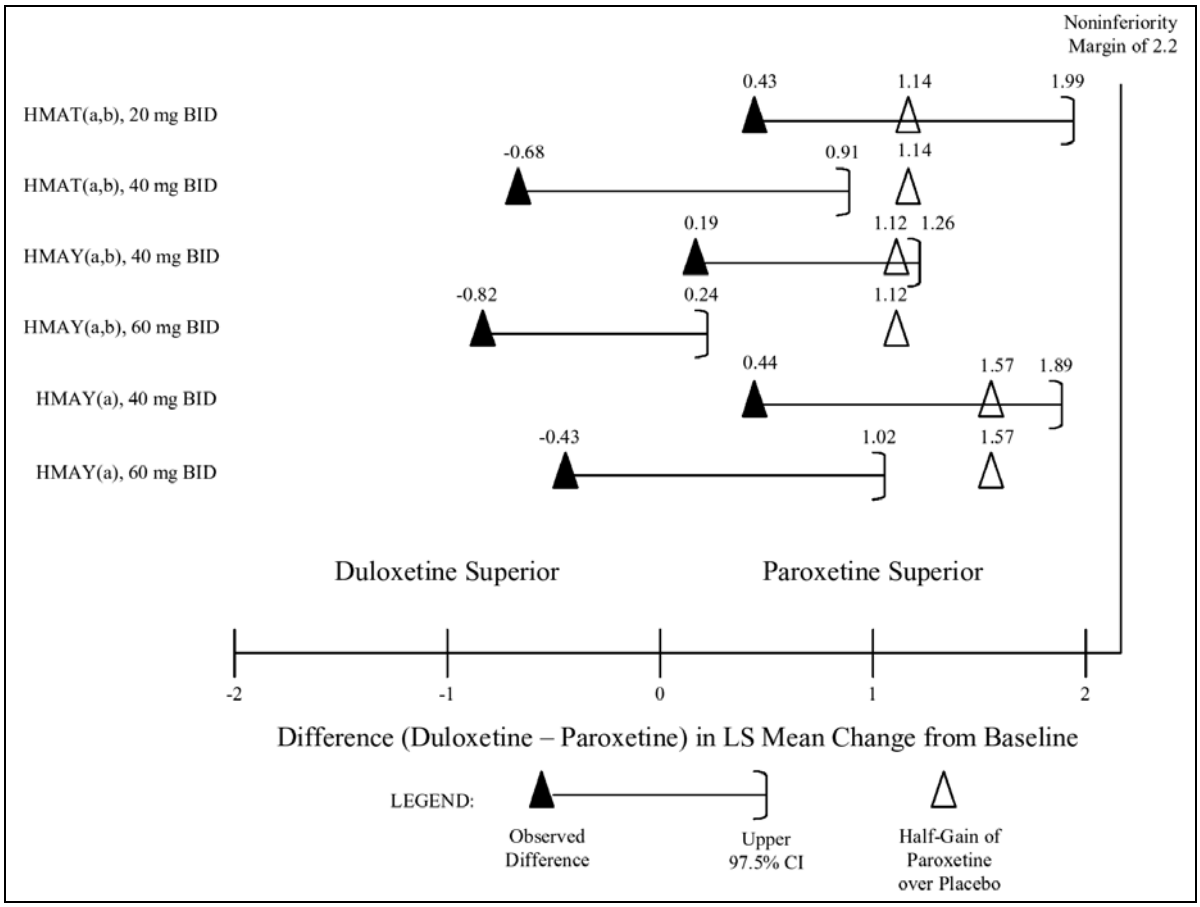
Abbreviations: HAMD17 = 17-item Hamilton Depression Rating Scale; BID = twice-daily; CI = confidence interval; DLX = duloxetine; LS = least squares,; PRX = paroxetine; QD = once-daily; SD = standard deviation.

There were four statistically positive acute studies(HMATb, HMAYa, HMBHa, and HMBHb), that is, studies in which duloxetine was statistically superior to placebo on the primary efficacy measure (change from baseline in HAMD17) and two negative studies.
The results of the response and remission rates were consistent with the primary efficacy results. These differences in the primary efficacy measures from placebo were seen at duloxetine doses of 20 mg BID, 60 mg QD, 40 mg BID, and 60 mg BID. However, these differences were not consistently seen throughout the studies and for the same doses: duloxetine 20 mg BID and 40 mg BID were superior to placebo in study HMATb but were not superior to placebo in the apparently identical Study HMATa; duloxetine 40 mg BID and 60 mg BID were superior to placebo in Study HMAYa but not in Study HMAYb, that were also apparently identical. These discrepancies could not be considered by themselves a matter of special concern, since negative studies are not uncommon in

MDD due to the lack of sensitivity. For this reason, the inclusion of an internal positive control adequately dosed is a crucial aspect in these studies. In this regard, although paroxetine is frequently uptitrated in clinical practice, and the available evidence of a dose-response relationship is lacking, 20 mg daily of paroxetine can be considered an acceptable active control.

