HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

8 July 2009

CYMBALTA 30 mg, hard gastro-resistant capsule
B/7 (CIP code: 370 237-5)
B/28 (CIP code: 365 864-5)

CYMBALTA 60 mg, hard gastro-resistant capsule
B/28 (CIP code: 365 865-1)
B/100 (CIP code: 570 777-3)

Applicant: LILLY

duloxetine
ATC code: N06AX21

List I

Date of the Marketing Authorisations (centralised procedure): 17 December 2004, 4 July 2005 (Diabetic Peripheral Neuropathic Pain in adult), 28 July 2008 (generalised anxiety disorder) – last variation: 25 March 2009

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance (pack of 7 and pack of 28) and approved for hospital use (pack of 7, pack of 28, and pack of 100) in the extension of indication “generalised anxiety disorder”.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Duloxetine

1.2. Indications

"**Treatment of generalised anxiety disorder**
Treatment of major depressive episodes (i.e. clear episodes)
Treatment of diabetic peripheral neuropathic pain in adults."

1.3. Dosage

In the extension of indication (generalised anxiety disorder):

"*Adults*
The recommended starting dose in patients with generalised anxiety disorder is 30 mg once daily with or without food. In patients with insufficient response the dose should be increased to 60 mg, which is the usual maintenance dose in most patients.
In patients with co-morbid major depressive disorder, the starting and maintenance dose is 60 mg once daily (please see also dosing recommendation above).
Doses up to 120 mg per day have been shown to be efficacious and have been evaluated from a safety perspective in clinical trials. In patients with insufficient response to 60 mg, escalation up to 90 mg or 120 mg may therefore be considered. Dose escalation should be based upon clinical response and tolerability.

After consolidation of the response, it is recommended to continue treatment for several months, in order to avoid relapse.

Elderly
No dosage adjustment is recommended for elderly patients solely on the basis of age. However, caution should be exercised when treating the elderly (see the Pharmacokinetic properties sections of the SPC).

Children and adolescents
The tolerance and efficacy of duloxetine in these age groups have not been studied. Therefore, administration of CYMBALTA to children and adolescents is not recommended (see the Warnings section of the SPC).

Hepatic impairment
CYMBALTA should not be used in patients with liver disease resulting in hepatic impairment (see Contraindications and Pharmacokinetic properties sections of the SPC).

Renal impairment
No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). See the Contraindications section of the SPC in the case of severe renal failure.

Discontinuation of treatment
Abrupt discontinuation of treatment should be avoided. When stopping treatment with CYMBALTA the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see section warnings and undesirable effects of the SPC). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

N : Central nervous system
N06 : Psychoanaleptics
N06A : Antidepressants
N06AX : Other antidepressants
N06AX21 : Duloxetine

2.2. Medicines in the same therapeutic category

Other serotonin and noradrenaline reuptake inhibitors:
EFFEXOR LP 37.5 and 75 mg (venlafaxine) and its generics

2.3. Medicines with a similar therapeutic aim

DEROXAT and DIVARIUS (paroxetine)

SEROPLEX (escitalopram)

LYRICA (pregabalin): no request for reimbursement in the indication generalised anxiety disorder (Marketing Authorisation of 20/03/06)

BUSPAR (buspirone) and its generics

The benzodiazepines indicated in the “symptomatic treatment of severe and/or incapacitating manifestations of anxiety.”

3. ANALYSIS OF THE AVAILABLE DATA

3.1. Efficacy

The dossier comprises 5 phase III studies carried out in patients with generalised anxiety disorder:
- 4 short-term randomised double-blind studies versus placebo;
- 1 randomised double-blind study versus placebo in prevention of relapse.

3.1.1 Short-term studies: HMBR, HMDT, HMDU, and HMDW

The efficacy and tolerance of duloxetine were assessed in patients with generalised anxiety disorder in 4 randomised double-blind studies versus placebo lasting 9 or 10 weeks; in two of the studies there was a venlafaxine arm.
The methodology described below was common to the 4 studies.

