HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

1 October 2008

EFFEXOR SR 37.5 mg prolonged-release capsule
B/30 (CIP: 346 563-3)

EFFEXOR SR 75 mg prolonged-release capsule
B/30 (CIP: 346 556-7)

Applicant: WYETH PHARMACEUTICALS FRANCE

Venlafaxine

ATC Code: N06AX16

List I

Date of Marketing Authorisation: 15/04/1998 (national procedure)

Dates of most recent amendments to marketing authorisation:
30/06/2008: amendments to paragraphs concerning adverse effects and warnings (suicidal ideation);
13/11/2007: extension of indication to "panic disorder with or without agoraphobia"

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication “Panic disorders, with or without agoraphobia”.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Venlafaxine

1.2. Indications
- “Major depressive episodes.
- Generalised anxiety disorder.
- Prevention of recurrence of depression in patients with unipolar disorder.
- Social anxiety disorder (social phobia).

- **Treatment for panic disorders, with or without agoraphobia. "**

1.3. Dosage
"Panic disorders, with or without agoraphobia
The recommended dose of EFFEXOR SR is 75 mg per day. It is recommended that a dose of 37.5mg/day of prolonged-release venlafaxine be used for the first 4-7 days. Dosage should then be increased to 75mg/day.
Patients not responding to the 75 mg/day dose may benefit from dose increases up to a maximum dose of 225 mg/day. EFFEXOR dosage increases can be made in 75 mg increments at intervals of around 2 weeks, or more rapidly, while still keeping a minimum period of 4 days between two increases.

In all cases:
Prolonged-release capsules should be taken as a single dose.
When the required therapeutic response has been achieved, treatment can gradually be reduced to the minimal dose that is compatible with maintained efficacy and safety.
The maximum dose for the prolonged-release form is 225 mg/day.

Duration of treatment
EFFEXOR SR has been shown to be effective as a long-term treatment of up to 6 months for generalised anxiety and panic disorder.
EFFEXOR SR has been shown to be effective as a short to medium term treatment (up to 6 months) for social phobia. Longer-term effectiveness has not been established.

As the treatment of major depressive episodes, generalised anxiety, social phobia and panic disorder typically requires continuous prescription of medication over several months, medication should be reviewed periodically, and dosage forms should be re-assessed on a case-by-case basis.

Method of administration
It is recommended that venlafaxine prolonged-release capsules be taken with food, at approximately the same time each day. Capsules should be swallowed whole.

Renal and/or hepatic impairment
In patients with renal impairment, the dose should be reduced. If glomerular filtration rate is less than 30 mL/min, the dose should be reduced by 50%.
The product should not be administered during dialysis.

In patients with mild and moderate hepatic impairment, in general a 50% dose reduction should be considered. A reduction of more than 50% may be necessary for some patients.

It may be necessary to treat such patients with immediate-release venlafaxine.

Elderly patients
In elderly patients, the fact that glomerular filtration rate is often reduced in old age should be taken into account, along with the caution required when prescribing or adjusting any anti-depressant.

Discontinuation of treatment
When stopping treatment with venlafaxine, 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. If the treatment course was longer than 6 weeks, the dose should be tapered down over at least 2 weeks.
The taper period will depend on the dose, the duration of treatment and the patient's characteristics. The patient should be advised not to discontinue the treatment without supervision. "

1.4. Special warnings and precautions for use (amendment to MA, dated 30 June 2008)

"Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which EFFEXOR SR is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

If there is a history of substance dependence, it is important to watch out for signs suggesting abuse or misuse.

The "recurrence of depressive episodes" indication concerns patients who have presented with at least three (including the episode currently being treated) major depressive episodes, of moderate to severe intensity.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification 2007

N : Nervous system
N06 : Psychoanaleptics
N06A : Antidepressant
N06AX : Other antidepressants
N06AX16 : Venlafaxine

2.2. Medicines with a similar therapeutic aim

Selective serotonin reuptake inhibitors (SSRI) indicated for "panic disorder with or without agoraphobia or prevention of panic attacks with or without agoraphobia":

- citalopram: SEROPRAM and generics,
- escitalopram: SEROPLEX,
- Paroxetine: DEROXAT, DIVARIUS and generics.