A non-inferiority comparison, based on the per-protocol subset of patients, between duloxetine and paroxetine 20 mg QD was also established in the HMAT and HMAY protocols. The validity of this non-inferiority approach is questionable due to a number of relevant reasons:
Based upon a pre-specified non-inferiority margin of 2.2, duloxetine at doses of 20 and 40 mg BID in studies HMATa and HMATb combined and 40 and 60 mg BID in studies HMAYa/b was noninferior to paroxetine. However, the specified non-inferiority margin appears quite wide (2.2 in the HAMD17), and the reason for its selection is not considered justified by the CHMP. In any case, and considering the observed differences in the HAMD17 between paroxetine and placebo in these four trials (from 0.48 in study HMAYb to 2,76 in study HMAYa) the proposed delta should not be accepted. A more stringent analysis using a noninferiority margin of one-half of the gain of paroxetine over placebo was also performed. Duloxetine at a dose of 40 mg BID (Studies HMATa and HMATb) and 60 mg BID (Studies HMAYa and HMAYb) was noninferior to paroxetine, as illustrated graphically by the presence of the upper confidence interval of the observed difference (black triangle and line) to the left of the symbol representing the half-gain of paroxetine over placebo (open triangle). For doses of duloxetine that were not found to be noninferior to paroxetine, paroxetine was not significantly superior to duloxetine.

Noninferiority comparisons of DLX vs. PRX, mean change HAMD17 total score, per-protocol patients



Even accepting that the actual results indicate non-inferiority, it was the view of the CHMP that there remainded the issue of the appropriateness of the severity of the patients treated.

Althought the efficacy of paroxetine in mild MDD has not been shown, the MAH has provided a stratified analysis by severity on the effect of paroxetine as compared to placebo. As expected, although there was no significant difference in treatment effects between subgroups, the magnitude of the effect is grater in more severe patients. However a superior effect of paroxetine over placebo is also observed in mild and moderate MDD. This issue was therefore resolved.

Subgroup Analysis for Change in HAMD17 Total Score Subgroups Defined by Baseline HAMD Score and Number of Previous Episodes of Depression . All Randomized Patients (Paroxetine Versus Placebo). Studies HMAT (a& b) and HMAY (a& b). Extracted from Table 2. 3 of the Applicant response.

Subgroup	N	Therapy	n	Baseline (mean)	Change (mean)	p-value
Base HAMD17 < 19	299	PLA	155	14.75	-5.19	.142
		PRX	144	14.59	-6.14	
Base HAMD17 ≥ 19	423	PLA	214	21.93	-7.88	<.001
		PRX	209	22.52	-10.31	
Base HAMD17 < 25	647	PLA	340	18.22	-6.63	.002
		PRX	307	18.22	-8.19	
Base HAMD17 ≥ 25	75	PLA	29	27.10	-8.14	.024
		PRX	46	26.39	-11.41	
Prev. Episode < 2	363	PLA	180	19.09	-8.24	.043
		PRX	183	19.23	-9.40	
Prev. Episode ≥ 2	358	PLA	188	18.77	-5.37	.0044
		PRX	170	19.34	-7.75	

Ancillary analyses

Analyses by subgroups have been provided.
A comparative analysis of efficacy in patients with different baseline HAMD17 score is presented. As expected, although there was no significant difference in treatment effects between subgroups, the treatment differences versus placebo tend to be numerically greater with higher degrees of severity. The difference did not reach statistical significance in patients with a baseline HAMD17 score >25 probably due to the small number of patients with severe depression enrolled (120 patients). These results suggest a similar response in patients with mild or moderate depressive episode (considering 19, the cut-off established by the Applicant, as the limit between mild to moderate severity). The effect in patients with severe MDD seems to be consistent, although the numbers are too low to draw valid conclusions.

A comparative analysis based on the number of previous episodes of MDD was also performed, which shows a significant difference in treatment effects between patients with at least two vs. less than two previous episodes of MDD, with greater treatment differences in patients with at least two previous episodes.

- Clinical studies in special populations

An analysis by patient's demographic characteristics was performed. No differences between gender were observed. Patients older than 65 years did not achieve statistically significant differences for the primary efficacy measure, while patients younger than 65 years did. In efficacy studies only 42 subjects older than 65 years have been compared with 39 placebo-treated controls. For responders, 15/42 patients responded on duloxetine and there was a tendency towards efficacy ($p<0.09$)compared with placebo treated controls. The applicant was asked to justify the extrapolation of efficacy to this age group. Although acknowledging the limited available data, the Applicant argued that there is no reason to expect that the efficacy of duloxetine in the elderly should be different from that observed in the adult population, and proposed to include related wording in section 4.2 of the SPC.
The CHMP still was of the opinion that the information on the efficacy of duloxetine in the elderly is limited and does not provide sound data supporting it, and asked the Applicant to commit to provide further data on the efficacy of duloxetine in elderly patients, and to further highlight in the relevant sections of the SPC, i.e 4.2, 4.4 and 5.2.

