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Committee for Medicinal Products for Human Use (CHMP)

Ariclaim, Cymbalta, Xeristar, Yentreve

Duloxetine

Procedure No. EMEA/H/C/000552/P46/034 - Ariclaim

EMEA/H/C/000572/P46/039 - Cymbalta

EMEA/H/C/000573/P46/040 - Xeristar

EMEA/H/C/000545/P46/033 - Yentreve

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

I. INTRODUCTION

On 2009-04-08, the MAH submitted a completed paediatric study for duloxetine, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for duloxetine and that no consequential regulatory action is required.

II. SCIENTIFIC DISCUSSION

II.1 Information on the development program

The MAH stated that the Study HMFN (An Open-Label Study of Tolerability, Safety, and Pharmacokinetics of Duloxetine in the Treatment of Children and Adolescents with Major Depressive Disorder) is a stand alone study. This is provided in line with the current 6 months reporting timeline.

II.2 Information on the pharmaceutical formulation used in the study

Duloxetine is authorised as 30 mg, 40 mg and 60 mg, hard gastro-resistant capsules. Duloxetine is not indicated for use in children. So far, no suitable paediatric formulation is available. No clinical studies have been conducted for patients less than 18 years of age, although post marketing, off-label use has been reported.

The study drug was provided in the form of 20 and 30 mg capsules of duloxetine enteric-coated pellets. Patients were given one to four capsules daily.

II.3 Clinical aspects

1. Introduction

The MAH submitted a final report for Study HMFN (An Open-Label Study of Tolerability, Safety, and Pharmacokinetics of Duloxetine in the Treatment of Children and Adolescents with Major Depressive Disorder).

2. Clinical study

Study F1J-MC-HMFN was a Phase 2, multicenter, open-label, single-arm study designed to evaluate the range of duloxetine tolerable doses and characterization of duloxetine pharmacokinetics in children and adolescents (aged 7 through 17 years) diagnosed with Major Depressive Disorder (MDD).

- **Methods**
  - **Objectives**

Primary Objective
To assess the safety and tolerability of duloxetine in children and adolescents diagnosed with MDD.

Secondary Objectives
• To characterize the pharmacokinetics of duloxetine at steady-state in children and adolescents.

• To compare the steady-state duloxetine pharmacokinetics in children and adolescents with historical adult duloxetine pharmacokinetics.
• To assess the efficacy of duloxetine at a proposed dose range of 20 to 120 mg once daily (QD).

- **Study design**

The study was up to 32 weeks in duration and consisted of 5 study periods:

- Study Period I: Screening (2 weeks)
- Study Period II: Dose Titration with Pharmacokinetic Sampling (10 weeks)
  Time to titrate each patient at 1- to 2-week intervals to the patient's highest tolerable dose up to a maximum dose of 120 mg QD based on safety, tolerability, and treatment response (CGI-Severity score).
- Study Period III: Safety and Tolerability (8 weeks)
  The duloxetine dose remained fixed throughout this Study Period.
- Study Period IV: Extended Safety and Tolerability (3 months)
  The patient's dose was escalated or decreased at the investigator's discretion.
- Study Period V: Taper Phase (2 weeks):
  Patients gradually reduced their duloxetine dose rather than abruptly discontinuing duloxetine.