Imipramine antidepressant indicated for "Prevention of panic attacks with or without agoraphobia"

- clomipramine: ANAFRANIL and generics,

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Evaluation of the efficacy and safety of EFFEXOR SR in this new indication is based on five clinical studies:

- Studies 391 and 353, which aimed to compare EFFEXOR SR (75 mg to 225 mg/day) with placebo in terms of percentage of patients free from panic attacks at 10 weeks;
- Study 354, which aimed to compare EFFEXOR SR (75 mg to 225 mg/day) with placebo in terms of time to recurrence at 6 months;
- Studies 398 and 399, which aimed to compare EFFEXOR SR (75 mg to 225 mg/day) with placebo in terms of percentage of patients free from panic attacks at 12 weeks; These studies also included a paroxetine arm.

3.1.1. Studies 391 and 353

Methodology: Phase III placebo-controlled, parallel-group, randomised double-blind studies, carried out on patients with panic disorder who were followed up for 10 weeks.

Inclusion criteria: Persons aged over 18 years with:

- a history of panic disorder as defined in the DSM-IV criteria for at least 6 months (study 391) or 3 months (study 353);
- a CGI-S (Clinical Global Impression Severity) score of ≥ 4;
- 4 or more panic attacks (study 391) during the 4 weeks prior to the selection period, and 2 during the selection period (respectively 8 and 4 symptoms in study 353).

Treatment:

- EFFEXOR 37.5 mg/day for 4 days, followed by an increase to 75 mg/day. Depending on clinical response, it was possible to increase the dosage after 14 days of treatment, with dosage not to exceed 225 mg/day.
- Placebo.

Primary endpoint: percentage of patients free from panic attack, defined as more than 4 symptoms on the PAAS* scale (Panic And Anticipatory Scale, see annex) after 10 weeks of treatment.

RESULTS: ITT analysis
On inclusion, patient characteristics were similar.

In study 391, 328 patients were evaluated (168 in the EFFEXOR group versus 160 in the placebo group).
After 10 weeks of follow-up, no difference was observed between the two groups in terms of percentage of patients who were free from panic attacks: 55% (88/168) patients in the EFFEXOR group versus 52.4% (88/160) in the placebo group (NS).

In study 353, 310 patients were evaluated (155 in the EFFEXOR group versus 155 in the placebo group).
After 10 weeks of follow-up, no difference was observed between the two groups in terms of percentage of patients who were free from panic attacks: 51% (79/155) patients in the EFFEXOR group versus 40.6% (63/155) in the placebo group (NS).

3.1.2. Study 354

Methodology: Phase III two-phase study involving patients with panic disorder:
- one open-label phase, lasting 12 weeks;
- one parallel-group, placebo-controlled, randomised double-blind phase, lasting 6 months.

Inclusion criteria: Persons aged over 18 years with:
- a history of panic disorder as defined in the DSM-IV criteria for at least 3 months;
- a CGI-S (Clinical Global Impression Severity) score of ≥ 4;
- 6 panic attacks during the 2 weeks prior to the selection period, and 3 during the selection period.

Treatment:
Open-label phase: n=291
EFFEXOR 37.5 mg/day for 1-7 days, followed by an increase to 75 mg/day. Depending on clinical response, it was possible to increase the dosage after 14 days of treatment, with dosage not to exceed 225 mg/day.

Double-blind phase: n=169 (intention-to-treat)
Only patients who responded to treatment during the open-label phase were included in the double-blind phase.
- EFFEXOR at the effective dose as determined during the open-label phase (n=89).
- Placebo (n=80)

Primary endpoint: time to relapse. Relapse was defined as appearance of two panic attacks during the same week, or as discontinuation of treatment because of lack of efficacy.

RESULTS: ITT analysis
On inclusion, patient characteristics were similar.

After 6 months of follow-up of responders who were included in the double-blind phase, time to relapse was significantly longer in the EFFEXOR group than in the placebo group ($p<0.001$).
In the absence of precise data relating to mean time to relapse in the study report, the significance observed in this study must be interpreted with care.

The cumulative relapse percentage was significantly higher in the EFFEXOR group than in the placebo group: 22.5% of patients 20/89 versus 50% of patients (40/80), p<0.001.

3.1.3. Studies 398 and 399

Methodology: Parallel-group, randomised double-blind studies versus placebo (primary analysis) and paroxetine (secondary analysis), carried out on patients with panic disorder who were followed up for 12 weeks.

Inclusion criteria: Persons aged over 18 years with:
- a history of panic disorder as defined in the DSM-IV criteria for at least 3 months;
- a CGI-S (Clinical Global Impression Severity) score of ≥ 4;
- 8 panic attacks during the 4 weeks prior to the selection period, and 4 during the selection period.