Main inclusion criteria:
- patients of at least 18 years of age followed up on an outpatient basis,
- generalised anxiety disorder according to the criteria of DSM-IV, of at least moderate intensity defined by the following scores:
  - a score ≥ 10 on the “anxiety” subscale of the Hospital Anxiety and Depression Scale[1] (HADS),
  - a score ≥ 9 on the Covi Anxiety Scale[2] (CAS),

[1] The HADS is made up of two 7-item subscales, one for anxiety and the other for depression, which can be evaluated independently. Each question can be given a score of 0 to 3 points, making a maximum of 21 points for each subscale.
[2] Covi Anxiety Scale: the severity of the anxiety is judged from the patient’s verbal response and the patient’s behaviour and somatic symptoms. Each of the 3 parameters is given a score from 0 to 4; the most severe score is 12 (Lipman & Covi, 1976).

- no item > 3 on the Raskin Depression Scale[3] (RDS)
- a CAS score higher than the score on the Raskin Depression Scale (RDS)
- a Clinical Global Impression severity (CGI-severity) scale[4] score ≥ 4 (moderate).

Main non-inclusion criteria:
- major depressive episode in the last 6 months, panic disorder, posttraumatic stress, eating disorders in the previous year, obsessive-compulsive disorder, bipolar disorder, psychosis, and somatoform or factitious disorders (axis I of DSM-IV);
- developmental and personality disorders that may interfere with compliance with the protocol (axis II of DSM-IV);
- substance abuse or substance dependence (including alcohol) in the last 6 months.

Treatments:

Table 1: Number of patients randomised, treatments, and study durations

Study	Number of patients		Treatments	Duration
	In total	Per group		
HMBR	513	168	duloxetine 60 mg/day duloxetine 120 mg/day placebo	9 weeks
		170		
		175		
HMDT	327	168	duloxetine 60-120 mg/day placebo	10 weeks
		159		
HMDU	487	162	duloxetine 60-120 mg/day venlafaxine 75-225 mg/day placebo	10 weeks
		164		
		161		
HMDW	581	84	duloxetine 20 mg/day duloxetine 60-120 mg/day venlafaxine 75-225 mg/day placebo	10 weeks
		158		
		169		
		170		

Primary endpoint: change in the score on the Hamilton Anxiety Scale[5] between inclusion and the end of the study.

Secondary endpoints included:
- percentage of responders, these being defined by a ≥ 50% reduction in the Hamilton Anxiety Scale score in comparison with baseline;
- percentage of patients in remission, these being defined by a score ≤ 7 on the Hamilton Anxiety Scale in comparison with baseline.

Results (see Table 2):

In the 4 studies, the decrease in the score on the Hamilton Anxiety Scale (primary endpoint) was significantly greater with duloxetine (-8 to -15 points) than with placebo (-6 to -12 points). In the HMDU and HMDW studies that included a venlafaxine arm, the decrease in the score on the Hamilton Anxiety Scale was significantly greater with venlafaxine 75 to 225 mg/day than with placebo.

[3] Raskin Depression Scale: the severity of the depression is judged from the patient's verbal response, the patient's behaviour, and the secondary symptoms of depression. Each of the 3 parameters is given a score from 0 to 4.

[4] CGI-Severity: A standard evaluation tool, the purpose of which is to enable the clinician to make a global evaluation of the improvement in the disease over time. Using a 7-point scale, the doctor assigns a score to the improvement in the patient's clinical condition following a treatment: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change 5 = minimally worse, 6 = much worse, 7 = very much worse.

[5] Hamilton Anxiety Scale: a 14-item scale made up of two 7-item subscales, one for the psychological component and the other for the somatic component. Each item is given a score from 0 to 4; 0 = no symptoms, 4 symptom severe. The total score is between 0 and 56, 56 being the most severe.

In the HMDW study, the decrease in the score on the Hamilton Anxiety Scale with duloxetine 20 mg/day was comparable to that observed with duloxetine 60 to 120 mg/day. The percentages discontinuing treatment because of lack of efficacy were similar in the 2 groups (2/84 or 2.4% versus 3/158 or 1.9%). Discontinuation of treatment because of adverse events occurred less with duloxetine 20 mg than with duloxetine 60 to 120 mg (4/84 or 4.8% versus 20/158 or 12.6%).