-Section 4.2 “Depression may have different features in the elderly which make it difficult to extrapolate efficacy and safety data from a younger population. Only limited clinical data on the use of CYMBALTA in elderly patients with major depressive disorders is available. Therefore, caution should be exercised when treating the elderly. Until more efficacy data are available the use of CYMBALTA in the very elderly population (>75 years) is not recommended.(see sections 4.4 and 5.2).
Section 4.4 “Only limited clinical data on the use of duloxetine in elderly patients with major depressive disorders is available. Therefore, caution should be exercised when treating the elderly (see Sections 4.2 and 5.2)”
-Section 5.2 “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. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).”

- Supportive studies

Studies HMAYa and HMAYb did also include a long-term treatment phase. Patients who met the response criterion (≥30% decrease in HAMD17 total score from baseline to Week 8) were eligible to enter in a 26 weeks double blind continuation treatment period. Maintenance of efficacy response with long-term treatment of duloxetine 40 mg BID, 60 mg BID, placebo, and paroxetine was defined as a >10% increase in HAMD17 total score. The Applicant claims that the results were similar when only patients with response defined as ≥50% reduction in HAMD17 total score at the end of the acute treatment phase were included.

A total of 273 and 293 patients entered the continuation phases of Studies HMAYa and HMAYb, respectively. Most patients in the duloxetine 40 mg BID (90.0% and 91.4%, respectively), 60 mg BID (93.2% and 85%, respectively), and placebo (70.7% and 84.3%, respectively) treatment groups maintained full response. In addition, patients treated with duloxetine 40 mg BID or 60 mg BID had statistically significantly longer time to first non-response compared with placebo-treated patients.

The results of these studies could be considered as supporting data, since according to the CPMP guidance (CPMP/EWP/518/97 Rev 1), the long-term efficacy should be demonstrated in terms of Relapse Prevention and Recurrence Prevention.

- Discussion on clinical efficacy

As previously commented no formal dose-finding studies have been performed. The only conclusion coming from the early phase II studies (“low doses studies”) regarding the dose recommendation was the lack of effect at doses up to 30 mg QD. Two additional phase II studies (HMAQa/b) showed a lack of effect with the 60 mg BID, however, these studies had only an exploratory nature and did not allow to draw valid conclusions. As a consequence, the Applicant started the phase III acute treatment studies using different dosages non-previously tested, that is: 20mg BID, 40 mg BID, 60 mg BID and 60 mg QD. Based on the results of these studies, the Applicant recommends the use of Duloxetine 60 mg QD as the starting and the effective maintenance dose in the treatment of MDD. The main argument given by the Applicant to support this dosage was that 60 mg QD was the only dosage that demonstrated superiority over placebo in the two studies in which was tested (in contrast to that seen for the remaining dosages for which superiority over placebo was only seen in a half of the studies in which were tested).
In addition, duloxetine 60 mg used once daily (HMBH a and b) was not compared to any active control.

The Applicant has provided several effect-size analyses indicating that the effect of the QD dosing is comparable to the BID regimens of duloxetine and the QD regimen of paroxetine. In the view of the CHMP there are a number of reasons precluding such conclusion being firmly drawn. As recognised by the MAH, those studies including paroxetine as the active comparator and a duloxetine BID regimen (HMAY and HMAT) were substantially different from study HMBH, in which the proposed

dosage (duloxetine 60 mg QD) was compared to placebo. Neither the severity of the enrolled population (milder in studies HMAT and HMAY) nor the study design (the first two studies had a lead in period with placebo) allow to make a reliable comparison between both duloxetine regimens. It cannot be ruled out that the differences among these studies (severity of the population and lead in period) may have lead to a relative overestimation of the effect of the 60 mg QD regimen. However, accepting that such differences among dose regimens might exist, the effect-size analysis clearly indicates that, if any, the dose response relationship for duloxetine (as for the SSRI) must be rather flat. In view of such circumstance, the CHMP agrees that the lowest daily effective dose level showing an effect of about a similar magnitude as that for paroxetine 20 mg is the preferred one.

Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials, and this regimen is proposed for clinical practice. As for the data submitted a dose-response relationship for duloxetine in MDD within the dose range of 80 to 120 mg daily is difficult to be concluded. Moreover, the data directly supporting the benefit of uptitrating the dose of duloxetine in patients not responding to the initially recommended dose are limited and only referred to the maintenance phase of the treatment. However, it is agreed that some kind of flexibility is needed in order to mimic what is clinical practice in the pharmacological treatment of MDD. An additional SPC statement, would allow the proposed posology, stating that no clinical evidence suggests that patients not responding to the initial recommended dose may benefit from dose uptitrations. .
Although inconsistent across similar studies, duloxetine has shown to be effective in the treatment of MDD.The applied dose 60 mg QD has been studied in two short-term and one relapse prevention study. In all three studies statistically significant effects have been demonstrated. The magnitude of effect, with respect to short-term effect as well as maintenance of effect, is comparable to what is usually seen for antidepressant drugs. The short-term effect is supported by similar effects demonstrated for BID administration in the dose range of 40-60 mg. Therefore it is concluded that an antidepressant effect has been adequately demonstrated.
Duloxetine has been shown to statistically significantly increase the time to relapse and to reduce the rate of relapse as compared to placebo.

Clinical safety

The integrated safety data were classified into three databases based on duloxetine dosage, treatment indications and study design.