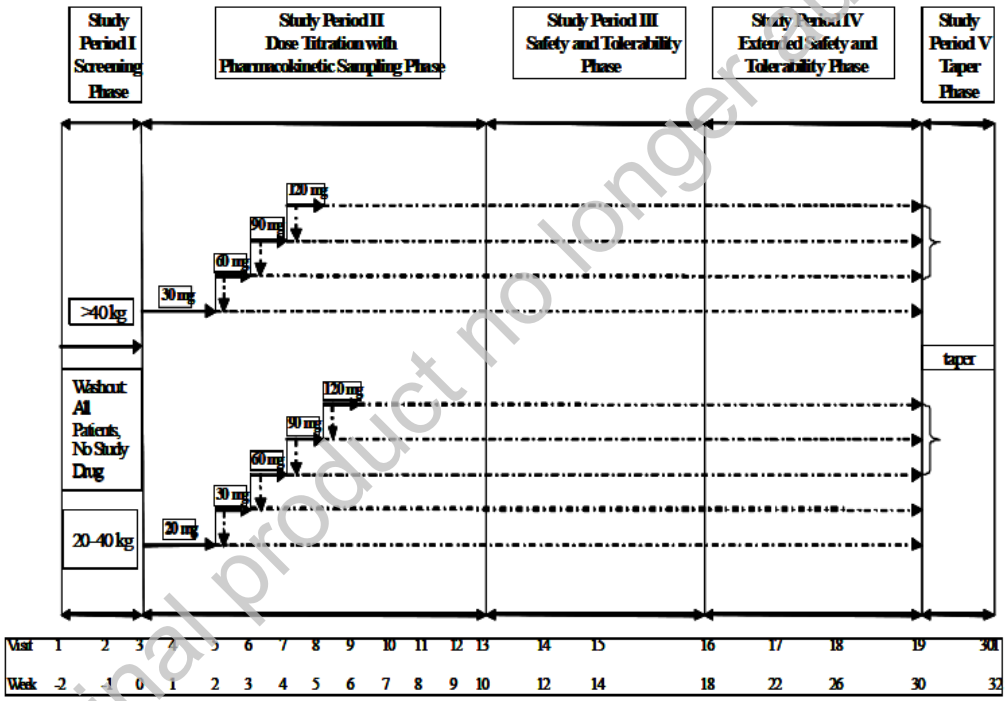


Figure HMFN.9.1 Study design.

- **Study population / Sample size**

Inclusion Criteria

Outpatient children and adolescents aged 7 to 17 years, who meet criteria for MDD without psychotic features, single or recurrent, as defined by the DSM-IV and confirmed by the K-SADS-PL, with a MDD severity of moderate or greater (a CDRS-R total score of ≥40 and a CGI-Severity rating of ≥4).

The K-SADS-PL was used as a supplementary diagnostic instrument. This clinician rated instrument assessed the extent of symptoms of MDD and other diagnoses and allowed for rating the worst part of an episode as well as symptoms over the past week.

Exclusion Criteria
Patients were excluded from the study if they had any diagnosis of bipolar disorder, psychotic depression, schizophrenia or other psychotic disorder, anorexia, bulimia, obsessive compulsive disorder, pervasive development disorder, borderline personality disorder, a current primary DSM-IV Axis I disorder other than MDD, a current secondary DSM-IV Axis I disorder that required any pharmacologic treatment, or if they had a significant suicide attempt within 1 year of Visit 1 or were a suicidal risk as defined in the protocol.

Approximately 64 patients were to be enrolled (within 4 age groups: 7 through 9 years, 10 through 12 years, 13 through 14 years, and 15 through 17 years of age) and to have approximately 4 study completers per age stratum with relatively equal male and female patients within this sample by the end of Study Period III.

- **Treatments**

All enrolled patients were assigned to duloxetine. Patients took duloxetine orally, in a dose range of 20 to 120 mg QD. The proposed starting dose of 20 or 30 mg QD was based on body weight (20 to 40 kg and >40 kg, respectively).

Concomitant medications with primarily central nervous system (CNS) activity were not allowed. Patients were allowed the episodic use of these medications to treat cold symptoms or insomnia.

- **Outcomes/endpoints**

The following efficacy measures were collected:

• The CDRS-R (Children's Depression Rating Scale-Revised) is a clinician-rated instrument designed to measure the presence and severity of depression in children. The scale consists of 17 items scored on a 1- to 5-point scale or 1- to 7-point scale. A rating of 1 indicates normal functioning. Total scores range from 17 to 113.

• The CGI-Severity Scale evaluates the severity of illness at the time of assessment. The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).

• The CGI-Improvement records the degree of the patient's improvement at the time of assessment since starting the study drug. The score ranges from 1 ("very much improved") to 7 ("very much worse").

Efficacy analyses were secondary for this study and included the following:
• Mean change from baseline to endpoint for CDRS-R Total score (LOCF) during Study Period II/III;
• Mean change from baseline to endpoint for CGI-Severity score (LOCF) during Study Period II/III;
• observed cases visit wise summaries during Study Period II/III for the CDRS-R Total score and for the CGI-Severity score.
The following safety measurements were collected:

- Adverse Events
- Adverse Event Monitoring with a Systemic Questionnaire: The C-SSRS and the Self-Harm Follow-up Form were used for additional monitoring of suicide-related events behavior and/or ideations.
- Concomitant Therapies
- Laboratory Data
- Vital Signs
- Electrocardiograms

Safety was assessed by summarizing AEs and changes in laboratory analytes, vital signs, and ECGs. Patients were included in the extent of exposure analyses if they had non-missing exposure data for the reporting interval.

Duloxetine steady-state plasma concentration from 64 patients (5 to 8 plasma concentrations per patient) was obtained to characterize the pharmacokinetics of duloxetine in paediatric patients. A population pharmacokinetic model was developed using a nonlinear mixed effects modelling program.

- **Statistical Methods**

Efficacy and safety analyses were conducted on an intent-to-treat (ITT) basis. Last-observation-carried-forward imputation was primarily used for missing data. Observed cases analyses use all data available with no imputation performed.