The percentage of responders varied according to the study and was significantly higher with duloxetine (42% to 65%) than with placebo (30% to 42%), except in the HMDU study (47% versus 37%).
The percentage of patients in remission was significantly higher with duloxetine (31% to 44%) than with placebo (19% to 20%) in 2 of the 4 studies.
The percentages of patients responding and in remission were significantly higher with venlafaxine (54% and 61%; 30% and 44%) than with placebo (37% and 42%; 19% and 20%) in the 2 studies that included a venlafaxine arm (HMDU and HMDW).

Table 2: Hamilton Anxiety Scale score and percentage of responders and of patients in remission (ITT results)

Study	Treatment	Mean initial Hamilton score	Change at end of study	p vs placebo	Responders at end of study n (%)	p vs placebo	Remission at end of study n (%)	p vs placebo
HMBR	duloxetine 60 mg/day	25.05	- 12.8	< 0.001	95 (58)	< 0.001	51 (31)	0.009
	duloxetine 120 mg/day	25.13	- 12.5	< 0.001	94 (56)	< 0.001	64 (38)	< 0.001
	placebo	25.82	- 8.4	-	53 (31)	-	33 (19)	-
HMDT	duloxetine 60 to 120 mg/day	22 .54	- 8.1	0.023	67 (42)	0.029	45 (28)	NS
	placebo	23.49	- 5.9	-	48 (30)	-	36 (23)	-
HMDU	duloxetine 60 to 120 mg/day	25.77	- 11.8	0.007	70 (47)	NS	34 (23)	NS
	venlafaxine 75 to 225 mg/day	24.92	- 12.4	< 0.001	86 (54)	0.001	48 (30)	0.016
	placebo	24.98	- 9.2	-	58 (37)	-	30 (19)	-
HMDW	duloxetine 20 mg/day	27.65	-14.7	0.007	50 (60)	0.009	35 (42)	< 0.001
	duloxetine 60 to 120 mg/day	27.74	- 15.3	< 0.001	98 (65)	< 0.001	67 (44)	< 0.001
	venlafaxine 75 to 225 mg/day	27.36	-15.5	< 0.001	97 (61)	< 0.001	70 (44)	< 0.001
	placebo	27.33	- 11.6	-	69 (42)	-	32 (20)	-

Pooled analysis of the HMDU and HMDW studies:
A pooled analysis was undertaken for 2 comparative studies which assessed the efficacy of duloxetine (60 to 120 mg/day) versus placebo and which had a venlafaxine arm (75 to 225 mg/day).
The statistical analysis was based on the following hypothesis: non-inferiority was established if the lower limit of the 97.5% confidence interval of the Hamilton Anxiety Scale score difference between duloxetine and venlafaxine was greater than the predetermined threshold of -1.5.
The lower limit of the 97.5% confidence interval of the Hamilton Anxiety Scale score difference between the duloxetine group and the venlafaxine group [-1.28; 1.67] was greater than the predetermined threshold of -1.5 points in the PP population (see Table 3).
A pooled analysis of the HMDU and HMDW studies produced results supporting the non-inferiority of duloxetine 60 to 120 mg/day in relation to venlafaxine 75 to 225 mg/day.

Table 3: Mean change in the score on the Hamilton Anxiety Scale between inclusion and the end of the study and confidence interval of the difference in the scores (PP results) (CI) (pooled analysis of HMDU and HMDW)

	placebo	Duloxetine 60-120 mg/day	Venlafaxine 75-225 mg/day	Duloxetine minus placebo	Venlafaxine minus placebo	Duloxetine minus venlafaxine
PP	-11.6	-15.4	-15.2	[-5.29; -2.35]	[-5.05; -2.19]	[-1.28; 1.67]

