HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 March 2007

CYMBALTA 30 mg, gastroresistant capsule
Polyvinylchloride (PVC), polyethylene (PE) and polychlorotrifluoroethylene (PCTFE) blister pack(s) sealed with an aluminium foil, containing 7 capsules (CIP 370 237-5) and 28 capsules (CIP 365 864-5)

CYMBALTA 60 mg, gastroresistant capsule
Polyvinylchloride (PVC), polyethylene (PE) and polychlorotrifluoroethylene (PCTFE) blister pack(s) sealed with an aluminium foil, containing 28 capsules (CIP 365 865-1)
Polyvinylchloride (PVC), polyethylene (PE) and polychlorotrifluoroethylene (PCTFE) blister pack(s) sealed with an aluminium foil, containing 100 capsules (CIP 570 777-3)

Applicant : LILLY

Duloxetine

List I

Date of the Marketing Authorisations (centralised procedure):
Treatment of major depressive episodes (i.e. characteristic symptoms) - 17 December 2004
Treatment of diabetic peripheral neuropathic pain in adults - 4 July 2005

Reason for request:

Inclusion of CYMBALTA 30 mg (B/7, B/28) and CYMBALTA 60 mg (B/28 and B/100) on the list of medicines approved for use by hospitals

Inclusion of CYMBALTA 30 mg (B/7 and B/28) and CYMBALTA 60 mg (B/28) on the list of medicines reimbursed by National Insurance

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Duloxetine

1.2. Indication

Treatment of major depressive episodes (i.e. characteristic symptoms).
Treatment of diabetic peripheral neuropathic pain in adults.

1.3. Dosage

For oral use.

Adults

Major depressive episodes
The starting and recommended maintenance dose is 60 mg once daily with or without food. Dosages above 60mg once daily, up to a maximum dose of 120mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. However, there is no clinical evidence suggesting that patients not responding to the initial recommended dose may benefit from dose up-titrations.
Therapeutic response is usually seen after 2-4 weeks of treatment. After achieving the expected therapeutic effect, it is recommended to continue treatment for several months in order to avoid relapse

Diabetic peripheral neuropathic pain
The starting and recommended maintenance dose is 60 mg once daily with or without food. Dosages above 60mg once daily, up to a maximum dose of 120mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The plasma concentration of duloxetine displays large interindividual variability. Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose.
Response to treatment should be evaluated after 2 months. Response to treatment beyond this period is unlikely.
The therapeutic benefit must be reassessed regularly (at least every 3 months).

Elderly patients

Major depressive episodes: no dosage adjustment is necessary according to age. However, as with any medicine, caution should be exercised when treating the elderly, especially with the dosage of 120 mg per day for which data is limited.

Diabetic peripheral neuropathic pain: no dosage adjustment is necessary according to age. However, caution should be exercised when treating the elderly.

Children and adolescents

The safety and efficacy of duloxetine have not been studied in these patients. Therefore, administration of CYMBALTA to children and adolescents is not recommended.

Hepatic impairment

CYMBALTA must not be used in the case of hepatic impairment.

Renal impairment

No dosage adjustment is necessary for patients with mild or moderate renal dysfonction (creatinine clearance 30 to 80 ml/min). See Section 4.3 of the SPC in the case of severe renal insufficiency.

Discontinuation of treatment

Abrupt discontinuation 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 Sections 4.4 and 4.8 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.

1.4. Pharmacodynamic properties

Duloxetine is a combined serotonin and noradrenaline reuptake inhibitor.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

N Central Nervous System
06 Psychoanaleptics
A Antidepressants
X Other antidepressants
21 Duloxetine

2.2. Medicines in the same therapeutic category

Treatment of major depressive episodes

- venlafaxine (EFFEXOR)
- milnacipran (IXEL)

Treatment of diabetic peripheral neuropathic pain in adults

None

2.3. Medicines with a similar therapeutic aim

Major depressive episodes: other antidepressants

Medicinal products indicated for neuropathic pain in adults

- clomipramine - ANAFRANIL (extension of indication of 12.06.2001)
- imipramine - TOFRANIL (extension of indication of 12.06.2001)
- desipramine - PERTOFRAN (extension of indication of 12.06.2001, not marketed)
- carbamazepine - TEGRETOL (extension of indication of 09.07.2001)

Medicinal product indicated for peripheral and central neuropathic pain in adults

- pregabalin - LYRICA

Medicinal product indicated for peripheral neuropathic pain in adults

- amitriptyline - LAROXYL (change in description of indication of 21.11.2005)

Medicinal products indicated for a particular type of peripheral neuropathy

- gabapentin - NEURONTIN: pain following shingles
- carbamazepine - TEGRETOL: trigeminal and glossopharyngeal neuralgia
- phenytoin - DI-HYDAN: trigeminal neuralgia.