A lock of all pharmacokinetic Study Period II data occurred after the last patient visit was completed for Study Period II for the purpose of assessing duloxetine doses for future Phase 3 studies. The number of patients that had completed through this time point was 58. In addition, an interim lock of all Study Period II/III data occurred for the purpose of assessing safety and tolerability, pharmacokinetics, and efficacy. Results for this interim analysis were submitted within a Briefing Document to the FDA; however, these results were not communicated to the investigators.

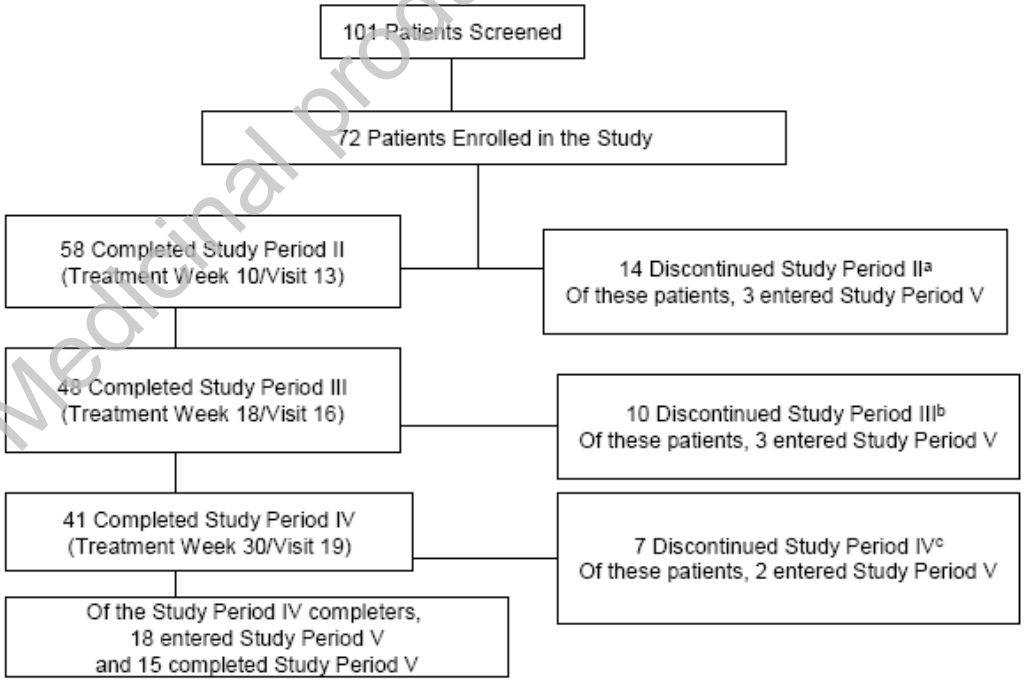
Subsequent to database lock, an error in the reporting database was discovered. This error remains in the reporting database that was used for all analyses in this clinical study report. It is believed that this error is minor and did not affect any conclusions in this clinical study report.

- Changes in the conduct of the study or planned analyses
  - Two additional blood draws for clinical chemistry tests were performed during Study Period II for Weeks 2 and 6.
  - Ad hoc analyses combining data from Study Periods II, III, and IV were completed to better characterize the longer-term safety and tolerability of duloxetine.
  - The incidence of sustained elevations in blood pressure was also evaluated.
  - Some changes to the planned pharmacokinetic analysis occurred following the review of the data and model evaluation: smoking status was not tested as a covariate, Schwartz formula was used to calculate the creatinine clearance in children less than 12 years of age, changes of criteria for retention of a covariate in the final model.

Results

- **Recruitment / Number analysed**

Figure HMFN.10.1. Patient disposition.



a Reasons for discontinuation: parent/caregiver decision (5 patients), adverse event (3 patients), lack of efficacy (1 patient), patient decision (1 patient), protocol violation (1 patient), physician decision (1 patient), lost to follow-up (2 patients).
b Reasons for discontinuation: parent/caregiver decision (4 patients), adverse event (0 patients), lack of efficacy (1 patient), patient decision (0 patients), protocol violation (2 patients), physician decision (2 patients), lost to follow-up (1 patient).
c Reasons for discontinuation: parent/caregiver decision (1 patient), adverse event (1 patient), lack of efficacy (1 patient),
patient decision (1 patient), protocol violation (0 patients), physician decision (0 patients), lost to follow-up (3 patient).

- **Baseline data**

Patients entered the study with moderate to moderately high levels of depression (mean baseline CDRS-R total score of 61.7, scores ranged from 40.0 to 81.0). Similarly, patients entered the study with moderate to severe illness, with a mean baseline CGI-Severity score of 4.5 (scores ranged from 4.0 to 6.0).