3.1.2 Long-term study: HMDV

The aim of this study was to assess the efficacy of duloxetine versus placebo for the prevention of relapse on a double-blind basis over a period of 26 weeks in 429 patients who had generalised anxiety disorder and who had responded to 26 weeks of open treatment with duloxetine.
In the open phase, the patients were treated with duloxetine 30 mg/day in the first week and then with 60 mg/day. The dosage could be increased to 90 and 120 mg/day.
Of the 887 patients included in the open phase, 429 patients responding (48.4%) to duloxetine were randomised to receive 26 weeks' double-blind treatment with either duloxetine 60 to 120 mg/day (216 patients) or placebo (213 patients). Responders were defined as those with a ≥ 50% decrease in their Hamilton Anxiety Scale score at the end of the open phase with a score < 11 and a CGI improvement score ≤ 2 on at least two consecutive visits.

The inclusion and non-inclusion criteria were identical to those of the short-term studies.

Primary endpoint: time to relapse defined as a CGI-severity score increase of at least 2 points to a score ≥ 4 and a diagnosis of generalised anxiety disorder according to the Mini International Neuropsychiatric Interview or discontinuation of treatment because of lack of efficacy.

Results:
In the 6-month double-blind treatment period, the time to relapse was increased in the duloxetine group (60 to 120 mg/day) in comparison with the placebo group (p value of the log-rank test < 0.001).
The percentage relapse was 13.7% (28/216) in the duloxetine group and 41.8% (84/123) in the placebo group.

3.2. Adverse effects

The tolerance data are generated from clinical studies, periodic safety update reports, national pharmacovigilance monitoring program, and risk management plan.

Tolerance in the double-blind clinical studies versus placebo undertaken in generalised anxiety disorder (1797 patients in duloxetine group, 665 in venlafaxine group, and 333 in placebo group):
The adverse events reported in the duloxetine group with an incidence ≥ 5% of patients and higher than that in the placebo group were: nausea (33.8% versus 10.2%), dry mouth (11.62% versus 3.6%), insomnia (7.6% versus 3.6%), fatigue (10.7% versus 3.5%), diarrhoea (7.9% versus 5.6%), dizziness (13.5% versus 7.5%), drowsiness (7.8% versus 1.8%), hyperhydrosis (7.4% versus 2.0%).
Overall, the most common adverse events in these studies were those usually described with duloxetine.

Due to limited data in the elderly population, a special warning was added to the SPC, and a study to evaluate tolerance and efficacy in elderly patients with generalised anxiety disorder will be performed.

Adverse events under close surveillance:
- hepatotoxicity: elevation of ASAT and alkaline phosphatases was greater in duloxetine-treated patients. No dose-effect relationship was observed.
- risk of suicide: eight cases of suicidal ideation were reported (1 in placebo group, 1 in venlafaxine group, and 6 in duloxetine group, of whom 4 occurred during the open phase of the relapse-prevention study). In a short-term study, a case of auto-aggressive behaviour was reported in the duloxetine group. Two suicide attempts attempted in duloxetine group, one of which led to completed suicide, were reported in the relapse-prevention study.

National pharmacovigilance monitoring program (evaluation carried out on 19 June 2008):
In France, a pharmacovigilance signal concerned suicide and suicide attempts. Whilst the descriptive profile of the cases was unremarkable compared to what would be expected for the therapeutic class and the treated population, concerns were raised with regard to the events frequency in the treated population and in comparison with other antidepressants. The *rapporteur* recommended surveillance of these cases.

Tolerance data from the PSURs:
The number of patients exposed to duloxetine between August 2004 and 2 February 2008 is estimated at 17 131 100: 16 722 400 received CYMBALTA and 406 700 received YENTREVE, which accounts for 5 185 800 patient-years.
In accordance with the data provided in the last two PSURs – 7 and 8 – (between 03/08/07 and 02/08/08), changes were made to the SPC in the "Undesirable effects" section (including the addition of restless legs syndrome and convulsions after treatment discontinuation) and the "Overdose" section (maximum reported dosage 5400 mg).