The primary safety database includes data from all Phase 2 and Phase 3 studies of patients with major depressive disorder (MDD) completed by the cut-off date of 25 April 2003. The primary safety database consists of acute and long-term data from Studies HMAQa, HMAQb, HMATa, HMATb, HMAYa, HMAYb, HMBHa, HMBHb, and HMAU. A total of 2241 patients in these studies received duloxetine at or above the recommended antidepressant dose of 60 mg QD. The primary safety database has five subdivisions:
· Overall MDD dataset, containing acute and long-term data from all duloxetine-treated patients in Studies HMAQ (a, b), HMAT (a, b), HMAY (a, b), HMBH (a, b), and HMAU.
· Placebo-controlled MDD dataset, containing acute data from placebo-controlled Studies HMAQ (a, b), HMAT (a, b), HMAY (a, b), and HMBH (a, b).
· Paroxetine-controlled MDD dataset, containing acute data from the 4 paroxetine-controlled MDD studies.
· Controlled, long-term MDD dataset, containing long-term (26-week continuation) data from placebo-controlled Studies HMAYa and HMAYb.
· Uncontrolled long-term MDD dataset, containing long-term (52-week) data from Study HMAU.

The secondary safety database includes data on duloxetine- and placebo-treated women from all completed double-blind stress urinary incontinence (SUI) studies in which subjects were randomly assigned to a dose of 40 mg twice daily (BID) throughout. Data from all women enrolled in the long-term, open-label SUI studies are also included.

The tertiary safety database consists of data from clinical pharmacology studies, completed SUI and MDD studies not included in the primary safety database, historical lower urinary tract disorder (LUTD) and historical low-dose MDD studies in which patients were randomised to a dose less than duloxetine 20 mg BID or to placebo, completed pain studies, and completed Japanese clinical studies.

A relapse prevention study (Study HMBC) provides further long-term controlled safety data for a period of up to 6 months and safety data from patients receiving 60 mg QD who increased their dose to 60 mg BID during a rescue therapy phase.

- Patient exposure

The safety database for duloxetine consists of 9173 patients. Of that total, 8545 were exposed to duloxetine in clinical studies, and 628 were exposed to duloxetine in clinical pharmacology studies. The data cut-off date for reporting deaths is 15 September 2003. The data cut-off dates for the remainder of the information were 07 March 2003 for SUI studies and 25 April 2003 for all others.

The primary MDD safety database comprises a total of 2418 patients who were exposed to duloxetine over the course of 9 completed clinical MDD studies, including long-term treatment of up to 52 weeks with duloxetine, equivalent to 1099 patient-years of exposure. The mean age of the patients was 43.59 years, ranging from 18 to 87 years (82.8% < 55 years of age); 70% were female and 64.4% were Caucasian.

Weight was the only baseline patient characteristic with a significant difference between treatment groups, with placebo-treated patients beginning treatment at a lower body weight (78.3 kg) than duloxetine-treated patients (79.7 kg). The demographic profile of patients in long-term studies was comparable to that observed in acute studies.

Of the 2418 duloxetine patients, 1046 (43.3%) participated in studies in Mexico or South America, 384 (15.9%) participated in studies in Europe, and 988 (40.9%) participated in studies in the United States or Canada. Demographics of populations tended to be similar.

A total of 2241 patients in these studies received duloxetine at or above the recommended antidepressant dose of 60-mg QD. A further 533 patients were exposed to duloxetine in the relapse-prevention Study HMBC, adding a further 160 patient-years of exposure in total. Considered together, the primary safety database plus Study HMBC add up to a total of 2,951 duloxetine exposures, and a total of 1,259 patient-years of exposure. Among these patients, 1,409 had > 6 months of exposure to duloxetine, and 445 had > 12 months of exposure to duloxetine. These numbers meet the ICH guidelines for exposure for new drugs.

- Adverse events

A total of 84.9% (2052/2418) of the duloxetine treated subjects in the overall MDD dataset reported one or more TEAEs. A total of 73.4% (836/1139) of duloxetine patients compared to 65.1% (506/777) of placebo subjects reported one or more TEAEs in the placebo-controlled MDD dataset. These figures were 64.1% (472/736) and 61.6% (221/359) of duloxetine and paroxetine patients in the paroxetine-controlled dataset.

Most adverse events reported by duloxetine-treated subjects in both the overall and placebo-controlled MDD datasets were in the MedDRA system organ classes of gastrointestinal tract and central nervous system. The common events included in these system organ classes were nausea, constipation, dry mouth, headache, and dizziness.

Treatment-emergent adverse events (TEAEs) 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 (19.9% vs 6.9%), dry mouth (14.6% vs 6.3%), constipation (11.4% vs 4.0%), insomnia (9.9% vs 6.0%), dizziness (8.9% vs 4.8%), fatigue (8.3% vs 3.7%), somnolence (7.1% vs 2.7%), increased sweating (6.1% vs 1.5%) and decreased appetite (5.9% vs 1.9%).