For the 72 enrolled patients, the mean age at first episode of MDD was 10.75 years of age, and the mean number of previous MDD episodes was <1 episode with a minimum and maximum range of 0-6 episodes.

The percent of patients who met the definition of compliance with study drug administration was greater than 85% at all visit intervals during Study Periods II, III, and IV.

Table HMFN.11.1. Patient Baseline Characteristics. All Enrolled Patients (N=72)

	Mean (SD)
Age (years)	12.5 (2.9)
Body Mass Index (kg/m^2)	23.7 (6.4)
CDRS-R total score	61.7 (9)
CGI-Severity	4.5 (0.6)
Categorical Demographics: n (%)	
Age distribution:	
≤12	31.(43.1)
>12	41 (56.9)
Gender	
Female	35 (48.6)
Male	37 (51.4)
Tobacco use:[a]*	
No	70 (97.2)
Yes	1 (1.4)
Origin:	
African	17 (23.6)
Caucasian	42 (58.3)
East Asian	1 (1.4)
Hispanic	11 (15.3)
Native American	1 (1.4)

Abbreviations: CDRS-R = Children's Depression Rating Scale-Revised; CGI-Severity = Clinician's Global Impression of Severity; N = total number of patients; n = number of patients in the category; SD = standard deviation.

a Based on cotinine level.

* These numbers do not add up to 100% because data was only available for 71 patients.

Source: FQPCIA21, FQPCIA41

- **Efficacy results**

The mean (SD) baseline CGI-Severity score for all enrolled patients was 4.5 (0.58); the mean change in the CGI-Severity score from baseline to endpoint for Study Period II/III was -2.11 (1.17). For those

patients who entered Study Period IV, the mean change in the CGI-Severity score from baseline to endpoint was -2.7 (1.07).

The mean (SD) baseline CDRS-R total score for all enrolled patients was 61.7 (9). For all randomized patients, the mean change in the CDRS-R total score from baseline to endpoint in Study Period II/III was -32.11 (12.9). For patients who entered Study Period IV, the mean change in the CDRS-R total score from baseline to endpoint was -38.8 (11.1).

CGI – Severity and CDRS - Total Score.- Change from Baseline. Treatment Phase II/III and Phase IV

Outcome	Period	Baseline		Endpoint		Change	
		Mean	SD	Mean	SD	Mean	SD
CGI-Sever score	II/III (n = 72)	4.50	0.59	2.39	1.00	-2.11	1.17
	IV (n= 45)	4.5	0.59	1.8	0.81	-2.7	1.07
CDRS total score	II/III (n = 72)	61.69	8.98	29.58	11.91	-32.11	12.92
	IV (n= 45)	61.8	9.28	22.9	6.42	-38.8	11.14

Abbreviations: N (II/III)= all enrolled patients with a baseline and at least one non-missing post-baseline data);N (IV) = number of patients with a baseline and at least one non-missing post-baseline value in treatment phase IV;SD = standard deviation.

For children ≤12 years, the mean change (SD) from baseline to endpoint in Study Period II/III was -34.3 (12.3) and, for patients who entered Study Period IV, the mean change from baseline to endpoint was -41.8 (9.9). For adolescents >12 years, the mean change from baseline to endpoint in Study Period II/III was -30.5 (13.3) and, for patients who entered Study Period IV the mean change from baseline to endpoint was -36.3 (11.7).

- **Pharmacokinetic results**

The population pharmacokinetic analysis dataset consisted of 319 duloxetine concentrations and associated dose, dosing time, sampling time, and patient demographic information from 29 children (7-12 years) and 33 adolescents (13-17 years). A total of 90 samples were below of quantitation limit.

Majority of the patients are nonsmokers, extensive CYP2D6 metabolizers (EMs) and Caucasians and received either 30-, 60- or 90 mg duloxetine dose. The percent of poor metabolizers (PMs) is consistent with the prevalence of 5% – 7% PMs in Caucasians. The typical duloxetine plasma concentrations increased in proportion to the increase in dose.

Table HMFN.11.10. Summary of Observed Duloxetine Plasma Concentrations Stratified by Duloxetine Dose[a]

Dose (mg)	20 (N = 14) (n = 16)	30 (N = 53) (n = 89)	60 (N = 41) (n = 97)	90 (N = 33) (n = 75)	120 (N = 19) (n = 42)
Concentration (ng/mL)	15.2 ± 12.0 (3.9 - 51.6)	20.8 ± 21.2 (0.5 - 144.5)	41.1 ± 34.7 (0.7 - 177.9)	57.6 ± 43.2 (1.7 - 249.6)	77.6± 54.6 (1.2 - 210.7)
Age (years)	9.8 ± 1.3 (7.9 - 12.1)	12.3 ± 2.7 (7.8 - 17.3)	12.0 ± 2.9 (7.9 - 17.6)	14.2 ± 2.5 (7.9 - 17.6)	13.3 ± 2.4 (9.1 - 17.3)
Body Weight (kg)	31.5 ± 3.6 (23.6 - 36.9)	53.7 ± 21.8 (25.7 - 111.1)	53.1 ± 23.4 (23.6 – 110.0)	63.0 ± 18.4 (23.2 - 107)	61.6 ± 21.3 (23.6 - 107)

Abbreviations: N = number of patients; n = number of duloxetine concentrations.