3. ANALYSIS OF THE AVAILABLE DATA

3.1. Depression

3.1.1 Studies submitted to the registration authorities

The submitted file presents the following comparative studies carried out for the indication of "major depressive episodes":

- Eight placebo-controlled comparative studies with a duration of 8 to 9 weeks. Six of these studies have an active arm (fluoxetine and paroxetine) - see pooled analysis, paragraph 3.1.4
- Two 12-week superiority studies versus venlafaxine - see pooled analysis, paragraph 3.1.4.
- One placebo-controlled comparative study for the prevention of relapses
- One placebo-controlled comparative study evaluating the effects of duloxetine on the cognitive functions of elderly patients presenting with a major depressive episode
- One placebo-controlled comparative study evaluating the pain symptoms of patients presenting with a major depressive episode

Duloxetine's clinical development included 3,158 patients (1,285 patient-years of exposure) presenting with a major depressive episode (i.e. characteristic symptoms), meeting DSM-IV criteria. The efficacy of duloxetine was demonstrated at dosages between 60 mg and 120 mg per day using the $HAMD_{17}$[1] scale for depression in short-term randomised, double-blind, placebo-controlled studies using fixed doses of duloxetine in adult outpatients presenting with a major depressive episode. A limited number of patients included in pivotal clinical trials had severe depression (baseline $HAMD_{17} \geq 25$).
A meta-analysis evaluating the efficacy of duloxetine versus placebo estimates the difference in the reduction of the $HAMD_{17}$ score between the two treatments at -2.2 points (95%CI -2.73;-1.66).

A randomised, double-blind study compared the efficacy and safety of a 60 mg/day dose of duloxetine versus placebo in preventing relapses in patients who responded to duloxetine in a 12 weeks open-label study. The estimate of the time to relapse occurrence, the primary endpoint, was higher with duloxetine (p=0.004). The estimate of the percentage of patients who had a relapse at 26 weeks was 17.4% with duloxetine and 28.5% with placebo.

A randomised, double-blind superiority study evaluated the effects of duloxetine versus placebo on the cognitive functions of the elderly ((≥ 65) presenting with a major depressive episode, meeting DSM-IV criteria. The primary efficacy endpoint was the variation after 8 weeks of treatment of a composite score that was established from 4 cognitive tests[2] (score 0 to 51). 311 patients with an average age of 73 were randomised in two groups: placebo (n=104), duloxetine 60 mg/day (n=207). The average initial composite score was 23 in both groups. The mean variation in composite scores was higher with duloxetine (1.95 vs 0.76 points with placebo, p=0.013). The mean variation in $HAMD_{17}$ scores in patients treated with duloxetine (60 mg/day) was higher than that observed with placebo. A dry mouth, nausea and diarrhoea were the most common adverse effects with duloxetine.

A randomised, double-blind superiority study[3] evaluated the efficacy and safety of duloxetine versus placebo on the pain symptoms of outpatients presenting with a major depressive episode, meeting DSM-IV criteria. The patients had a baseline $HAMD_{17}$ score of 15 or above and a CGI-S score of at least 4 points.
The primary efficacy endpoint was the variation rated by the patient after 9 weeks of treatment of the score of item 5 "intensity of pain on average" from the Brief Pain Inventory (BPI) questionnaire[4] on physical pain.

282 patients were randomised in two groups: placebo (n=141), duloxetine 60 mg/day (n=141).

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1 Hamilton Rating Scale for Depression - scale for the severity of depression based on 17 items (score 0 to 53).
Hamilton M. Development of a rating scale for primary depressive illness. Br. J of Social and Clin. Psychology 1967; 6: 278-96.

2 Verbal Learning and Recall Test, Symbol Digit Substitution Test, 2 Digit Cancellation Test, Letter-Number Sequencing Test.

3 Brannan SK et al. Journal of Psychiatric Research 2005;39:43-53.

4 Cleeland CS, Ryan KM. Pain assessment: global use of the Brief pain Inventory. Annals of the Academy of Medicine. Singapore 1994;23:129-38.
Questionnaire with 9 items. Items 3 to 6 (intensity of pain evaluated by the patient) - item 5: intensity of the pain on average (score 0 to 10) - item 9 (interference with daily life) made up of 7 sub-items, each rated from 0 to 10.

The initial scores for item 5 in the BPI questionnaire were 4.6 in the duloxetine group and 4.85 in the placebo group. The mean variations in these scores did not differ between the two treatment groups (-2.3 vs. -1.8 with placebo, ns). Similarly, the variations in the $HAMD_{17}$ scores did not differ from those observed with placebo.

3.1.2 Additional file submitted to the Committee

Three studies were submitted to the Committee at the end of December 2006. These studies were not submitted to the registration authorities. Two of them have not been published.

The HMDH randomised, double-blind superiority study evaluated the efficacy and safety of duloxetine versus placebo on the pain symptoms of outpatients presenting with a major depressive episode, meeting DSM-IV criteria.
The patients had a baseline MADRS score of 20 or above and a CGI-S score of at least 4 points. The patients had at least a history of major depressive episode.
The primary efficacy endpoint was the variation in the score of item 5 in the BPI questionnaire (intensity of the pain on average), evaluated by the patient after 8 weeks of treatment: duloxetine 30 mg/day (first week) then duloxetine 60 mg/day.
327 patients were randomised in two groups: placebo (n=165), duloxetine 60 mg/day (n=162).
The average initial scores for item 5 in the BPI questionnaire were 5.7. The mean variations in these scores differed between the two treatment groups: -1.64 with placebo (n=159) vs -2.57 with duloxetine (n=156). The adjusted difference between the treatments was moderate [-0.94 (95% CI -1.48; -0.40), p<0.001]. The analysis of the averages of the 7 sub-items in item 9 “interference with daily life” (score 0 to 10) showed a difference versus placebo of -1.15 points.