Common Adverse Events by Decreasing Frequency
All Randomized Patients
Placebo-Controlled, Paroxetine-Controlled, and Overall MDD Datasets

	Placebo-Controlled			Paroxetine-Controlled			Overall
	DLX N=1139	PBO N=777		DLX N=736	PRX N=359		DLX N=2418
Event	%	%	p-val [a]	%	%	p-val [a]	%
Nausea	19.9	6.9	<.001	14.4	12.0	.302	27.6
Headache NOS	15.0	16.9	.278	12.5	12.3	1.00	23.5
Dry mouth	14.6	6.3	<.001	8.6	7.8	.727	19.4
Constipation	11.4	4.0	<.001	10.3	7.8	.190	16.8
Insomnia	9.9	6.0	.002	9.0	6.1	.123	21.5
Dizziness	8.9	4.8	<.001	6.1	5.8	1.00	16.6
Fatigue	8.3	3.7	<.001	5.4	5.0	.886	9.5
Diarrhea NOS	7.7	5.5	.065	5.6	6.1	.782	11.1
Somnolence	7.1	2.7	<.001	5.8	6.4	.688	19.2
Sweating increased	6.1	1.5	<.001	5.7	4.2	.314	10.9
Appetite decreased NOS	5.9	1.9	<.001	4.2	1.4	.017	7.1
Vomiting NOS	4.6	2.6	.027	3.5	2.8	.591	7.0
Vision blurred	3.6	1.3	.002	2.3	2.8	.679	3.2
Tremor	2.7	0.8	.002	2.7	3.1	.846	6.2
Libido decreased	2.5	0.5	<.001	2.0	2.2	.825	3.4
Weight decreased	2.4	0.5	.001	1.8	0.3	.044	2.7
Anorgasmia	2.2	0.0	<.001	2.2	1.7	.653	1.5
Hot flushes NOS	2.1	0.8	.024	1.8	0.8	.291	1.7
Erectile dysfunction NOS[b]	4.2	0.8	.013	N/A	N/A		6.6
Ejaculation delayed[b]	2.6	0.8	.138	N/A	N/A		4.9
Ejaculation disorder[b]	2.1	0.4	.096	N/A	N/A		3.3

Abbreviations: DLX = duloxetine; N/A = not available; NOS = not otherwise specified; PBO = placebo; PRX = paroxetine; p-val = p-value.

[a] Fisher's exact test. [b]Adjusted for gender.

Source: FQTESB1A, FQTESB1P, FQTESB1O, FQTESSMC

The frequencies of these same common TEAEs for the secondary and tertiary safety databases are generally consistent with the primary safety database

The only significant difference observed between duloxetine and paroxetine in paroxetine-controlled dataset was for appetite decreased, for which the incidence was higher for duloxetine. As paroxetine, a SSRI, appears to have a similar profile, most events appear to referable to the serotonergic system.

Most TEAEs appeared early on in duloxetine treatment. Nausea and dizziness fell off during the first few weeks of treatment. Dry mouth, constipation, insomnia, somnolence, and decreased appetite also appear early but subside more slowly. Two adverse events, fatigue and increased sweating, persisted during treatment with duloxetine.

The adverse events reported regarding sexual dysfunction, dizziness and syncope, hypomania and manic reactions, bleeding disorders, and self-directed harm risk are considered due to the pharmacodynamic action of duloxetine and/or the underlying disease.
There were 4 treatment-emergent seizure events reported during the duloxetine clinical program. All of them were reported in duloxetine-treated patients. No placebo- or paroxetine-treated patients experienced seizures. There were no cases of seizures among patients included in the secondary safety database.

Long-term safety data up to 52 weeks provided show a comparable profile to that described for the acute phase except for weight increased, viral infection NOS, anxiety, back pain and arthralgia.

- Serious adverse event/deaths/other significant events

Serious adverse events

In the overall MDD dataset, the incidence of SAEs for duloxetine-treated patients was 3.1%. Duloxetine group showed a lower incidence of SAEs in short-term controlled studies than that reported by placebo or paroxetine.
Of the 13.5% (10/74) of SAEs in the duloxetine group that were considered by investigators to be related or possibly related to study drug, half could be considered related to the patients' disease states (abnormal behavior, hypomania, mania, suicidal ideation, uncontrollable anger). The others were abdominal pain, allergic reaction, confusional state, and syncope, the latter concerning a patient who fainted after consumption of alcohol.

Summary of Serious Adverse Events
All Enrolled or Randomized Patients
Primary Safety Database

	Duloxetine			Placebo			Paroxetine		
MDD Dataset	**n/N**	**%**	**Possibly Related to Study Drug**	**n/N**	**%**	**Possibly Related to Study Drug**	**n/N**	**%**	**Possibly Related to Study Drug**
Overall [a]	74/2418	3.1	10						
Placebo-controlled	3/1139	0.3	0	5/777	0.6	1			
Paroxetine-controlled	2/736	0.3	0				4/359	1.1	0
Controlled long-term	7/297	1.7	0	1/129	0.8	0	0/140	0.0	0
Uncontrolled long-term	64/1279	5.0	10						

Abbreviations: MDD = major depressive disorder; n = number of patients with an event; N = total number of patients in dataset.