[a] Summary statistics reported as Mean ± Standard Deviation (Minimum – Maximum)

The median dose-normalized duloxetine concentration is similar in EMs (0.55 ng/mL/mg) and Ultra rapid metabolizers (UMs) (0.48 ng/mL/mg); however, the median dose-normalized duloxetine concentrations are nearly 3-fold higher in PMs (1.69 ng/mL/mg). However, there was considerable overlap in the observed concentrations for the PMs and EMs patients.

As in adults, the duloxetine plasma-concentration time data in paediatric patients are adequately described by a one-compartment pharmacokinetic model. The base model is able to determine the inter-patient variability in CL/F and V/F with covariance using the omega block. The residual error is described by a proportional/additive error model.

Table HMFN.11.11. Population Pharmacokinetic Parameters and Variability Estimates from the Base and Final Models

		Base Model			Final Model		
	Units	Estimate	%SEE	95% CI	Estimate	%SEE	95% CI
CL/F	L/hr	81.0	6.6	71.4 – 93.3	-	-	-
$CL/F_{,female}$	L/hr	-	-	-	66.3	10.0	55.8 - 80.2
$CL/F_{,male}$ [a]	L/hr	-	-	-	96.1	-	-
Effect of Gender on CL/F	-	-	-	-	0.45	44.0	0.110 - 0.872
V/F	L	557	15.0	342 - 966	682	15.0	360 - 1160
K_a	hr^{-1}	0.105	13.3	0.0680 - 0.176	0.12	8.84	0.0774 - 0.176
Interpatient Variability (Ω)							
CL/F	%	47.7	25.4	-	43.6	27.2	-
V/F	%	92.4	48.6	-	44.5	68.5	-
Residual Error (Σ)							
Proportional	%	51.1	13.1	-	52.0	13.1	-
Additive	ng/mL	3.62	19.9	-	3.79	16.8	-

Abbreviations: CI = confidence interval; CL/F = oral clearance; K_a = absorption rate constant; SEE = standard error of the estimate; V/F = oral volume of distribution.

[a] $CL/F_{,male} = CL/F_{,female} * (1 + 0.45)$

Gender is the only covariate that had a statistically significant influence on CL/F. CL/F of duloxetine in female patients is approximately 30% lower as compared with the male patients. Given the interpatient and intrapatient variability, there is considerable overlap in duloxetine concentration-time profile in females and males as shown in the model predictions.

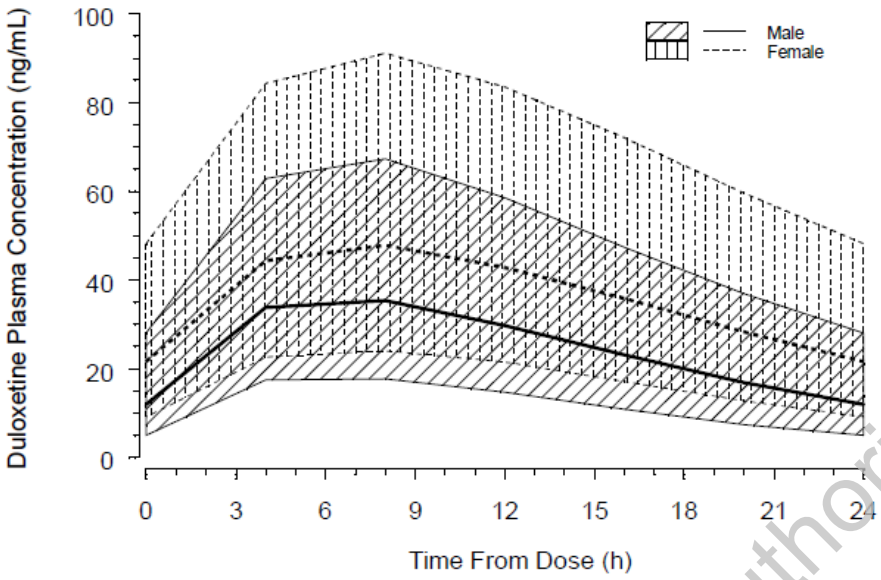
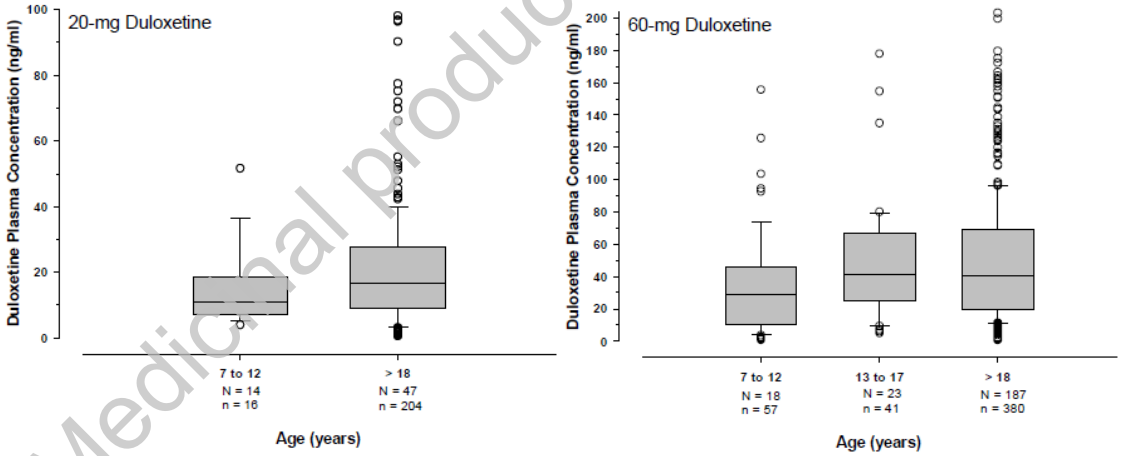