Five-year European Marketing Authorisation renewal (April 2009):
- Regarding hepatotoxicity:
In the studies, duloxetine was associated with ALAT elevation > 3 times the upper normal limit with a frequency of approximately 1%; there were no reported cases of fulminant hepatitis or liver failure. However, as of 2 August 2008, a total of 942 spontaneous cases of potential liver disorders were reported, including 142 clinically significant cases (15%). Of these 142 cases, 10 were classified as probably drug related and 58 as possibly drug-related. They included liver failure (22 cases), severe liver disease (96 cases), and death (24 cases). These cases were reported mainly in women (77%) and occurred in the first few months of treatment, or early in this period in the most severe cases. In the liver failure cases, no case without other cause or risk factor was identified.

- Regarding cardiovascular events:
In the clinical studies, duloxetine was associated with a small but persistent increase in blood pressure. A large number of cases of hypertensive crisis and clinically significant hypertension were reported, and following PSUR 3, a contraindication was added in the SPC with regard to the initiation of duloxetine in patients with uncontrolled hypertension that could expose them to a potential risk of hypertensive crisis. Cases of ventricular arrhythmia were reported.

- Regarding the risk of suicide:
The SPC for CYMBALTA, as for all antidepressants, contains a special warning regarding the use of antidepressants in children and adolescents, due to an increased risk of suicidal and hostile thoughts shown in clinical studies.
The increased risk of suicidal thoughts and behaviour in young adults between 18 and 24 years old with a major depressive episode and other psychiatric disorders, identified in meta-analyses was also suggested in duloxetine studies versus placebo.

Risk management plan (RMP):
The results of several studies including those regarding the risks of hepatotoxicity and suicide are not yet available. The RMP for CYMBALTA includes 2 observational cohort studies.

A retrospective study (F1J-MC-B021) carried out in the USA aimed to assess the hepatic and cardiac tolerance of CYMBALTA by comparing the incidence of hepatic and cardiovascular events in 6 groups of 30,000 patients: depressive treated or untreated patients, and untreated non-depressive untreated patients.

In June 2008, the results covering the period from August 2004 to August 2006 were evaluated. The patient numbers were much smaller than expected: 15 000 patients given duloxetine versus 15 000 given venlafaxine, 12 000 given duloxetine versus 12 000 given selective serotonin reuptake inhibitors, 6 300 given duloxetine versus 6 300 given tricyclic antidepressants and 4 500 given duloxetine versus 4 500 untreated, were analyzed.
- Regarding hepatic events: in the ITT analysis, the results using the incidence rate ratio (or IRR) for the overall hepatic events endpoint tend to confirm an increased risk in comparison with venlafaxine (14 cases versus 5 ; IRR = 0.34 [$CI_{95\%}$ 0.12-0.95]), but are not significant for the other comparisons:
    - tricyclic antidepressants versus duloxetine: IRR = 0.56 [$CI_{95\%}$ 0.18-1.71]
    - untreated versus duloxetine: IRR = 0.64 [$CI_{95\%}$ 0.15-2.67]
    - SSRI versus duloxetine: IRR =1.08 [$CI_{95\%}$: 0.46-2.57]

In the per-protocol analysis limited to the severest hepatic events (8 cases in 10 000 patient-years with duloxetine versus 6 in 29 000 patient-years in the untreated subjects), the risk was significantly increased with duloxetine in comparison to untreated subjects (IRR = 4.30 [1.45-12.81]).
- Regarding cardiovascular events: the data do not show an increased risk with duloxetine, on either the composite endpoint or each event.

The other study involving 10 000 to 12 000 patients carried out among prescribers in the United Kingdom aims to estimate the incidence of hepatotoxicity, Stevens-Johnson syndrome, suicide, and cardiovascular events in the 6 months after prescription of duloxetine. A report should be available in 2009.

Initial results are available from the 3rd analysis of the General Practice Research Database study of the proprietary product YENTREVE (duloxetine) indicated in the treatment of moderate to severe stress urinary incontinence at a dosage of 40 mg twice daily; the results cover the period to April 2008 and relate to 1 346 exposed patients versus 5 383 non-exposed patients, with a mean duration of follow-up of 1.7 years. This study is to be continued since these results remain non-significant.