Treatment:
- EFFEXOR 37.5 mg/day for 1-7 days followed by increase to 75 mg/day between the 8th and 14th day and to 15 mg/day from the 15th day, and increased to 225 mg/day after 21 days in study 399 only.
  Two EFFEXOR groups were randomised in each study:
  - 75 mg/day and 150 mg/day in study 398,
  - 75 mg/day and 225 mg/day in study 399,
- Placebo,
- Paroxetine 10 mg/day for 1-7 days followed by increase to 20 mg/day between the 8th and 14th day and to 30 mg/day between the 15th and 21st days, and increased to 40 mg/day after 22 days.

Primary endpoint: percentage of patients free from panic attack, defined as more than 4 symptoms on the PAAS* scale (Panic And Anticipatory Scale, see annex) after 12 weeks of treatment.

RESULTS: ITT analysis
On inclusion, patient characteristics were similar.

In study 398, 634 patients were evaluated, in 4 groups:
- EFFEXOR 75 mg/day (n=158)
- EFFEXOR 150 mg/day (n=159)
- Placebo, n=156,
- Paroxetine 40 mg/day (n=161)

After 12 weeks of follow-up, the percentages of patients who were free from panic attacks was significantly higher in the treated groups than in the placebo group (p<0.01): 54.1% (85/157) in the EFFEXOR 75 mg/day group, 61.4% (97/158) in the EFFEXOR 150 mg/day group, 60% (96/160) with paroxetine 40 mg/day, and 34.4% (53/154) in the placebo group.
In study 399, 624 patients were evaluated, in 4 groups:
- EFFEXOR 75 mg/day (n=156)
- EFFEXOR 225 mg/day (n=160)
- Placebo, n=157,
- Paroxetine 40 mg/day (n=151)

After 12 weeks of follow-up, the percentages of patients who were free from panic attacks was significantly higher in the treated groups than in the placebo group (p<0.01): 64.1% (100/156) in the EFFEXOR 75 mg/day group, 70% (112/160) in the EFFEXOR 225 mg/day group, 58.9% (89/151) with paroxetine 40 mg/day, and 46.5% (73/157) in the placebo group.

3.2. Adverse effects

Evaluation of the safety of EFFEXOR was based on data:
- from 4 placebo-controlled clinical studies, lasting 10-12 weeks,
- and from one study (354) lasting 24 weeks.

In these five studies, 1259 patients were treated with EFFEXOR, between 75 mg/day and 225 mg/day.

Table 3: The most common adverse events (>10%)

Studies	Treatments	Asthenia	Headache	Insomnia	Excessive sweating	Dry mouth	Gastrointestinal disorders	Ejaculation disorders
391	EFFEXOR Placebo	14% 10%	33% 30%	19% 4%	16% 3%	18% 8%	25%[n] 14%	15% 0%
353	EFFEXOR Placebo	-	27% 26%	16% 6%	-	15% 6%	12%[c] - 21%[n] 4% - 10%	-
398	EFFEXOR 75 EFFEXOR 150 Placebo Paroxetine	-	21% 21% 21% 30%	11% 17% 11% 14%	8% 13% 4% 10%	-	23%[n] 17% 13% 23%	-
399	EFFEXOR 75 EFFEXOR 225 Placebo Paroxetine	18% 25% 10% 24%	33% 32% 34% 23%	18% 20% 14% 17%	4% 10% 2% 6%	-	19%[n] – 10%[c] 20% - 14% 17% - 6% 24% - 6%	5% 11% 0 18%

c=constipation, n=nausea

Study 354:

During the open-label phase, 267/313 patients, (85%) experienced adverse events, with the commonest being: headache (38%), nausea (31%), insomnia (19%), dizziness and dry mouth (18%), drowsiness (13%).

During the double-blind phase, 131/176 patients (74%) experienced adverse events: 71/92 (77%) in the EFFEXOR group versus 60/84 (71%) in the placebo group.
The most frequently observed (>10%) adverse events were:
- headache: 26/92 (28%) in the EFFEXOR group versus 16/84 (19%) in the placebo group.
- diarrhoea: 9/92 (10%) versus 5/84 (6%),
- dizziness: 9/92 (10%) versus 15/84 (18%).

3.3. Conclusions

The efficacy and safety of EFFEXOR were evaluated using five studies (391, 353, 354, 398 and 399) involving patients with panic disorder with or without agoraphobia.