Figure HMFN.11.3. Predicted duloxetine plasma concentration-time profile during the steady state dosing interval of 24 hours following once-daily oral administration of 60 mg duloxetine. Concentrations were simulated for 1000 patients.

Dose-normalized duloxetine concentrations following QD dosing regimen demonstrate that the duloxetine concentration in paediatric patients (children: 0.57 and adolescents: 0.56 ng/mL/mg) is slightly lower than those observed in adults (0.7 ng/mL/mg). However, there is considerable overlap in the concentration range and the range of concentration in paediatric patients are within the range observed in adults.

Figure HMFN.11.5. Observed Duloxetine plasma concentrations at steady state in pediatric and adult patients following oral administration of duloxetine as 20 or 60 mg once-daily dosing regimen.



N = number of patients; n = number of concentrations. The middle line of the box represents the median; the top and bottom margins of the box represent the 75th and 25th percentiles; the whiskers extend to the 10th and 90th percentiles, solid circles represent concentrations outside the 10th and 90th percentile.

- **Safety results**

All 72 patients enrolled in this study were exposed to duloxetine during Study Period II/III with an overall mean duration of exposure of 106.7 days. Twenty patients initiated duloxetine treatment at 20 mg QD and 52 patients initiated duloxetine treatment at 30 mg QD based on body weight. A majority of patients (52/72; 72%) had a modal duloxetine dose of 60, 90, or 120 mg QD, 17 patients had a modal dose of 30 mg QD, and 3 patients had a modal dose of 20 mg QD.

The majority of patients (55/72; 76%) required escalation of the duloxetine dose to 60, 90, or 120 mg QD during Study Period II in order to optimize efficacy. No patients with a modal dose of duloxetine 20 mg completed Study Period III. The 48 patients who entered Study Period IV had a mean duration of exposure during Study Period IV of 77.5 days. Nine patients (12.5%) required dose decreases due to tolerability, and of these 9 patients, patients required dose decreases to below duloxetine 60 mg QD.

Analysis results for Study Period II/III and Study Period IV are presented separately in this study report. During Study Period II/III, nausea was the most common TEAE (18 patients, 25%). Other TEAEs reported by at least 5% of patients during this study period were headache, vomiting, nasopharyngitis, dizziness, sedation, somnolence, abdominal pain upper, fatigue, decreased appetite, dry mouth, gasteroenteritis viral, and rhinorrhea. During Study Period IV, no TEAE was reported by more than 2 patients. Dry mouth (4.2%), fatigue (4.2%) and somnolence (4.2%) were the most common TEAEs reported during Study Period IV.

Table HMFN.12.8. Overview of Adverse Events Number and Percentage of Patients All Enrolled Patients

Adverse Event[a]	Number (%) of Patients Study Period II-V N = 72
Deaths	0 (0)
Serious adverse events	5 (6.9%)
Discontinuations due to an adverse event	4 (5.6%)
Treatment-emergent adverse events	
Study Period II/III	57 (79.2%)
Study Period IV	21 (43.8%)

[a] Patients may be counted in more than one category.