The DUROSA study of the proprietary product YENTREVE carried out in Germany had not, by the start of 2008, revealed any tolerance signal in the monitoring of 9 300 patients treated with duloxetine and 4 000 patients treated with another urological therapy.

The risk of suicide was evaluated in a US study undertaken using the PharMetrics database, in which 150 000 patients treated with duloxetine were identified. The results of these studies are being evaluated by the CHMP.

3.3. Conclusion

In 4 randomised double-blind studies (HMBR, HMDT, HMDU, and HMDW) carried out over 9 or 10 weeks in patients with generalised anxiety disorder, the decrease in the score on the Hamilton Anxiety Scale (primary endpoint) was significantly greater with duloxetine at dosages of 20 to 120 mg/day (-8 to -15 points) than with placebo (-6 to -12 points).
The percentage of responders varied according to the study and was significantly higher with duloxetine (42 to 65%) than with placebo (30 to 42%), except in the HMDU study. The percentage of patients in remission was significantly higher with duloxetine (31 to 44%) than with placebo (19 to 20%) in 2 of the 4 short-term studies.
During a 6-month period of treatment the time to relapse observed with duloxetine (60 to 120 mg/day) was increased in comparison with that observed with placebo in patients who had responded to 26 weeks of open treatment with duloxetine.

With regard to safety data, after 4 years of marketing experience, the main identified risks remain such as risk of hepatotoxicity, suicide-related events event, or cardiovascular events. The results of several studies undertaken as part of the risk management plan are not yet available.

In clinical trials, duloxetine was associated with ASAT elevation ≥ 3 times the upper normal limit with a frequency of approximately 1%. As of 2 August 2008, data from spontaneous reports raise concern reporting 942 cases of possible liver disorders, 142 of them clinically significant: 22 cases of liver failure, 96 cases of severe liver disease, and 24 deaths.

Clinical study data relating to suicidal ideation, auto-aggression, and suicide indicate that safety concern about the risk of suicide remains. Questions are raised on the frequency in the treated population and in comparison with other antidepressants with regard to the data from the national pharmacovigilance monitoring program. Studies performed in the urological and psychiatric indications are being continued.
There is no cardiovascular safety concern. Nevertheless, cases of ventricular arrhythmia have been reported.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Generalised anxiety disorder is characterised by excessive anxiety and worry, occurring more days than not for a period of at least 6 months, about a certain number of events or activities. The anxiety, worry, and physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning[6].

The efficacy/adverse effects ratio is low, given the tolerance profile.

Public health benefit:

Generalised anxiety represents a considerable public health burden, given the frequency of this disorder and its impact.

The therapeutic need is covered by existing therapies (other antidepressants and behavioural and cognitive therapy in particular). Whilst it is useful to have a further alternative for the disabling forms of this disorder, it cannot be considered a public health priority.

In the light of the clinical trial data and in view of the existence of these other therapies, it is not expected that the proprietary product CYMBALTA will have any impact on morbidity/mortality and on quality of life.

There is no guarantee that the trial data can be carried over into actual practice:

- because of the difficulty of identifying the disorder (particularly in general medicine)
- because compliance is likely to be lower in real-life conditions than in the trial situation
- due to uncertainty over the tolerance of CYMBALTA (particularly psychiatric and hepatic tolerance)
- because the profile of treated patients may differ from that of trial patients (numerous exclusion criteria, including psychiatric comorbidities, initiation or modification of psychotherapy)

Consequently, in the current state of knowledge and in view of the other treatments available at present, it is not expected that the proprietary product CYMBALTA will benefit public health in this indication.

[6] Diagnostic criteria of generalised anxiety disorder (DSM-IV)

It is a symptomatic treatment.

Pharmacological and non-pharmacological alternatives exist.

The actual benefit of these proprietary products in this indication is not sufficient to permit reimbursement by National Health Insurance, due to safety concerns, especially with regard to hepatotoxicity and the risk of suicide.

4.2. Transparency Committee recommendations

The transparency Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the extension of the indication and at the dosages in the Marketing Authorisation.