In studies 391 and 353, after 10 weeks of follow-up, no difference was observed between the EFFEXOR and placebo groups in terms of percentage of patients who were free from panic attacks:
- Study 391: 55% with EFFEXOR versus 52.4% with placebo (NS),
- Study 353: 51% with EFFEXOR versus 40.6% with placebo (NS).

In studies 398 and 399, after 12 weeks of follow-up, the percentages of patients who were free from panic attacks was significantly higher in the treated groups than in the placebo group ($p<0.01$):
- Study 398: 54.1% (85/157) with EFFEXOR 75 mg/day, 61.4% (97/158) with EFFEXOR 150 mg/day, 60% (96/160) with paroxetine 40 mg/day, and 34.4% (53/154) with placebo.
- Study 399: 64.1% (100/156) with EFFEXOR 75 mg/day, 70% (112/160) with EFFEXOR 225 mg/day, 58.9% (89/151) with paroxetine 40 mg/day, and 46.5% (73/157) with placebo.

In study 354, after 6 months of follow-up of responders who were included in the double-blind phase, time to relapse was significantly longer in the EFFEXOR group than in the placebo group ($p<0.001$). In the absence of precise data relating to mean time to relapse in the study report, the significance observed in this study must be interpreted with care.
The cumulative relapse percentage was significantly higher in the EFFEXOR group than in the placebo group: 22.5% of patients 20/89 versus 50% of patients (40/80), $p<0.001$.

The most commonly observed adverse events during these studies (>10%) were as follows: headache, dry mouth, insomnia, excessive sweating (particularly at night), gastrointestinal disorders and ejaculation disorders.

There are no available data concerning direct comparison with other antidepressants indicated in the treatment of panic disorder.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Panic disorder is characterised by the occurrence of recurrent and unexpected panic attacks followed by persistent feelings for at least one month of fear that another panic attack will occur, of worry as to the possible implications or consequences of these panic attacks, or significant changes in behaviour relating to the attacks. The natural history of the disorder usually follows a chronic pattern (periodic manifestations interspersed with remission, or continuous symptoms). Fears of a further attack or of the consequences of such an attack are often associated with the development of avoidant behaviour, which can meet the criteria for agoraphobia, and can be socially disabling.

These products are designed to treat the symptoms of panic disorder.

These proprietary products are used in first-line treatment.

The efficacy/adverse effects ratio for these products is high.

Public Health Benefit:
In terms of public health, the burden represented by panic disorder is significant, considering how common they are and how much impact they have on functional and social abilities.
Clinical requirements are covered by existing therapies (in particular other antidepressants and cognitive behavioural therapy). It could be useful to have an additional treatment alternative for the disabling forms of these disorders, but this cannot be said to be a public health priority.
Given the fact that therapeutic alternatives exist, and given the clinical trial data (the efficacy versus placebo is not reproducible, the effect size is similar to that of paroxetine, there are no data concerning the social consequences of these disorders), EFFEXOR SR is not expected to have an impact on morbidity, mortality of quality if life.
In addition, it is not certain that the results of these trials can be transposed into clinical practice, particularly because of the lack of data on the long-term effects of EFFEXOR SR (or even the medium-term effects, in comparison with paroxetine).
Accordingly, in the current state of knowledge and taking into account other therapies available at this time, the proprietary medicine EFFEXOR SR is not expected to benefit public health benefit in this indication.

There are therapeutic alternatives to this product.

The actual benefit provided by these products in this indication is substantial.

4.2. Improvement in actual benefit

In panic disorder with or without agoraphobia, EFFEXOR SR does not provide an improvement in actual benefit (IAB V) in comparison with other medicines available for this indication.

4.3. Therapeutic use [1,2]

Panic disorder is characterised by:

1) the occurrence of recurrent and unexpected panic attacks;
2) anticipatory anxiety for at least one month after panic attacks (fear of a further panic attack, or worries concerning possible consequences of these attacks).

Panic disorder must be treated as early as possible in order to prevent secondary agoraphobia and other consequences (e.g. multiple phobias, depression, suicide attempts).

Objectives:

- prevent attacks from occurring.
- eliminate anticipatory anxiety.
- end avoidant behaviour.

Treatment methods:

Two main types of intervention are recommended:

- psychotherapy;
- drug treatment (antidepressants).

There is no way of knowing in advance which intervention will be more effective for an individual patient.

- Treatment of acute phase (first 12 weeks):

Cognitive behavioural therapy (CBT) is the first choice of psychotherapy. The optimal length of treatment is 12-25 sessions of around 45 minutes each. Shorter courses of CBT can be offered, accompanied by a plan for self-treatment of anxiety.

If pharmacological treatment is required, SSRIs (paroxetine, escitalopram, citalopram) and venlafaxine are first-line treatments. Paroxetine and citalopram are the active substances that have undergone the most testing, both in the short term (8-12 weeks) and in the long term (1 year)[2]. Clomipramine (an imipramine antidepressant) can also be offered.

The choice of drug is dependent on the patient's age, response to previous treatments, the risk of deliberate or accidental overdose, toleration and patient preferences.

Antidepressants can prevent further panic attacks, but have no therapeutic effect on the attacks themselves once they begin.

CBT and medication have overall been shown to have similar levels of efficacy. A combination of drug treatment and CBT is not recommended.

- Long-term treatment

After the 12 weeks, evaluation of the efficacy of the treatment should enable a decision to be made as to whether to continue or alter the treatment regimen. There is no scientific data that suggests an optimal length of treatment.

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[1] "Long-term psychiatric conditions: Severe anxiety disorders" ["Affections psychiatriques de longue durée: Troubles anxieux graves"], HAS long-term condition (ALD) guide, June 2007.

2 "Bon usage des médicaments antidépresseurs dans le traitement des troubles dépressifs et des troubles anxieux de l'adulte" ["Proper use of antidepressants in the treatment of depressive and anxiety disorders in adults"], Afssaps Guidelines and leaflet, October 2006.

4.4. Target Population

The target population for EFFEXOR consists of adult patients with panic disorder.

The size of this population can be estimated on the basis of the following data:
- the percentage prevalence over one year of panic disorder is between 0.5% and 1.2%[3],[4]
- according to INSEE (French national statistics bureau), the number of people in France aged over 18 is around 48 million;
- according to experts, 25% of these patients could be treated with cognitive behavioural therapy alone;
- according to a European study[5], only 23% of patients see a medical professional for panic disorder.

These data thus show that the number of adult patients with panic disorder who could be treated with EFFEXOR is between 42,000 and 100,000.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicinal products approved for use by hospitals and various public services in the extension of indication "panic disorder with or without agoraphobia".

Packaging: appropriate for the prescription conditions for this indication.

Reimbursement rate: 65%

3 Lépine JP *et al*. "Prévalence et comorbidité des troubles psychiatriques dans la population générale française: résultats de l'étude épidemiologique ESEMeD/MHEDEA 2000/ (ESEMeD)" ["Prevalence and cormorbities of psychiatric disorders in the general population in France: results of the ESEMeD/MHEDEA epidemiological study 2000/ (ESEMeD)"], Encéphale 2005; 31: 182-94.
4 DSM-IV - Diagnostic and Statistical Manual of Mental Disorders
5 Alonso *et al*. "Overview of key data from the European study of epidemiology of mental disorders (ESEMeD)" j Clin Psychiatry, 2007;68 (suppl 2).

APPENDIX

ATTACHMENT 11. PANIC AND ANTICIPATORY ANXIETY SCALE (PAAS)

INSTRUCTIONS: Interviewer enters the corresponding number as indicated for each item listed below. Interviewer provides patient with panic and anticipatory anxiety symptom list in order for patient to differentiate the meanings of full-symptom attacks, limited-symptom attacks, situational attacks, unexpected attacks, and anticipatory anxiety.

FULL-SYMPTOM PANIC ATTACKS (4 or MORE SYMPTOMS):

		SITUATIONAL ATTACKS (occur when or just about to go into a situation likely from experience to bring on an attack)		UNEXPECTED ATTACKS (occur with little or no provocation, i.e. when NOT in a situation likely to bring on an attack
1.	Number of attacks.			
2.	Average duration of each attack (in minutes).			
3.	Average intensity of attacks (enter number from 0 = none to 10 = extreme).			

LIMITED-SYMPTOM PANIC ATTACKS (3 or less Symptoms):

		SITUATIONAL ATTACKS (occur when or just about to go into a situation likely from experience to bring on an attack)		UNEXPECTED ATTACKS (occur with little or no provocation, i.e. when NOT in a situation likely to bring on an attack
1.	Number of attacks.			
2.	Average duration of each attack (in minutes).			
3.	Average intensity of attacks (enter number from 0 = none to 10 = extreme).			

ANTICIPATORY ANXIETY:

1.	Percentage of wake time spent with anxiety that occurs in anticipation of facing a phobic situation or of having a panic attack (enter three digit number from 000 through 100 %).	
2.	Average intensity of anticipatory anxiety (enter number from 0 = none to 10 = extreme).	