Table HMFN.12.9. Treatment-Emergent Adverse Events by Decreasing Frequency All Enrolled Patients Study Period II/III

Preferred Term	Duloxetine (N = 72) n (%)
Nausea	18(25.0)
Headache	10(13.9)
Vomiting	10(13.9)
Nasopharyngitis	9(12.5)
Dizziness	7(9.7)
Sedation	7(9.7)
Somnolence	7(9.7)
Abdominal pain upper	6(8.3)
Fatigue	5(6.9)
Decreased appetite	4(5.6)
Dry mouth	4(5.6)
Gastroenteritis viral	4(5.6)
Rhinorrhoea	4(5.6)
Bruxism	3(4.2)
Cough	3(4.2)
Influenza	3(4.2)
Insomnia	3(4.2)
Oppositional defiant disorder	3(4.2)
Pharyngolaryngeal pain	3(4.2)
Skin laceration	3(4.2)
Anxiety	2(2.8)

Abbreviations: N = total number of enrolled patients; n = number of patients with specified treatment-emergent adverse event.

Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

There were no deaths reported during the study. Overall, 5 patients reported a total of 6 SAEs. All 6 SAEs had an onset date during Study Period II/III. None of the SAEs reported were considered by the investigator to be related to study drug, and none of these patients were identified as CYP2D6 poor metabolizers.

- A male experienced the SAE of worsening of oppositional defiant disorder (ODD). The patient had a history of ODD, but was not taking any concomitant medications.
- A female experienced the SAE of self-injurious behaviour. The patient had a history of sexual abuse and MDD. She was receiving acetylsalicylic acid as concomitant medication for plantar warts.
- A female patient experienced the SAE of self-injurious behaviour. The patient had no previous history of such behaviour and was not taking any concomitant medications.
- A female assigned to open-label duloxetine for the treatment of MDD experienced the SAE of worsening of depression and suicidal ideation. The patient had a history of separation anxiety (resolved in 2005) and a motor vehicle accident (2006), which resulted in whiplash, intermittent headaches, dizziness, back, neck, and shoulder pain. The patient was taking the concomitant medications of omega-3 supplement and calcium with magnesium.
- A female assigned to open-label duloxetine for the treatment of MDD, experienced the SAE of viral gastroenteritis. The patient had no relevant medical history and was not taking any concomitant medications.

Adverse Events Reported as Reason for Discontinuation
Three patients reported 1 AE each (nausea, rash, attention deficit/hyperactivity disorder) that led to discontinuation during Study Period II/III. These events were considered to be related to study treatment. One patient reported an AE that led to discontinuation during Study Period IV (irritability), and the event was not considered to be related to study treatment.

Suicide-Related Outcomes

- Children's Depression Rating Scale Item 13

An emergence of any suicidal ideation was reported for Study Period II/III; that is, the percentage of patients with score less than or equal to 2 at all baseline visits and greater than 2 within the study period was 2.8%. There was no incidence of emergence of substantial suicidal ideation in either Study Period II/III or Study Period IV; that is, the percentage of patients with score less than or equal to 2 at all baseline visits and greater than 4 within the study period was 0%. The incidence of worsening of suicidal ideation (that is, the maximum score within the study period was greater than the maximum baseline score) was 8.3% for Study Period II/III and 2.1% for Study Period IV. However, an improvement of suicidal ideation (that is, a decrease from the maximum baseline score) was also shown in both Study Period II/III and Study Period IV; >35% of patients had a decrease from the maximum suicidal ideation baseline score during these study periods.

CDRS – Item 13.- Treatment Emergent Worsening Treatment Phase II/III and Phase IV

	Phase II/III (N = 72)	**Phase IV** (N = 48)
	Responders n (%)	**Responders n (%)**
Emergence of Any Suicidal Ideation	2 (2.8)	0 (0.0)
Emergence of Substantial Suicidal Ideation	0 (0.0)	0 (0.0)
Improvement of Suicidal Ideation	26 (36.1)	19 (39.6)
Worsening of Suicidal Ideation	6 (8.3)	1 (2.1)

- Columbia Suicide Severity Rating Scale

One (1.4%) nonfatal suicide event was reported. This event was the only event reported for the suicidal behaviour (1-5) category in the C-SSRS during Study Period II/III. During Study Period II/III, 1 (1.4%) patients experienced worsening of suicidal ideation from baseline
at any time during Study Periods II or III.

No suicidal behaviours (1-5 category in the C-SSRS) were reported during Study Period IV. During Study Period IV, 1 (2.2%) patient experienced worsening of suicidal ideation from baseline at anytime during Study Period IV.

Out of 19 patients who reported suicidal ideation at baseline, 17 (89.5%) reported an improvement in suicidal ideation at last observation during Study Periods II and III (Table HMFN.14.51). For patients who had suicidal ideation at baseline and continued in the study through Study Period IV (N=8), all 8 patients (100%) reported an improvement in suicidal ideation at last observation during Study Period IV.