The HMCR[1] randomised, double-blind non-inferiority study compared the efficacy and safety of duloxetine 60 mg/day versus escitalopram 10 mg/day in the treatment of a major depressive episode, meeting DSM-IV criteria. The study had a placebo arm.
The primary efficacy endpoint was the percentage of patients with a decrease of at least 20% in their score on the Maier subscale[2] after 2 weeks of treatment ($\Delta = 10\%$).
684 patients were randomised in three groups: duloxetine (n=273), escitalopram (n=274), placebo (n=137) for a double-blind period of 8 weeks. The average initial $HAMD_{17}$ scores were 18.
511 patients completed the double-blind period of 8 weeks: 195 patients with duloxetine, 216 patients with escitalopram and 100 with placebo.
The per protocol analysis showed the non-inferiority between the active treatments based on the percentage of patients with a decrease of at least 20% in their score on the Maier subscale after 2 weeks of treatment [+8.6% (95% CI -0.52; 17.7)]. The percentages of responders (defined as those with a decrease of at least 50% in their $HAMD_{17}$ score) observed with active treatments after 8 weeks of treatment did not differ compared to the placebo: 49% with duloxetine, 45% with escitalopram and 37% with placebo.

The HMDG study compared openly two methods of duloxetine treatment initialisation in patients who had an incomplete response to at least 5 weeks of SSRI treatment. The patients had a baseline $HAMD_{17}$ score of 15 or above and a CGI-S score of at least 3 points.
The primary endpoint was the variation in the $HAMD_{17}$ score after 10 weeks in relation to the baseline value.
368 patients were randomised. Treatment with duloxetine was initiated just after abrupt discontinuation of the SSRI (n=183) or during a gradual withdrawal from the SSRI over 2 weeks (n=185). After 2 weeks of treatment at a dosage of 60 mg/day, duloxetine was administered at a dose of 60 to 120 mg/day for 8 weeks. The ITT analysis of the data did not highlight any difference in the variation of the $HAMD_{17}$ scores between the two methods of treatment initialisation: around -10 points in both groups.

1 Nierenberg AA et al. Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. Current Medical Research and Opinion. 2007;23(2): 401-16.

2 Maier subscale: sum of items 1,2, 7, 8, 9, 10 in the $HAMD_{17}$ scale (score 0 to 24) - Item 1 (depressed mood), item 2 (feelings of guilt), item 7 (work and activities), item 8 (retardation), item 9 (agitation), item 10 (psychic anxiety).

3.1.3 Meta-analyses of duloxetine versus active comparators

Two meta-analyses of duloxetine versus active comparators were provided:

a. Meta-analysis versus SSRIs

The purpose of this meta-analysis was to compare the efficacy and safety of duloxetine versus selective serotonin reuptake inhibitors in the acute treatment of a major depressive episode.
The systematic search carried out using the PubMED and MedLine computerised bibliographic databases focused on randomised, double-blind, placebo-controlled comparative trials conducted for the acute treatment of a major depressive episode and including an ITT data analysis.
Thirty-four studies were selected.

Active treatment	Number of studies	Number of patients	
		Active product	Placebo
Duloxetine†	5	686	513
Citalopram	4	895	493
Escitalopram	3	590	462
Fluoxetine*	9	1004	544
Paroxetine**	11	703	679
Sertraline	2	304	117

* 5 studies with fluoxetine versus placebo
** 9 studies with paroxetine versus placebo
† HMAQa, HMATb, HMBHa, HMBHb, HMAYa studies

The results are expressed versus SSRIs based on the average difference in variations compared to baseline for the continuous variables (HAMD, MADRS, CGI) and by the odds ratio for the binary variables (response, remission).

Efficacy endpoint	Average difference/odds ratio	Standard deviation	95% CI
HAMD (standardised)	-0.231	0.116	-0.463; -0.003
MADRS	0.657	0.952	-1.214; 2.505
CGI-Severity	-0.005	0.117	-0.234; 0.229
Response*	1.067	1.250	0.692; 1.654
Remission**	1.305	1.270	0.822; 2.085

* reduction in HAMD or MADRS score compared to the baseline above 50%
** HAMD ≤ 7 (≤ 7 or 8 for SSRI studies)

The safety results are expressed in odds ratio.

Criterion	Odds ratio	Standard deviation	95% CI
Early discontinuation	1.160	1.169	0.851; 1.576
- adverse events	0.930	1.322	0.544; 1.632
- inadequate or no efficacy	0.781	1.267	0.494; 1.259
Anorexia	1.112	1.637	0.433; 3.034
Constipation	1.247	1.526	0.556; 2.927
Diarrhoea	0.788	1.283	0.486; 1.280
Vertigo	1.587	1.317	0.920; 2.689
Dry mouth	2.052	1.269	1.283; 3.251
Headaches	0.912	1.212	0.629; 1.334
Insomnia	0.832	1.279	0.515; 1.351
Nausea	1.364	1.264	0.851; 2.157
Nervousness	0.774	1.421	0.401; 1.615
Drowsiness	1.229	1.351	0.691; 2.234

The analysis of the data highlighted a statistically significant difference, which is debatable in terms of clinical relevance (-0.2 points) between duloxetine and SSRIs, in the standardised HAMD score. The other efficacy endpoints did not differ between the two types of treatment. A “dry mouth” was the most common event with duloxetine.

b. Meta-analysis versus venlafaxine

The purpose of this meta-analysis was to compare the efficacy and safety of duloxetine versus venlafaxine in the acute treatment of a major depressive episode.
The systematic search carried out using the PubMED and MedLine computerised bibliographic databases focused on randomised, double-blind, placebo-controlled comparative trails conducted for the acute treatment of a major depressive episode with an ITT data analysis.

Eleven studies were selected.

Active treatment	Number of studies	Number of patients	
		Active product	Placebo
Duloxetine	5	686	513
Venlafaxine	6	854	587

The results are expressed versus venlafaxine based on the average difference in variations compared to baseline for the continuous variables (HAMD, MADRS, CGI) and by the odds ratio for the binary variables (response, remission).

Efficacy endpoint	Average difference/odds ratio	Standard deviation	95% CI
HAMD (standardised)	-0.153	0.248	-0.645; 0.335
CGI-Severity	-0.101	0.596	-1.298; 1.075
Response*	0.968	1.582	0.393; 2.392
Remission**	1.032	1.954	0.279; 3.861

* reduction in HAMD or MADRS score compared to the baseline is above 50%
** HAMD ≤ 7 (≤ 7 or 8 for SSRI studies)

The safety results are expressed in odds ratio.

Criterion	Odds ratio	Standard deviation	95% CI
Early discontinuation	1.361	1.215	0.935; 1.991
- adverse events	0.518	1.375	0.277; 0.981
- inadequate or no efficacy	1.601	1.406	0.832; 3.161
Anorexia	0.907	1.517	0.408; 2.113
Constipation	0.584	1.611	0.230; 1.507
Diarrhoea	0.995	1.530	0.438; 2.318
Vertigo	0.517	1.362	0.273; 0.942
Dry mouth	1.194	1.368	0.653; 2.235
Headaches	0.835	1.352	0.457; 1.482
Insomnia	0.691	1.382	0.367; 1.327
Nausea	0.677	1.538	0.283; 1.574
Nervousness	0.407	1.592	0.163; 1.024
Drowsiness	0.923	1.385	0.489; 1.773

The analysis of the different efficacy endpoints did not highlight any difference between the two treatments. Early discontinuation for adverse events and vertigo were less common with duloxetine.

3.1.4 Pooled data analysis versus active comparators

Two pooled comparative data analyses of duloxetine versus SSRIs and versus venlafaxine were provided.
Swindle's pooled analysis[1] involved 6 comparative studies which assessed the efficacy of duloxetine (60 to 120 mg/day) versus placebo, containing a SSRI arm (fluoxetine 20 mg/day or paroxetine 20 mg/day). The duloxetine doses ranged from 60 mg/day to 120 mg/day (maximum recommended dosage analysed in 4 of the studies selected). The maximum recommended dosages for fluoxetine and paroxetine are 60 mg/day and 50 mg/day respectively.

Perahia's pooled analysis[2] of data from two superiority studies comparing duloxetine (60 mg/day) and venlafaxine (150 mg/day) does not indicate any difference between the two treatments with regard to the primary endpoint of the GBR score [Global Benefice Risk, 8 categories, score -5 (risk > benefit) to +5 (benefit > risk)] defined based on the "remission" efficacy criterion and safety criteria (adverse events and/or early discontinuation of treatment).

3.2. Diabetic peripheral neuropathic pain

Three randomised, double-blind superiority studies (HMAW[3], HMAVa[4], HMAVb[5]) compared the efficacy and safety of duloxetine (20 mg/day, 60 g/day and 120 mg/day) versus placebo in the treatment of peripheral neuropathic pain in patients with type 1 or type 2 diabetes.
Patients meeting the diagnostic criteria of a major depressive episode were excluded.
The neuropathy diagnosis was confirmed by an MNSI score[6] of at least 3. Daily neuropathic pain had been occurring for at least 6 months.

The primary efficacy endpoint was the variation, compared to baseline, in the weekly mean of the average pain scores over 24 hours based on Likert's scale[7] after 12 weeks of treatment.

1,139 patients with an average age of 60 were randomised. Over 80% of the patients had type 2 diabetes. The mean time the patients had diabetes was 10 to 14 years. The average duration of the diabetic neuropathy was 4 years The patients had an average baseline score for minimum pain of 4 on the Likert scale (0-10) and a glycosylated haemoglobin (HbA1c) less than or equal to 12%.

The initial average MNSI scores were 5 to 6. The initial average scores for the severity of pain on Likert's scale were 6.

The average reductions in the pain scores measured on Likert's scale were higher with duloxetine than with placebo (-0.90 to -1.32 points with duloxetine 60 mg/day, -0.87 to -1.45 points with duloxetine 120 mg/day versus placebo, $p<0.001$). A decrease in pain of at least 50% was observed in 40 to 50% of patients treated with duloxetine and 25 to 30% of patients who received the placebo.

The following adverse events were most commonly reported with duloxetine: nausea, vomiting, vertigo, constipation, loss of appetite, anorexia, fatigue.

Conclusion

Duloxetine administered at the doses of 60 mg/day and 120 mg/day reduced the pain symptoms for diabetic peripheral neuropathy. The mean variations in the pain scores measured on Likert's scale were higher with duloxetine (-0.9 to -1.45 points vs placebo).
No efficacy data has been published from controlled studies for periods of treatment longer than 12 weeks.

1 Poster - Analysis report not available
2 Poster - Analysis report not available
3 Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs placebo in patients with painful diabetic neuropathy. Pain 2005 Jul;116(1-2):109-18.
4 Poster - Study report
5 Raskin J, FRCPC, Yili L, Pritchett. A double-Blind, Randomized Multicenter Trial Comparing Duloxetine with Placebo in the Management of Diabetic Peripheral Neuropathic Pain. American Academy of Pain Medicine. Volume 6 - Number 5, 2005.
6 MNSI: Michigan Neuropathy Screening Instrument (Sheehan et al., 1988)
7 Likert scale -11-point scale (score 0 to 10)

3.3. Safety data

The data is taken from the regular updated pharmacovigilance reports: PSUR 1 (03.08.2004 - 02.02.2005), PSUR 2 (03.02.2005 - 02.08.2005), PSUR 3 (03.08.2005 - 02.02.2006) and PSUR 4 (03.02.2006 - 02.08.2006).

The number of patients exposed to duloxetine since August 2004 (first approval) is estimated at 5,083,000: 4,845,000 have received CYMBALTA, 237,000 have received YENTREVE, i.e. 1,551,000 patient years (1,495,000 for CYMBALTA and 56,000 for YENTREVE).

Between 3 February 2006 and 2 August 2006 (PSUR 4), the number of patients exposed to duloxetine is estimated at 3,552,000. The number of patients exposed as part of clinical studies is estimated at 4,491.
2,950 reports have been filed over this period, including 2,921 spontaneous reports. 583 (20%) were considered as serious (29 deaths). The indication was mentioned in 61% of cases: depressive disorders (71.5%), urinary incontinence (10%), diabetic peripheral neuropathy (7%).
The distribution of events by body structure and function has remained unchanged compared to that of the initial regular safety reports. The most commonly reported events are psychiatric disorders (17%), gastrointestinal problems (16%) and nervous system disorders (15%).

Among the areas addressed in the previous regular safety reports, liver disorders (cytolysis) and psychiatric disorders (suicide risk) have been especially identified.
A review of liver disorders and events linked to suicide had been carried out as part of PSUR 3. At that time around 23,900 patients had been exposed to duloxetine during clinical trials: 14,627 patients during placebo-controlled studies (n=8504 with duloxetine, n=6123 with placebo).

a. Hepatic toxicity

During placebo-controlled studies:
- an increase in ALT transaminase levels to over 3 times the upper limit of the normal range (ULN) was reported in 1% of patients.
- an increase to over 5 times the ULN was reported in 0.6% of patients.
- an increase to over 10 times the ULN was reported in 0.2% of patients (13 cases).

An increase in aminotransferase levels was more common in studies carried out on urinary incontinence.

Among the spontaneous reports of liver abnormalities with duloxetine collected in the 18-month post-marketing period, a total of 256 cases of liver disorders were identified. Nine cases were fatal. In 77 cases the treatment was classified as the possible cause, in 7 cases the probable cause, in 45 cases the unlikely cause and there was insufficient proof in 127 cases. In at least 44 patients another aetiology or risk factors had been identified.
In the majority of cases, the event occurred in the first 2 months of treatment with an average dosage of 58 mg/day (30 to 180 mg/day).
There was little evidence presented for the hepatic events reported. The nature of the hepatic disorder had only been identified in 46 patients: cytolysis (35 cases), cholestasis (7 cases), mixed (4 cases).
Eleven cases of hepatic impairment were reported, 7 of which were fatal. In most cases, risk factors were assoicated (alcohol, paracetamol overdose etc.). In 3 cases, the onset of the hepatic disorder in the early days of treatment, the improvement or disappearance of the event when the treatment was discontinued and the absence of any clearly identified risk factors suggest that the problems were possibly linked to taking duloxetine. One case of fatal hepatic necrosis and a case of fatal hepatic encephalopathy were reported.

Over the period covered by PSUR 4, 150 new cases of liver disorders were identified. Three cases were fatal. In 50 cases the treatment was classified as the possible cause, in 19 cases the probable cause, in 26 cases the unlikely cause and there was insufficient proof in 55 cases.

The laboratory estimates the rate of occurrence of hepatic disorders reported with duloxetine at 26.2 per 100,000 patient-years. The rate of occurrence of hepatic disorders considered to be likely or possible is estimated at 9.9 for 100,000 patient-years. There may be some general under-reporting, but no definite figures can be given for this. The estimate of the rate of occurrence of medication-related liver disorders in the general population, as published in the literature, is between 0.7 and 40.6 per 100,000 patient-years.

b. Suicide risk

During the placebo-controlled studies (14,486 patients including 8,423 treated with duloxetine), suicidal thoughts were reported in 38 patients (0.45%) treated with duloxetine and in 23 patients with placebo (0.38%). One suicide was observed in the duloxetine group and one in the placebo group. 7 attempted suicides in the duloxetine group and 2 attempted suicides in the placebo group were reported. The data does not suggest any increased suicide risk for psychiatric indications (RR=0.97 95% CI 0.59-1.61). The RR is 2.37 (95% CI 1.06-5.27) for urological indications.

The study data versus active comparators (escitalopram, fluoxetine, paroxetine, venlafaxine) showed an increased suicide risk with duloxetine in relation to the comparators (4,026 patients including 2,281 treated with duloxetine):

- suicide: duloxetine 1 case (0.04%)
- attempted suicide: duloxetine 7 cases (0.31%), comparator 1 case (0.06%)
- suicidal thoughts: duloxetine 20 cases (0.88%), comparator 5 cases (0.29%)

The relative risk (RR) for events linked to suicide, coded from 1 to 4[1] is 3.44 (95% CI 1.42-8.32). The relative risk (RR) for events linked to suicide, coded from 1 to 9 is 3.25 (95% CI 1.51-7.0).
Excluding the trial including with a very low duloxetine group, the results showed RRs of 2.1 (95% CI 0.7-6.8) and 2.3 (95% CI 0.9-5.8) respectively.

Among the reports of psychiatric problems collected in the 18-month post-marketing period, 524 events linked to suicide were identified. 276 cases were evaluated:

- suicide (55 cases)
- attempted suicide (116 cases)
- suicidal thoughts (203 cases)

Among the cases where the indication is mentioned, 84% of the patients were receiving duloxetine for depression.
The condition improved or disappeared when the treatment was discontinued in 117 cases (out of 174 cases reported).

The level of behaviour and thoughts linked to suicide was estimated at 39.7 per 100,000 patient-years (18.4 per 100,000 patients-years for suicide-type behaviour).

Over the period covered by PSUR 4, 192 events linked to suicide were identified. 162 cases were evaluated:

- suicide (29 cases)
- attempted suicide (44 cases)
- suicidal thoughts (89 cases)

Among the cases where the indication is mentioned, 82% of the patients were receiving duloxetine for depression.
An improvement in the condition was observed when the treatment was discontinued in 58 cases (out of 68 cases reported).

8 Suicide-related events - code 1 (completed suicide), code 2 (suicide attempt), code 3 (preparatory acts toward imminent suicidal behavior), code 4 (suicidal ideation), code 5 (self-injurious behavior), code 6 (not enough information, fatal), code 9 (not enough information, nonfatal).

3.4. Conclusion

3.4.1 Major depressive episodes

The efficacy of duloxetine at dosages between 60 mg and 120 mg per day was demonstrated versus placebo in the treatment of major depressive episodes in short-term studies. A meta-analysis evaluating the efficacy of duloxetine versus placebo estimates the difference in the reduction of the $HAMD_{17}$ score between the two treatments at -2.2 points (95%CI -2.73;-1.66).
During a 26-week period of treatment, the risk of relapse observed with duloxetine (60 mg/day) was lower than that observed with placebo in patients who responded to duloxetine as part of 12 weeks of open-label treatment.

The meta-analyses which compared duloxetine versus SSRIs and venlafaxine did not show any clinically relevant differences in efficacy between the different products.

Two studies evaluated the efficacy of duloxetine versus placebo in treating pain symptoms associated with a major depressive episode The primary endpoint of both these studies was the variation in the score for item 5 “intensity of the pain on average” (score 0 to 10) in the BPI questionnaire. The HMDH study showed an improvement of 0.94 points compared to placebo after 10 weeks of treatment. The analysis of the data from the second study does not show any difference versus placebo.
The Committee regrets the absence of any study providing a direct comparison against active treatments.

3.4.2 Diabetic neuropathic pain

The placebo-controlled comparative studies for the treatment of diabetic peripheral neuropathic pain demonstrated the efficacy of duloxetine (60-120 mg/day) in the short term (12 weeks). The clinical benefit observed versus placebo was moderate, in the range of 1 to 1.5 points on Likert’s scale (0-10). The maintenance of duloxetine’s efficacy over the medium term (6 months of treatment) remains to be assessed.
The Committee regrets the absence of any study providing a direct comparison against active treatments, especially against imipramines. The file does not contain any results offering relevant indirect comparisons in this indication.

3.4.3 Safety data

There are currently insufficient factors to be able to attribute any major hepatic toxicity to duloxetine. However, the incidence of abnormalities observed in clinical trials does not eliminate the possibility of this.
The data from the spontaneous reports encourages efforts to continue monitoring duloxetine’s hepatic safety (taking into account that under-reporting will be probable).

In the case of suicide risk, the placebo-controlled studies have not highlighted any increased risk with duloxetine. But the risk of events linked with suicide is twice more common with duloxetine than with the comparative antidepressant used in studies versus active treatment. No conclusion can be made based on the figures from spontaneous reports. The likelihood of having an answer from spontaneous reports is low, unless a very important risk is involved, outside the limits established in the general population.

Since Cymbalta was first approved, several amendments have been made to the SPC in Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects.

Following an assessment of the data from PSUR 1 and 2, liver disorders were mentioned in Section 4.4 Special warnings and precautions for use:

Hepatitis/Increased Liver Enzymes
Cases of liver injury, including severe elevations of liver enzymes (> 10 times upper limit of normal), hepatitis, and jaundice have been reported with duloxetine. Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury (opinion of the European Commission of 29 March 2006).

Following an assessment of the data from PSUR 3, “hepatic failure” was mentioned in Section 4.8 Undesirable effects. The paragraph about blood pressure and heart rate in Section 4.4 Special warnings and precautions for use has been amended. Patients with uncontrolled hypertension are mentioned in Section 4.3 Contraindications.

The European Medicines Evaluation Agency believes that the benefit/risk balance is favourable for duloxetine for all indications. However, the concerns raised with regard to safety must be followed up. The company must submit changes to update the SPC, provide cumulative reviews, particularly about severe hepatic adverse effects, suicide-related events and cardiovascular effects (in particular arrhythmia and heart failure) and set up as soon as possible clinical trials as part of the risk management plan.

The European Risk Management Plan (final report dated 22 January 2007) includes a retrospective cohort study in the US with the main objective of identifying the severe hepatic events and cardiovascular accidents which have occurred with antidepressants (duloxetine, venlafaxine, SSRIs, tricyclic antidepressants, nefazodone), determining their prevalence and searching for a possible link between the incidence of hepatic events and dose (around 30,000 patients being treated with duloxetine are expected). Monitoring prescriptions for duloxetine is planned by a panel of GPs in the UK.

In France, a national pharmacovigilance monitoring is planned. Measures of risk minimisation are also planned.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Major depressive episodes

The main features of a major depressive episode include a depressed mood or a loss of interest in or pleasure from almost all activities. The level of functional impairment linked with a major depressive episode varies, but distress and/or impairment at a social or professional level exists, even if the intensity is only slight. The most serious consequences of a major depressive episode are attempted suicide and actual suicide.

These medicinal products are intended to treat the symptoms of a major depressive episode.

These medicinal products have a moderate efficacy/adverse events ratio.

There are alternatives available to these medicinal products.

Public health benefit:

Major depressive episodes are a major public health burden. Improving their management is a public health need. However, it cannot be inferred, based on the data available, that CYMBALTA will provide an answer to this need that is different from that provided by the other available treatments. In view of the efficacy data available from the clinical studies and indirect comparisons made and taking into account the recent amendments made to the SPC regarding duloxetine’s safety (especially hepatic), no impact is expected from CYMBALTA on morbi-mortality for this indication in relation to existing antidepressants.

Consequently, CYMBALTA is not expected to have a public health benefit for this indication.

The clinical benefit of CYMBALTA in the treatment of major depressive episodes is substantial.

Diabetic neuropathic pain

Among the sensory disorders caused by diabetic neuropathy, pain is the most common of the neurological manifestations. This pain may be diffuse, muscular, neuralgic occurring in paroxysms, or causalgic. It may have a major psychosocial impact and result in adversely affecting quality of life.

These medicinal products are intended to treat the symptoms of diabetic peripheral neuropathic pain.

The efficacy/adverse events ratio of these medicinal products is moderate after 12 weeks of treatment. The efficacy/adverse effects ratio in the medium term remains to be determined.

There are alternative drugs available.

Public health benefit:

The public health burden represented by diabetic peripheral neuropathic pain is moderate. There is a therapeutic need insofar as existing treatments are not very effective. However, it cannot be inferred, based on the data available, that CYMBALTA will provide an additional solution to answer to this need,, in relation to the current management of the condition. It is difficult to reach a conclusion about CYMBALTA's contribution in terms of morbidity (including quality of life) insofar as the clinical studies have been carried out versus placebo and over too short a period for a public health approach. As a result, no impact is expected on morbidity from CYMBALTA compared to the medicines available for this indication.
Consequently, CYMBALTA is not expected to have a public health benefit for this indication.

The actual benefit of CYMBALTA in the treatment of diabetic peripheral neuropathic pain is substantial.

4.2. Improvement in actual benefit

Major depressive episodes

CYMBALTA does not offer any improvement in actual benefit (IAB V) compared to other antidepressants used in the management of major depressive episodes (i.e. characteristic symptoms).

Diabetic peripheral neuropathic pain

In view of the absence of any comparative data, CYMBALTA does not offer any improvement in actual benefit (IAB V) compared to other treatments normally used to treat diabetic peripheral neuropathic pain.

4.3. Therapeutic use

Major depressive episodes[i,ii]

In the case of a minor depressive episode, psychotherapy is proposed as the first-line treatment, depending on accessibility of this type of treatment and patient's preference. Otherwise, antidepressants may be proposed.

In the case of a moderate depressive episode, antidepressants are proposed as the first-line treatment. A combination of antidepressants and psychotherapy may be proposed in the case of psychosocial problems that have a marked impact on the patient's life.

In the case of a severe depressive episode, antidepressants must be used *(grade A)*.
The choice of medicinal product must be limited to medicines for which the SPC mentions the availability of conclusive studies in patients with severe depression.

It is recommended to reassess the response to the treatment after 4 to 8 weeks of treatment in order to assess its efficacy.

Discontinuing medicinal treatment for an isolated depressive episode may be discussed 6 months after clinical remission has been achieved. The dosage must be reduced very gradually over several weeks.

Diabetic peripheral neuropathic pain[iii,iv,v,vi,vii]

Diabetic peripheral neuropathy is defined by the presence of symptoms and/or signs of peripheral nerve impairment secondary to diabetes. The neurological signs are diverse and may manifest in the form of sensory disorders, motor disorders, reflex abnormalities or cranial nerve damage. Distal symmetrical neuropathy is the most common clinical forms.

An improvement in monitoring blood glucose levels is an important aspect in the treatment of diabetic neuropathy.

A variety of therapeutic approaches have been recommended for neuropathic pain, mainly based on their aetiology, the symptoms presented by the patient or on the physiopathological mechanisms. The ideal approach needs to take into account the diversity and considerable disparity of clinical situations which may evolve over time with the same patient.

Neuropathic pain responds poorly, or not at all, to usual analgesic treatments (NSAIDs, paracetamol, salicylates).

Medicated analgesic treatments for neuropathy are based, by common consent, on the use of tricyclic antidepressants or antiepileptics acting on the sodium or calcium channels. These treatments have a modest efficacy. Their safety profile may limit their prescription. It is still difficult to identify the responders to these different treatments.
Due to the efficacy of treatments often being incomplete, combinations of analgesics with complementary action mechanisms may be proposed.

The patient's optimum therapeutic management may require regular assessment and adjustments of the treatment strategy as the underlying disease evolves.

The treatment of chronic pain must often include some form of management which does not use medication, comprising physical and/or psychotherapeutic treatments.

4.4. Target population

Treatment of major depressive episodes (i.e. characteristic symptoms)

The prevalence of characterized depressive episodes that lasted from one year among the general population can be estimated at around 5%,

As of 1 January 2006, the population of mainland France and its overseas departments is estimated at 62.9 million inhabitants. The number of adults can be estimated at 48 million. Extrapolating the prevalence data to the French population gives an estimate of 2.4 million to the number of adult patients suffering from a major depressive episode.

Treatment of diabetic peripheral neuropathic pain in adults

The prevalence of diabetes in the French population is estimated at 3%, i.e. 2,238,500 people.

A large disparity in the frequency of diabetic neuropathy is observed in the different studies (non-specific symptoms, variable diagnostic criteria etc.).
Two key factors influence the frequency and severity of neuropathy: the duration of the disease and the quality of blood glucose level monitoring.

In a study carried out in France[1], the prevalence of peripheral neuropathy symptoms observed was 8.9%. Diabetic neuropathy was defined by a bilateral absence of Achilles reflexes and/or an abnormal perception of vibrations associated with at least one symptom (pain, muscular weakness, sensibility reduction).

According to the data from two studies[2,3] supplied by the company, 7 to 16% of diabetic patients suffer from painful diabetic neuropathy, which is around 157,000 to 365,000 people in France.

4.5. Recommendations of the Transparency Committee

The Transparency Committee recommends the inclusion of the medicinal products CYMBALTA 30 mg (B/7, B/28) and 60 mg (B/28) in the list of medicinal products reimbursed by National Insurance and of the medicinal products CYMBALTA 30 mg (B/7, B/28) and CYMBALTA 60 mg (B/28 and B/100) in the list of medicinal products approved for use by hospitals and various public services for the indications and dosages in the marketing authorisation.

9 Delcourt C, Papoz L. Le diabète et ses complications dans la population française. Ed. INSERM, 1996.

4.5.1 Packaging

The packaging is adapted to prescription requirements.

4.5.2 Reimbursement rate: 65%

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10 Daoui C, MacFarlane IA, Woodward A, Nurmikko TJ, Bundred PE, Benbow SJ. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. Diabet Med 2004;21:976-82.

11 Lilly prevalence study, 2005.

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[i] Prise en charge d'un épisode dépressif isolé de l'adulte en ambulatoire - ANAES guidelines, May 2002.

[ii] Bon usage des médicaments antidépresseurs dans le traitement des troubles dépressifs et des troubles anxieux de l'adulte. Afssaps, October 2006.

[iii] Attal N, Bouhassira D. Traitement pharmacologique des douleurs neuropathiques. EMC 17-023-2005.

[iv] Chen H, et al. Contemporary management of neuropathic pain for the primary care physician. Mayo Clin Proc 2004;79:1533-1545

[v] Eisenberg E et al. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of non-malignant origin: systematic review and meta-analysis of randomized controlled trials. JAMA. 2005;293(24):3043-52.

[vi] Dworkin RH et al. Advances in Neuropathic Pain. Diagnosis, mechanisms, and Treatment Recommendations. Arch Neurol 2003;60:1524-34.

[vii] Attal N et al. EFNS guidelines on pharmacological treatment of neuropathic pain. European Journal of Neurology 2006,13:1153-69.