Source: AE144004, AE140005, AE14101Q, AE142019

In Study HMBC, during the acute therapy phase, few (3.0%) patients experienced SAEs. During the continuation therapy phase, no statistically significant differences in SAEs were observed between duloxetine (3.7%) and placebo (1.4%). No SAEs occurred during the rescue phase. One patient experienced an SAE during the follow-up therapy phase, which was first experienced during the acute therapy phase.

The SAE profile in the secondary safety database (patients with SUI) did not differ substantially from that of the primary safety database (patients with MDD). In the tertiary safety database, a relatively high incidence of cardiovascular SAEs was observed compared with the other databases. This is probably because of the patient population, part of which was selected for having diabetes mellitus.

Deaths

In the entire clinical program involving over 11,000 patients, 23 deaths were reported. Eight of these were patients taking placebo or an active comparator. Of the remaining 15 patients on duloxetine, one death was considered by the investigator to be possibly related to study drug. Four duloxetine-treated patients and 1 placebo-treated patient died in the primary (MDD) safety database, and none of the deaths were judged related to study drug.

The most frequent cause of death was suicide, which accounted for 6 deaths across all treatments. There were 4 suicide deaths out of a total of 8545 duloxetine-treated patients (0.05%) compared with 1 suicide death out of a total of 2553 placebo-treated patients (< 0.04%). The remaining suicide death

occurred in an imipramine-treated patient The only case of suicide in a duloxetine-treated patient, which was judged by the investigator to be possibly related to study drug occurred in a female patient enrolled in an early low-dose Japanese duloxetine study. The patient was taking what is now known to be a subtherapeutic dose of 10 mg QD duloxetine. It is highly likely, therefore, that the patient's depression would have been untreated, or at best partially treated, on this dose, increasing the likelihood of self-harm.
The applicant has committed to perform a suicide post-marketing surveillance program for all medicinal products containing duloxetine.

- Laboratory findings

Clinical laboratory tests (clinical chemistry, haematology, and urinalysis) were performed at baseline (Visit 1) and at various postbaseline visits. Analyses of all datasets in the primary safety database included mean change from baseline to endpoint and treatment-emergent abnormal high, low, or both, values at anytime using reference ranges defined by Covance Central Laboratory Services.

In the primary safety database, small and clinically non-relevant mean changes from baseline in a number of analytes were observed at endpoint across all MDD datasets. For duloxetine-treated patients, there were small mean decreases in chloride, sodium, inorganic phosphorous and uric acid values from baseline to endpoint that were significant when compared with placebo.

Significant decreases in the mean hematocrit and hemoglobin values of duloxetine-treated patients compared with placebo-treated patients were minor and not clinically meaningful. Though there was a significant baseline-to-endpoint change in mean cell volume (MCV) values, few clinically significant treatment-emergent changes were observed in the duloxetine-treated group. These changes seem to have been transient, and for the most part the associated hematocrit and hemoglobin values remained within normal limits. No significant difference was observed between duloxetine and placebo treatment groups with respect to changes in mean white blood cells (WBC) values from baseline to endpoint.

Duloxetine patients showed greater percentages of abnormal values of aspartate transaminase, alanine transaminase, and alkaline phosphatase than placebo patients. The incidence of ALT ≥ 3X ULN was 0.95% for patients taking duloxetine compared with 0.23% of patients taking placebo. Values of ALT exceeding 10X ULN were 0.1% (4/3671) in duloxetine-treated patients. Females (4-fold versus males), ≥ 65 years (2.8-fold versus < 65 years) and SUI patients (2.5-fold compared to MDD patients) showed a higher risk of elevated values of ALT. There were 6 cases (4 in duloxetine, 2 in placebo) of previously defined as severe hepatic injury (concurrent elevation of ALT and bilirubin). All duloxetine treated patients showed additional external factors (alcohol abuse, gall bladder disease) that could explain, partly at last, the hepatic enzyme affection. This issue has been extensively and properly discussed by the Applicant.

Compared with placebo, duloxetine was associated with a significant difference in mean pulse (1.4 bpm vs. –0.6 bpm for placebo) and systolic BP (0.8 mmHg vs. –1.4 mm Hg for placebo). There was no significant difference in the incidence of sustained hypertension (sustained increases of either systolic or diastolic pressures) between the duloxetine-treated (1.3%) and placebo-treated (0.8%) groups in the placebo-controlled trials. When the effect was analysed in elderly patients, no evidence of a more pronounced effect was observed. Neither a dose relationship could be established.
The Applicant has committed to provide data on effect on blood pressure of duloxetine in a subgroup of patients with pre-treatment diastolic BP of 90 mmHg or more.

When effects of duloxetine on ECG parameters were assessed a decrease in both QT and PR intervals was observed in patients treated with duloxetine (QTcF: mean decrease of 1.46 msec in duloxetine compared to mean increase of 1.00 msec in placebo patients). It was not translated to abnormal ECGs . Long-term ECG findings were consistent with acute treatment.

- Safety in special populations

Safety data were analysed according to subgroups based on age, gender and race.
Apart from dizziness, which was more common in older patients, there were no clinically relevant interactions in the incidence of adverse events or in sustained elevation in blood pressure observed for duloxetine treatment by age. Duloxetine has been studied for a number of other indications, including stress urinary incontinence (SUI), diabetic neuropathic pain (DNP), and fibromyalgia syndrome (FMS). The overall duloxetine exposures database consisted of 1157 patients ≥65 years old. Although elderly were considered scarcely represented in the MDD dataset (4.3%, 143) these data do not indicate that duloxetine has a different safety profile in the elderly with MDD. However, the Applicant has been commited to provide additional clinical data in elderly patients with MDD.
Females tended to report more nausea, dizziness, insomnia and headache, although differences are not considered of relevance.
Non-Caucasian patients reported most AEs more frequently than did Caucasian patients.

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.

Twenty-eight pregnancies exposed to duloxetine at various doses were reported from all three safety databases. All exposures were in the first trimester. Fourteen had pregnancies that delivered apparently normal babies at term, and 3 delivered after premature rupture of membranes and/or preterm labour, with none of the infants surviving.

No clinical trials have been conducted in the depressed paediatric population. Due to lack of clinical experience duloxetine should not be used in children and adolescents under the age of 18 years for the treatment of major depressive episode. Safety and efficacy from data collected in adults with major depressive episode cannot be extrapolated to the paediatric population.

- Safety related to drug-drug interactions and other interactions

Globally, 73.2% of patients in the overall MDD dataset used one or more concomitant medications. The most frequently reported concomitant medications were nonnarcotic analgesics, with the number one concomitant medication taken by patients in the overall MDD dataset being ibuprofen (15.8%); number two was paracetamol (15.4%).

Potential interaction with analgesics was examined by comparing adverse events reported by patients who took analgesics with those who did not. Reports of headaches were more than twice as common among the group that took analgesics, which is not unexpected, given that this is the likely reason for such medication. Other events more commonly reported by patients taking analgesics, such as fatigue, diarrhoea, and sweating, may be related to concurrent illnesses, with medications such as paracetamol (acetaminophen) likely being taken for fever or body pain.

A significant difference was observed in the percentage of patients that used paracetamol in the paroxetine-controlled MDD dataset, with the highest percentage in the duloxetine-treated group (10.9% versus 7.0%, $p = 0.049$). This is likely a coincidental finding, for no significant difference was observed between duloxetine and paroxetine for TEAEs related to pain. The most frequently reported concomitant medications were again non-narcotic analgesics.

- Discontinuation due to adverse events

The overall percentage of duloxetine-treated patients completing acute and long-term studies was 54.9%. The acute phase was completed by 71.8% and 76.7% of patients in placebo- and paroxetine-controlled studies, with similar discontinuation rates for duloxetine and comparators. The overall incidence of discontinuation due to adverse events was greater for the duloxetine group, compared

both with placebo (9.7% vs 4.2%; p<.001) and paroxetine (8.6% vs 7.0%; p=0.408. Nausea was the most common adverse event leading to discontinuation.

In long-term studies adverse events represented 3.7% of discontinuations in duloxetine 60 mg QD-treated patients (3.5% placebo) in controlled studies and 17% in uncontrolled studies.

Discontinuation-emergent symptoms following abrupt discontinuation after short-term treatment reported with a significantly greater frequency by duloxetine-treated than placebo-treated subjects included dizziness, nausea, headache NOS, paraesthesia, vomiting, irritability, and nightmare. Patients previously taking the highest dose of duloxetine (120 mg) were more likely to report adverse events upon discontinuation.

Lower incidence of discontinuation adverse events were reported after long-term treatment. Tapering dose for a 3-day period did not seem to modify it, probably due to the shortness of the tapering period. Consistent with duloxetine for the treatment of SUI, a warning avoiding an abrupt discontinuation is included in the SPC.

- Post marketing experience

Duloxetine had not been approved for marketing in any country at the time it was evaluated by the CHMP.

- Discussion on clinical safety

The total duloxetine database included 9173 duloxetine-treated patients in all indications. The primary MDD data safety database comprises a total of 2951 patients of which 2774 patients received duloxetine at or above the recommended antidepressant dose of 60 mg QD. Among these patients, 1,409 had > 6 months of exposure to duloxetine, and 445 had < 12 months of exposure to duloxetine; a total of 1259 patients years.

Nausea was the most frequently reported adverse event, occurring at the beginning of treatment and decreasing over time. The most common AEs were nausea (20%), headache (15%), dry mouth (15%), constipation (11%), and insomnia (10%). Dizziness, fatigue, diarrhea, somnolence, sweating increased, and appetite decreased occurred in 5-10% of the duloxetine patients. Another 10 AEs including vomiting, vision blurred, tremor occurred in 2-5% of the duloxetine treated patients. In the long-term studies, the incidence of TEAEs in duloxetine-treated patients was relatively low and confirms the safety profile obtained in the short-term studies.

The overall tolerability of duloxetine in the clinical studies was comparable to paroxetine 20 mg QD but there was a trend that some events, such as GI and decreased appetite being reported less often for paroxetine 20 mg. There was no clear dose-ADR relationship. In fact, the highest frequencies reported were for the 60 mg OD dose applied for. The most likely explanation for this finding is differences in the design of the different studies.

In total, 9.7% of duloxetine patients discontinued treatment for AEs vs. 4.2% in the placebo controlled MDD dataset. In the one-year open-label study the rate of discontinuations due to adverse events was 17%. The adverse events most frequently leading to discontinuation of patients were nausea and somnolence.

Except for nausea, there were similar AEs frequencies reported for men and women, in spite of the possible higher exposure in women than in men.

Some patients may experience symptoms on discontinuation of duloxetine, particularly if treatment is stopped abruptly. When discontinuing duloxetine after more than 1 week of therapy, it is generally recommended that the dose be tapered over no less than 2 weeks before discontinuation in an effort to decrease the risk of discontinuation symptoms. As a general recommendation, the dose should be reduced by half or administered on alternate days during this period. The precise regimen followed

should however take into account the individual circumstances of the patient, such as duration of treatment, dose at discontinuation etc. This fact is clearly stated in the proposed SPC.

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. The SPC requests for close supervision of high-risk patients during drug therapy.

Overall the safety profile is as expected for a drug with this pharmacological profile. No apparent, unexpected, serious adverse events have been detected in the extensive MDD program.

5. Overall conclusions and benefit/risk assessment

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 both serotonin and norepinephrine reuptake and a relatively weak inhibitor of dopamine reuptake. The effectiveness of duloxetine in the treatment of MDD is linked to its inhibition of presynaptic neuron reuptake of serotonin and norepinephrine in the central nervous system, resulting in elevated levels of serotonin and norepinephrine in the synaptic cleft, enhancing monoaminergic neurotransmission. Although no specific animal models for MDD are available, the in vivo pharmacodynamic studies provide indirect evidence for the potential clinical efficacy of duloxetine.
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 database of duloxetine for the acute treatment of MDD is based on 6 adequately designed placebo controlled studies. Four of these studies also included an active comparator. There was also a relapse prevention study, HMBC.
Patients included had a HAMD17 total score ≥15 (≥18 for Study HMBC) and a CGI-Severity score ≥4 at Visits 1 and 2. The primary efficacy measure used in all duloxetine Phase III studies of MDD was mean change from baseline on the HAMD17 total score. Similar methodology and patient eligibility based on the same clinical algorithm, was also used.
Although some inconsistency in the results of the different studies is observed, it seems clear that duloxetine possesses a superior antidepressant effect as compared to placebo.
One deficiency found during the evaluation refers to the lack of direct comparison between the finally selected dose (60 mg QD) and an active comparator, although on the basis of the pooled analysis the size of the effect seems to be about the same magnitude as that for paroxetine 20 mg.
In addition, patients with severe MDD and elderly patients are clearly underrepresented in the available efficacy database.

Safety

The total duloxetine database included 9173 duloxetine-treated patients in all indications. The primary MDD data safety database comprises a total of 2951 patients of which 2774 patients received duloxetine at or above the recommended antidepressant dose of 60 mg QD. This represents 1259 patient-years of exposure at or above the recommended dose.
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)
Adverse reactions occurred significantly more often in the duloxetine group than in the placebo group, being nausea (20%), the most frequently reported adverse event. Other common adverse reactions were headache (15%), dry mouth (15%), constipation (11%), and insomnia (10%). Dizziness, fatigue, diarrhea, somnolence, sweating increased, and appetite decreased occurred in 5-10% of the duloxetine patients. Other adverse reactions including vomiting, vision blurred, tremor occurred in 2-5% of the duloxetine treated patients. In the long-term studies, the incidence of TEAEs in duloxetine-treated patients was relatively low and confirms the safety profile obtained in the short-term studies.
In total, 9.7% of duloxetine patients discontinued treatment for adverse reactionss versus 4.2% for placebo in the placebo controlled MDD dataset. The adverse events most frequently leading to discontinuation of patients was nausea.
In conclusion, the safety profile of duloxetine does not identify any unexpected or serious adverse reaction which would create special concern, and is comparable to that known for SSRIs.

Benefit/risk assessment

Major Depressive Disorder is the most common mood disorder, with a lifetime prevalence of about 15% and as high as 25% in women. Despite the availability of effective treatments, many persons with depressive disorders are disabled, and at risk of suicide.
Duloxetine would represent a new alternative for the treatment of this condition, based on its *in vitro* and *in vivo* proven capacity to inhibit both serotonin and norepinephrine reuptake.
The Applicant has provided evidence of the antidepressant effect of duloxetine as compared to placebo in both short-term and long-term studies.
Although some concerns remain, in particular the lack of an adequate database to support efficacy in elderly population, and the lack of direct comparison between the finally selected dose (60 mg once daily) and an active comparator, the tolerability profile of duloxetine seems acceptable. Therefore, it seems clear that duloxetine might have a place among treatments of Major Depressive Disorder, and a positive benefit/risk in MDD can be concluded.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensusthat the benefit/risk ratio of duloxetine in the treatment of treatment of major depressive episodes, was favourable and therefore recommended the granting of the marketing authorisation.