Clinical Laboratory Evaluation
Baseline to endpoint changes were observed for some laboratory analytes; however, these changes were small relative to baseline and relative to the standard deviation.

Greater than 5% of patients experienced low hematocrit (8, 13.3%), high creatine phosphokinase (6, 8.7%), and high inorganic phosphorus (16, 25.8%) during Study Period II/III. The only laboratory value with a potentially clinically significant change experienced by greater than 5% of patients was inorganic phosphorus (7.7%) during Study Period IV. Transient elevations in creatine phosphokinase and inorganic phosphorus have also been observed in duloxetine-treated adults.

One patient experienced a potentially clinically significant (PCS) elevation of alanine aminotransferase (ALT). After approximately 14 weeks, the patient's ALT reached 5X upper limit of normal (ULN), but total bilirubin, AST, GGT, and CPK were all normal. A retest revealed that the ALT elevation had returned to normal within 3 days while the patient continued to take study drug, and the event appeared to be an isolated elevation.

Vital Signs, Physical Findings, and Other Observations Related to Safety

During Study Periods II/III and Study Period IV, patients experienced mean increases in diastolic blood pressure, systolic blood pressure, and weight as well as a mean decrease in pulse. Small increases in systolic and diastolic blood pressure have also been observed in duloxetine-treated adults.

Overall, approximately 20% of patients experienced PCS high diastolic blood pressure and approximately 10% of patients experienced PCS high systolic blood pressure, while 3% of patients experienced PCS high pulse at anytime. The percentage of enrolled patients with sustained elevation of blood pressure, either diastolic or systolic, was 5.6% (4/72). One patient experienced sustained elevation of diastolic blood pressure, and 3 patients experienced sustained elevation of systolic blood pressure.

3. Discussion on clinical aspects

Duloxetine has been approved in the European Union for the treatment of severe urinary incontinence (Ariclaim, Yentreve) and for the treatment of major depressive disorders, the treatment of diabetic peripheral neuropathic pain and the treatment of generalised anxiety disorder (Cymbalta, Xeristar).

Treatment of children and adolescents with duloxetine is not recommended in the approved SPC. This study was conducted as part of a paediatric plan committed with the FDA. In the EU there is no agreed PIP for duloxetine and therefore this is provided as a standalone study in line with the current 6 months reporting timeline.

This study was conducted to provide preliminary results on safety and pharmacokinetics in paediatric MDD population. A total of 72 patients aged 7 to 17 years were titrated from 20 (or 30) mg to 120 mg and 41 were treated up to 30 weeks. Two third of patients were escalated up to 60, 90 or 120 mg dosage, what it is within the range of adult dosage recommendations. The safety profile of duloxetine at those dosages in paediatric population resulted in general similar to that observed in adults. The fragmented method of reporting of AEs by study period hampered having a global view of the product. Nevertheless, no new safety findings have been observed. Of concern, two suicidal ideations and two self-injurious behaviour AEs were reported. The evaluation of specific suicide-related outcomes does not provide additional concerns on this issue, what could be considered expectable in the context of the condition.

Duloxetine plasma concentrations increased in proportion to the increase of the dose. Gender (and not age, body weight, creatinine clearance, CYP2D6 status, or dose) was the only characteristic that seemed to influence the pharmacokinetic of duloxetine. As it was observed in adults the inter- and intrapatient variability is very high, with an overlap in duloxetine concentration-time profile in females and males.
Children and adolescents involved in the trial suffered a moderate depression. About 7% of patients had previously been treated with psychotherapy and over 40% received antidepressant drugs. Of note, amphetamine-derived drugs and atomoxetine were reported by 27/72 patients although apparently only 3 patients reported concomitant attention deficit/hyperactivity disorder diagnose. Efficacy parameters measured after 8 weeks and 18 weeks of treatment showed lower scores (response) with respect to baseline scores. The open label design and the small size of the trial make these results inconclusive.

According to the MAH statement, results from this study will be informative for the designs of larger, controlled, Phase III studies. At present the current benefit/risk ratio of duloxetine use in children, which is considered negative, should remain without changes in the SPC.

Rapporteur's Overall Conclusion AND RECOMMENDATION

- **Overall conclusion**

The additional data provided in this submission do not change the current benefit/risk ratio of duloxetine use in children, which is considered negative, as stated in currently approved SPC. According to the MAH's conclusion, given that there were no new safety findings in paediatric MDD patients relative to adult patients in this open label study, the additional data provided in this submission do no warrant an update of the product information.

- **Recommendation**

X Fulfilled:

No regulatory action required

ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable