HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 March 2008

SEROPLEX 5 mg, tablet
Pack of 14 tablets (CIP: 364 289-7)
Pack of 100 tablets (CIP: 563 706-7)

SEROPLEX 10 mg scored film-coated tablet
Pack of 28 tablets (CIP: 359 937-4)
Pack of 100 tablets (CIP: 563 707-3)

SEROPLEX 20 mg scored film-coated tablet
Pack of 28 tablets (CIP: 359 941-1)
Pack of 100 tablets (CIP: 563 710-4)

Applicant: LUNDBECK SAS

Escitalopram

List I

ATC Code: N06AB10

Date of Marketing Authorisation (MA) and its variations:
21 August 2002: 5-mg, 10-mg and 20-mg tablets
3 June 2004: extension of indication “treatment of social anxiety disorder (social phobia)”
21 November 2005: extension of indication “treatment of generalised anxiety disorder”
13 July 2007: extension of indication “treatment of obsessive-compulsive disorder”

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication “treatment of social anxiety (social phobia) disorder”.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Escitalopram

1.2. Indications

"Treatment of major depressive episodes (i.e. characteristic symptoms),
Treatment of panic disorder with or without agoraphobia,
Treatment of generalised anxiety disorder
Treatment of obsessive-compulsive disorder

Treatment of "social anxiety" disorder (social phobia)"

1.3. Dosage

"The safety of dosages greater than 20 mg per day has not been demonstrated. SEROPLEX® is administered once daily during or between meals.

Social anxiety disorder (social phobia): The usual dosage is 10 mg per day. Two to 4 weeks are generally necessary to obtain relief from symptoms. Subsequently, depending on individual therapeutic response, the dose may be reduced to 5 mg per day or increased to a maximum of 20 mg per day.
Social anxiety disorder is a disease with a chronic course and treatment for 12 weeks is recommended to consolidate the therapeutic response. Long-term treatment of responders has been studied for 6 months and can be considered on an individual basis to prevent relapse; treatment benefits should be re-evaluated at regular intervals.
"Social anxiety disorder" is a well-defined diagnostic terminology of a specific disorder, which should not be confounded with excessive shyness. Pharmacotherapy is only indicated if the disorder interferes significantly with professional and social activities. The relative role of this treatment compared to cognitive behavioural therapy has not been assessed. Pharmacotherapy is part of an overall therapeutic strategy.

Persons aged over 65 years: The efficacy of escitalopram in social anxiety disorder has not been studied in elderly subjects.

Children and adolescents (< 18 years): Escitalopram should not be used in the treatment of children and adolescents under the age of 18 years.

Reduced renal function: No dose adjustment is required in patients with mild to moderate renal impairment. Caution is advised in patients with severely reduced renal function (Cl_{CR} less than 30 ml/min).

Reduced hepatic function: An initial dose of 5 mg daily for the first two weeks of treatment is recommended in patients with mild or moderate hepatic impairment. Depending on individual patient response, the dose may be increased to 10 mg per day. Caution and extra vigilant dose titration is advised in patients with severely reduced hepatic function.

Poor metabolisers of CYP2C19: In patients who are known to be poor metabolisers of the isoenzyme CYP2C19, an initial dose of 5 mg daily during the first two weeks of treatment is

recommended. Depending on individual patient response, the dose may be increased to 10 mg per day.

Discontinuation symptoms seen when stopping treatment: Abrupt discontinuation should be avoided. When stopping escitalopram treatment, the dose should be gradually reduced over a period of at least one to two weeks in order to limit the risk of discontinuation reactions. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, resuming the previously prescribed dose may be considered. Subsequently, the doctor may continue decreasing the dose, but at a more gradual rate."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

N : Nervous system
N06 : Psychoanaleptics
N06A : Antidepressants
N06AB : Selective serotonin reuptake inhibitors (SSRI)
N06AB10 : Escitalopram

2.2. Medicines in the same therapeutic category

Other selective serotonin reuptake inhibitor indicated in the treatment of "social anxiety" disorder (social phobia): Paroxetine: DEROXAT 20 mg tablet, DEROXAT 20 mg/ml oral solution and its generics and DIVARIUS 20 mg tab; MA indication: "Characterised social anxiety disorder (social phobias) when it significantly disturbs professional and social activities."

2.3. Medicines with a similar therapeutic aim

Venlafaxine: EFFEXOR XR 37.5 mg, EFFEXOR XR 75mg

3. ANALYSIS OF AVAILABLE DATA

3.1. Treatment of "social anxiety" disorder (social phobia)

The applicant submitted the results of the 3 pivotal clinical studies of the MA:

- One 24-week phase III study v*ersus* placebo evaluated the efficacy and safety of escitalopram in patients with social anxiety disorder (SAD) (study 99270);
- One 12-week phase III, placebo-controlled, flexible-dose study evaluated the efficacy and safety of escitalopram in patients with SAD (study 99012);
- One 24-week phase III study v*ersus* placebo evaluated the efficacy of escitalopram in the prevention of relapse in patients with SAD and responders to escitalopram treatment (study 99269);

3.2. Comparative studies *versus* placebo 99270, 99012, and 99269

Objective, primary efficacy endpoint and exclusion criterion of studies 99270 and 99012: To assess the efficacy of escitalopram *versus* placebo and safety in patients with SAD.

The primary efficacy endpoint was the change in the total LSAS[1] score (*Leibowitz Social Anxiety Scale)* between inclusion and week 12.

Patients with major depressive disorder (maximum score of 18 on the MADRS *Montgomery and Asberg Depression Rating Scale*), or of any other DSM IV axis 1 or other mental disorders were excluded from these studies.

Study 99270

Type of Study: randomised, double-blind, placebo-controlled study with a paroxetine comparator arm. The total duration of follow-up was 24 weeks. This trial was not designed for a direct comparison between the escitalopram and paroxetine groups, but only for a comparison of each treatment group (ESC5, 10 or 20 mg/day) with placebo

Secondary endpoint: Change in LSAS total score between baseline and week 24 of treatment.

Inclusion criteria:

- outpatients ≥ 18 years and ≤ 65 years
- patients with SAD (according to DSM-IV criteria),
- patients with a LSAS score ≥ 70 and exhibiting fear or avoidance traits in at least four social situations including at least 2 related to relational problems,
- patients with a SDS score (*Sheehan Disability Scale*) ≥ 5 (score investigating work, social life, family life).

[1] Liebowitz MR. *Social Phobia. Mod Probl Pharmacopsychiatry* 1987;22:141-173. Definition: the objective of the questionnaire is to evaluate the variety of social interaction and performance situations that individuals with social phobia may fear and/or avoid. It is also a measuring instrument used to evaluate the effectiveness of treatments in this disorder. The questionnaire includes 24 items. Each item is composed of a given situation in which the level of anxiety (0-3 = none, minor, moderate, serious) and degree of avoidance (0 - 3 = never, from time to time, often, usually) are quantified.
Scale from 0 to 72. 72 is the most severe score; the score is calculated from the patient's social anxiety and avoidance evaluated during an interview.

Concerning the inclusion criteria, it may be remarked that a relatively low threshold was chosen for the SDS score.

Efficacy results:
The analysis of the data for the primary endpoint showed that escitalopram at dosages of 5 mg/day and 20 mg/day had a significantly higher efficacy than placebo at 12 weeks: the change in the LSAS score was -29.48 for the placebo arm *versus* -38.66 in the escitalopram 5 mg/day group and -39.79 in the escitalopram 20 mg/day group (table 1).

Table 1: Results of study 99270

Endpoint	**Placebo (N=165)**	**Escitalopram 5 mg/day (N=166)**	**Escitalopram 10 mg/day (N=164)**	**Escitalopram 20 mg/day (N=163)**	***Paroxetine 20 mg/day (N=167)***
Baseline LSAS scores mean/standard deviation	96/14.46	94.30/16.30	92.38/14.93	93.98/13.99	*94.14/14.91*
Adjusted mean Δ_{12} LSAS (at week 12)[¥]	-29.48	-38.66 p=0.001	-34.55 p=0.059	-39.79 p<0.001	*-39.31*
Adjusted mean Δ_{24} LSAS (at week 24)[¥]	-34.04	-44.51	-41.50	-49.13	*-45.87*

[¥]LOCF: *Last Observation Carried Forward*

Safety results

No serious treatment-related adverse event was observed. The most frequently reported treatment-related adverse events were as follows:
- placebo: headaches, nausea and rhinitis
- paroxetine: nausea, dizziness, fatigue
- escitalopram: nausea, headaches, insomnia, dizziness, rhinitis

These adverse events concerned 121 (72.5%) patients in the escitalopram 5 mg/day arm, 126 (75.5%) patients in the escitalopram 10 mg/day arm and 140 (82.4%) patients in the escitalopram 20 mg/day arm. They affected 101 (61 %) patients in the placebo arm and 140 (82.9%) patients in the paroxetine arm.
Seven adverse reactions (nausea, fatigue, dizziness, depression, drowsiness, anxiety, hyperhidrosis) caused discontinuation of treatment in more than 2 patients whatever the treatment group (escitalopram, paroxetine, placebo).

Study 99012

Type of Study: Randomised, double-blind, placebo-controlled study. The total length of follow-up was 12 weeks.
The starting dose was 10 mg/day and the daily dosage could be increased to 20 mg/day in patients not presenting a satisfactory therapeutic response during visits at 4, 6 or 8 weeks if there were no adverse reactions.

Inclusion criteria:
- outpatients ≥ 18 years and ≤ 65 years
- patients with social anxiety disorder (according to DSM-IV criteria),
- patients with a LSAS score ≥ 70 and exhibiting fear or avoidance traits in at least four social situations with at least 2 concerning relational problems.

Efficacy results: The analysis of the data for the primary efficacy endpoint i.e. the change in the LSAS score, showed the superiority of for flexible doses of 10-20mg (- 34.45) *versus* placebo (- 27.16) after 12 weeks of treatment (table 2).

Table 2: Results of study 99012

Endpoint	Placebo (N =176)	Escitalopram 10-20 mg/day (N=177)
Baseline LSAS scores mean/standard deviation	95.44/16.35	96.32/17.35
Δ_{12} LSAS (at 12 weeks) [¥]	-27.16	-34.45
Difference between adjusted mean Δ LSAS of the 2 groups	-7.29 p=0.005	

[¥]LOCF: *Last Observation Carried Forward*

Safety results

No death was observed during the trial.
The most common adverse reactions in the escitalopram arm were headaches, nausea, and fatigue. The adverse reactions most frequently causing treatment discontinuation were headaches and diarrhoea in the escitalopram arm and headache in the placebo arm. These adverse reactions concerned 103 (58.2%) patients in the placebo arm and 136 (75.1%) patients in the escitalopram arm.

Study 99269

Objective: evaluate the effect of escitalopram on the prevention of relapses of SAD, in patients responding to treatment with escitalopram. The secondary objective was to evaluate the safety of escitalopram.

Type of Study: randomised, double-blind, placebo-controlled, flexible dose study. The starting dose was 10 mg/day and the investigators could increase this to 20 mg/day during visits at weeks 2, 4 or 8. Patients responding to treatment at 12 weeks (CGI-I[2] *scale* =1 or 2) were randomly assigned to one of the escitalopram arms or to the placebo group.

Primary efficacy endpoint: time to relapse of SAD during the double-blind treatment period. Relapse was defined as an increase from baseline in LSAS total score of at least 10 points, or loss of efficacy, as judged by the investigator.

Inclusion criteria:

- Outpatients ≥ 18 years and ≤ 80 years
- Patients with social anxiety disorder (according to DSM-IV criteria)
- Patients with a LSAS score ≥ 70 and exhibiting fear or avoidance traits in at least four social situations with at least 2 related to relational problems
- Patients with an SDS score ≥ 5.

Exclusion criteria:

- Patients with major depressive disorder (maximum score of 18 on MADRS[3])

[2] *Clinical Global Impression - Improvement.* Score=1 (improved)- Score=2 (very improved)

[3] *Montgomery and Asberg Depression Rating Scale 8-item rating scale scored from 0 to 6*

Efficacy results:
The patients included in the double-blind phase *versus* placebo had previously received escitalopram treatment open-label. Patients not responding during this open-label period were excluded from the study so all patients included in the double-blind phase were responders to escitalopram at 12 weeks. The results are shown in tables 3 and 4.

Table 3: Characteristics of the groups at baseline (study 99269)

	At start of the open-label period	**At start of randomization**	
	Escitalopram 10-20mg/day (N=517)	Escitalopram 10-20mg/day (N=190)	Placebo (N =181)
LSAS	94.8 (moderate)	44.3 (low)	43.2

*LOCF: *Last Observation Carried Forward*

Table 4: Relapses on the LSAS score between week 12 and the last visit at week 24 during the double-blind phase (study 99269)

	Placebo (N =181)	**Escitalopram 10-20 mg/day (N=190)**	
Number of relapses (proportion) (LOCF)	91 (50.3%)	42 (22.1%)	p<0.001
Mean time to relapse (LOCF)	103.5 days	135.3 days	p<0.001 (log rank test)

The results showed a superiority of escitalopram compared to placebo on the time to relapse of SAD.

Safety results
One death was observed during the trial, but it was considered to be unrelated to treatment. The most frequent treatment-related adverse events in the escitalopram arm were headaches, flu-like symptoms, fatigue. During the double-blind period, 130 (71.4%) adverse reactions were observed in the placebo arm versus 119 (62.6%) in the escitalopram arm.

3.3. Conclusion

The efficacy of escitalopram was evaluated during three randomised placebo-controlled studies.
The first study compared dosages of 5, 10 and 20 mg/day of escitalopram to a placebo and also included a paroxetine arm (20 mg/day). The study was not designed to directly compare the escitalopram and paroxetine groups. Escitalopram at dosages of 5 and 20 mg/day was found to have a statistically significant effect on the LSAS score at 12 weeks of treatment. The change in the score was -29.48 for the placebo arm *versus* -38.66 in the escitalopram 5 mg/day group and -39.79 in the escitalopram 20 mg/day group. The difference was not significant for the escitalopram 10 mg/day group.
In the second study, escitalopram at a flexible dosage from 10 to 20 mg/day, was superior (change in LSAS score: -34.45) to placebo (change: -27.16) at 12 weeks of treatment on the LSAS score after 12 weeks of treatment.

In the third study, the maintenance of the efficacy of escitalopram (10 to 20 mg/day) over 6 months was demonstrated *versus* placebo in initially responding patients. The percentage of relapses was 22.1% in the escitalopram group *versus* 50.3% in the placebo group. The time to relapse was significantly longer in the escitalopram group (135.3 days) than in the placebo group (103.5 days).
No serious treatment-related adverse event was observed during these studies. The Transparency Committee regrets the absence of a direct comparison with paroxetine and notes a high incidence of possibly treatment-related adverse events.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Social phobia[4] is a marked and persistent fear of social or performance situations in which a feeling of anxiety may occur.
Social phobia often has a continuous course. It frequently lasts throughout life although the disorder may become less severe or disappear during adulthood.

These proprietary medicinal products provide symptomatic treatment of social anxiety disorder.

The efficacy/safety ratio of these products at 12 weeks is moderate.

Paroxetine is a pharmacological alternative to these products. The therapeutic use of these pharmacotherapies in social anxiety disorder, in particular with respect to psychotherapy, remains to be evaluated.

Public health benefit: The public health burden of social phobia is high, taking into account the incidence of this disorder and its repercussions.

The therapeutic need is covered by existing therapies (other antidepressants and behavioural and cognitive therapy in particular). Although alternative drugs may be useful for disabling forms of this condition, this cannot be considered to be a public health priority.

Based on clinical trial data (only *versus* placebo) and taking into account the existence of these other therapies, the proprietary medicine SEROPLEX is not expected to impact morbidity and mortality or quality of life.

Extrapolation of clinical trial data to clinical practise is unsure because of the difficulty in detecting this disorder (in particular in general medicine) and because adherence to treatment is probably lower under real-life conditions than during a trial.

Consequently, given our current knowledge and taking into account other therapies available at this time, the proprietary drug SEROPLEX is not expected to have a public health benefit in this indication.

[4] DSM-IV: Diagnostic and Statistical Manual of Mental Disorders.

The Actual Benefit of these proprietary drugs in this indication is moderate.

4.2. Improvement in actual benefit

In the indication "Social anxiety disorder (Social phobia)", SEROPLEX does not improve actual benefit (IAB level V) compared to the other available medicinal products.

4.3. Therapeutic use

The diagnosis of social phobia is only justified if the avoidance, fear or anxious anticipation of the performance or social condition significantly interferes with an individual's way of life, professional activities or social life or if the subject experiences marked suffering because of the phobia[3].

Recommended first-line treatment in social phobia is either cognitive-behavioural therapy (CBT) or antidepressants. The action of antidepressants with an MA in social phobia is more rapid than CBT, because of their ease of use and the low incidence of adverse reactions[5].
As social phobia and the other psychiatric disorders that are often associated with it have a chronic course and because of the fluctuations in disease severity according to the demands of life, individually-tailored patient management is required to determine therapeutic strategy. Whatever strategy is implemented (pharmacological and/or psychological) its benefit must be reassessed during treatment.

4.4. Target Population

The target population of SEROPLEX is difficult to estimate as insufficient data are available about:
- the number of persons requiring pharmacotherapy for anxiety and,
- the overlap between populations in the five indications.

The reported prevalence may vary according to the threshold used to determine symptoms or discomfort and according to the number of social conditions that are specifically reviewed.

According to the DGS National Technical Group for Defining Public Health Goals[6], the lifetime prevalence of social phobia in France is between 0.5% and 4%. According to AFSSAPS recommendations, social phobia, or SAD has a prevalence over a one-year period of 1.7% in France[4].
According to the SPC (section 4.2), the efficacy of SEROPLEX in SAD has not been studied in the elderly.
According to INSEE, the French general population concerned by the indication (adult population aged under 65 years) was 37,516,736 on 1 January 2008.
These data suggest that the population of patients presenting a social anxiety disorder is between 190,000 and 1,500,000 patients in France.

Forty to 50% of these patients might have a comorbid disease such as major depressive episode, generalised anxiety or chronic alcoholism (not counted in the indication of escitalopram).

Between 95,000 and 750,000 patients therefore have SAD alone. The proportion of patients presenting severe disturbances in their professional or social activities because of this

[5] Antidepressant medications in the treatment of depressive disorders and anxiety disorders in adults, Afssaps Guideline 2006
[6] Chronic delirious psychoses, bipolar disorders, depressive disorders, neurotic and anxiety disorders - DGS/GTNDO Report of 10.03 2003

disorder may be estimated to be approximately 25%. Consequently, the target population is between 24,000 and 190,000.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication “Social anxiety disorder (Social phobia)”.

The Transparency Committee draws the Economic Committee for Health Products’ (CEPS) attention to the fact that the dossier for this extension of indication (MA 2004) was only submitted in 2007.

The Transparency Committee requests to perform a follow-up study of SEROPLEX under real-life conditions of use in social anxiety disorder (or social phobia). This must describe in particular:

- The characteristics of treated patients (sex, age, severity, comorbidity, prior therapies including behavioural and cognitive therapies etc.),
- The characteristics of prescribers (general practitioners, hospital or private specialists),
- Treatment procedures (dosages, duration of treatment, concomitant therapies: Pharmacotherapies, behavioural and cognitive therapies etc.),
- Frequency of treatment discontinuation and reasons for discontinuation,
- Clinical course of patients during treatment.

The duration of the study must be justified by an independent scientific committee.

4.5.1 Packaging

These are not appropriate for the prescription conditions.
The Committee points out that in its deliberation of 20 July 2005 it recommended a harmonisation of the package size to 30 days for treatments lasting for one month, and consequently a 90-day pack for treatments lasting three months.

Reimbursement rate 65 %.

HAUTE AUTORITÉ DE SANTÉ

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SEROPLEX 10 mg, film-coated tablet
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Pack of 100 tablets (CIP: 563 707-3)

SEROPLEX 20 mg, film-coated tablet
Pack of 28 tablets (CIP: 359 941-1)
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Applicant: Lundbeck SAS

Escitalopram

List I
ATC Code: N06AB10

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21 November 2005: extension of indication “treatment of generalised anxiety disorder”
13 July 2007: extension of indication “treatment of obsessive-compulsive disorder”

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication “treatment of generalised anxiety disorder”.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient

Escitalopram

1.2 Indications

"Treatment of major depressive episodes (i.e. characteristic symptoms),
Treatment of panic disorder with or without agoraphobia,
Treatment of "social anxiety" disorder (social phobia)
Treatment of obsessive-compulsive disorder

Treatment of generalised anxiety disorder."

1.3 Dosage

"The safety of dosages greater than 20 mg per day has not been demonstrated. Escitalopram is administered once daily during or between meals.

Generalised anxiety: the starting dose is 10 mg once daily. Depending on individual therapeutic response, the dose may be increased to a maximum of 20 mg per day. Long-term treatment of responders at the dosage of 20 mg per day was studied for at least 6 months. The benefit of treatment and the dosage must be reassessed at regular intervals.

Persons aged over 65 years: a starting dose corresponding to half the usually recommended dosage and a lower maximum dosage must be considered.

Children and adolescents (< 18 years): Escitalopram is not recommended in children and adolescents under the age of 18 years.

Reduced renal function: No dose adjustment is required in patients with mild to moderate renal impairment. Caution is advised in patients with severely reduced renal function (Cl_{CR} less than 30 ml/min).

Reduced hepatic function: An initial dose of 5 mg daily for the first two weeks of treatment is recommended in patients with mild or moderate hepatic impairment. Depending on individual patient response, the dose may be increased to 10 mg per day. Caution and extra vigilant dose titration is advised in patients with severely reduced hepatic function.

Poor metabolisers of CYP2C19: For patients who are known to be poor metabolisers with respect to the isoenzyme CYP2C19, an initial dose of 5 mg daily during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg per day.

Discontinuation symptoms seen when stopping treatment: Abrupt discontinuation should be avoided. When stopping escitalopram treatment, the dose should be gradually reduced over a period of at least one to two weeks in order to limit the risk of discontinuation reactions. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, resuming the previously prescribed dose may be considered. Subsequently, the doctor may continue decreasing the dose, but at a more gradual rate."

2. SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification

N	: Nervous system
N06	: Psychoanaleptics
N06A	: Antidepressants
N06AB	: Selective serotonin reuptake inhibitors (SSRI)
N06AB10	: Escitalopram

2.2 Medicines in the same therapeutic category

Other selective serotonin reuptake inhibitor indicated in generalised anxiety:

- Paroxetine: DEROXAT 20 mg tablet, DEROXAT 20 mg/mL oral solution and its generics; MA indication: “Generalised Anxiety, occurring for at least 6 months”.
  DIVARIUS 20 mg, tablet.

2.3 Medicines with a similar therapeutic aim

Buspirone**:** BUSPAR 10 mg tab, and its generics
Venlafaxine: EFFEXOR XR 37.5 mg, EFFEXOR XR 75mg

3. ANALYSIS OF AVAILABLE DATA

The applicant submitted 6 clinical studies evaluated by EMEA:

- 3 placebo-controlled studies evaluated the efficacy and safety of escitalopram in patients with generalised anxiety disorder (studies SCT-MD-05, SCT-MD-06, SCT-MD-07);
- 1 placebo-controlled study evaluated the efficacy of escitalopram in the prevention of relapses in patients with generalised anxiety disorder (study 99769);
- 1 study versus paroxetine evaluated the efficacy of escitalopram in patients with generalised anxiety disorder (study SCT-MD-20);
- 1 escitalopram dose-finding study (5, 10 or 20 mg/day) *versus* placebo, not described here (study 99815);
- Studies SCT-MD-05, -06, and -07 had a common 24-week, open-label extension phase, the SCT-MD-17 study. The results of this study will not be described here.

3.1 Comparative studies versus placebo SCT-MD-05, -06, and -07.

These 3 studies had the same objective and design. They are described in table 1 below:
Table 1: Comparative studies of escitalopram *versus* placebo

	Objective	**Design**	**Study sample size**	**Primary efficacy endpoint**
Study SCT-MD-05	Evaluation of the efficacy and safety of escitalopram versus placebo in patients with generalised anxiety disorder.	Randomised, double-blind, placebo-controlled studies. Length of studies: 8 weeks	N = 254 Escitalopram 10 mg/day or 20 mg/day N = 126 Placebo N = 128 ITT Population = 252	Change in Hamilton anxiety scale[7] total score between baseline and study end.
Study SCT-MD-06			N = 287 Escitalopram 10 mg/day or 20 mg/day N = 145 Placebo N = 142 ITT Population = 281	
Study SCT-MD-07			N = 315 Escitalopram 10 mg/day or 20 mg/day N = 158 Placebo N = 157 ITT Population = 307	

Inclusion criteria common to the 3 studies: Included patients had to have generalised anxiety disorder according to the DSM-IV criteria with a Hamilton anxiety score ≥ 18, a Hamilton

[7] Hamilton anxiety Scale: 14-item scale, total score of between 0 and 56. 56 is the most severe. Each item is scored from 0 to 4. 0 no symptoms, 4 severe symptoms.
Hamilton depression scale: 17-item scale in which 52 is the most severe score. According to Beck, score < 7 = no depression; from 8 to 15: minor depression; score ≥ 16 = major depression

depression score ≤ 17, and a Covi anxiety scale score[8] greater than the Raskin[9] depression scale score[9].

Efficacy results:

Table 2: results of studies SCT-MD-05, -06, -07 (ITT population)

	Placebo			Escitalopram		
	SCT-MD-05	**SCT-MD-06**	**SCT-MD-07**	**SCT-MD-05**	**SCT-MD-06**	**SCT-MD-07**
Mean baseline Hamilton score	22.1 ± 0.3	22.6 ± 0.3	23.2 ± 0.3	22.8 ± 0.3	22.6 ± 0.3	23.6 ± 0.4
Change at end of study	-7.7 ± 0.6	-7.6 ± 0.5	-7.4 ± 0.6	-9.6 ± 0.6*	-9.2 ± 0.5*	-11,3 ± 0.6**

* p < 0.05 versus placebo
** p < 0.01 versus placebo

There was a significantly greater reduction in the Hamilton score in patients treated by escitalopram than in placebo-treated patients in the 3 studies. Co-morbid depression does not seem to have been completely ruled out. The Transparency Committee remarked that a HAM-A inclusion score ≥ 18 constitutes a relatively low threshold.

Safety results:
51 patients stopped treatment during the study because of an adverse event: 36 patients in the escitalopram groups versus 15 patients in the placebo groups.
The most common adverse reactions (incidence ≥ 10 %) were: headache, ejaculation disorder, nausea, insomnia, fatigue, drowsiness, oral dryness.

3.2 Study 99769

This was a randomised double-blind study *versus* placebo, with the objective of evaluating the efficacy of escitalopram in the prevention of relapses in patients with generalised anxiety disorder.
The patients had been previously treated by escitalopram open-label at 10 mg/day for the first week and then 20 mg/day during the following weeks, for 12 weeks. Patients were then randomly assigned to receive escitalopram or placebo in a double-blind manner and followed between 26 and 78 weeks.

Inclusion criteria: Included patients had to have generalised anxiety disorder according to DSM-IV criteria with a baseline HAM-A score ≥ 20 and the HAM-A score had to be ≤ 10 at the end of the open-label period.
Primary endpoint: Time to relapse. Relapse was defined by a HAM-A score ≥ 15 or loss of efficacy as judged by the investigator.
Efficacy results: The study included 491 patients in the open-label phase and 375 of them were included in the double-blind phase (escitalopram group n = 187, placebo group n = 188).
The time to relapse of patients treated by escitalopram (239.4 days) was significantly longer than in patients treated by placebo (223 days) (log-rank test p < 0.001). The relapse rate of patients treated by escitalopram was significantly lower than for patients treated by placebo: 19 % *versus* 56 % (p < 0.001).
The patients included in the double-blind phase *versus* placebo had previously received escitalopram treatment open-label. Patients not responding during this open-label period were excluded from the study so all patients included in the double-blind phase were responders to escitalopram.

8 COVI anxiety scale: the severity of the anxiety is assessed from the patient's verbal response, behaviour and somatic symptoms. Each of these criteria is scored from 0 to 4. 12 is the most severe score.
9 Raskin depression scale: the severity of the depression is assessed from the patient's verbal response, behaviour and secondary depression symptoms. Each of these criteria is scored from 0 to 4.

The Transparency Committee regrets the absence of a direct comparison with paroxetine.

Safety results:
132 patients (70.6%) in the escitalopram group had a possibly treatment-related adverse event *versus* 107 patients (56.9%) in the placebo group.
During the double-blind period; the incidence of rhinitis (17% versus 6%) and weight gain (6% *versus* 1%) was higher in escitalopram-treated patients than in placebo-treated patients ($p < 0.05$).

3.3 Study SCT-MD-20

This was a randomised double-blind study versus paroxetine with the objective of comparing the efficacy of escitalopram and paroxetine in patients with generalised anxiety disorder during 24 weeks of treatment.
Inclusion criteria: included patients had generalised anxiety disorder according to DSM-IV criteria.
The dosage of escitalopram was 10 mg/day during the first 4 weeks of treatment and it could then be increased to 20 mg/day according to the patients' clinical response.
The dosage of paroxetine was 20 mg/day during the first 2 weeks of treatment and it could then be increased by 10 mg/day every 2 weeks up to a maximum of 50 mg/day.
Primary endpoint: Total score change in Hamilton anxiety scale between baseline and study end at 24 weeks.
Efficacy results: the study included 123 patients and the ITT population was 121 patients:

- escitalopram group: n = 60;
- paroxetine group: n = 61;

Table 3: results of study SCT-MD-20 (ITT population)

	Escitalopram	**Paroxetine**
Mean baseline HAM-A score	23.7 ± 0.46	23.4 ± 0.44
Mean final HAM-A score	8.3 ± 0.87	10.1 ± 0.94
Change at study end	- 15.3 ± 0.80	-13.3 ± 1,02
95 % CI	1.90 [-0.54; 4.35] p = 0.125	

The observed difference in the change in HAM-A score between the escitalopram-treated patients and paroxetine-treated patients was not significant.
Safety results:
During the study, 51 patients stopped their treatment, i.e. 41.5% of patients. In the paroxetine group, 29 patients stopped their treatment (46.8%) *versus* 22 patients in the escitalopram group (36.1 %). The main cause of treatment discontinuation was the occurrence of adverse events: 14 in the paroxetine group (22.6 %) *versus* 4 in the escitalopram group (6.6 %) ($p < 0.05$).
Adverse events with an incidence higher than 10% which were 2 times more frequent in the escitalopram group than in the paroxetine group were diarrhoea (21.3% *versus* 8.1%) and upper airway infections (14.8% *versus* 4.8%).
Adverse events with incidences greater than 10% which were 2 times more frequent in the paroxetine group than in the escitalopram group were ejaculation disorders in men (30% *versus* 14.8%), anorgasmia in women (26.2% *versus* 5.9%), loss of libido (22.6% *versus* 4.9%), constipation (14.5% *versus* 1.6%), increased sweating (11.3% *versus* 3.3%) and self-inflicted injury (11.3% *versus* 4.9 %).

3.4 Conclusions of the studies

Studies SCT-MD-05, -06 and -07 showed the efficacy of escitalopram 10 mg/day or 20 mg/day on the change in the Hamilton anxiety score *versus* a placebo treatment in patients with generalised anxiety disorder as defined by DSM-IV criteria. The change in HAM-A score after 8 weeks of treatment was between -9.2 and -11.3 *versus* -7.4 and -7.7 in the placebo group.

Study 99769 showed that the efficacy of escitalopram was maintained in patients initially responding to this treatment: the time to relapse was significantly longer in these patients than in placebo-treated patients who also initially responded to escitalopram. The relapse rate for patients treated by escitalopram was significantly lower than for patients treated by placebo: 19 % *versus* 56 %. The Transparency Committee regrets the absence of a direct comparison with paroxetine in order to evaluate the efficacy of escitalopram *versus* an active comparator in the prevention of relapse in patients with generalised anxiety disorder.

Study SCT-MD-20 compared the efficacy of escitalopram and paroxetine on the change in HAM-A score in subjects with generalised anxiety disorders: after 24 weeks of treatment, the change in the HAM-A score was the same in the 2 treatment groups: -15.3 in the paroxetine group *versus* -13.3 in the paroxetine group (95% CI: 1.90 [-0.54; 4.35] p = 0.125).

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit

Generalised anxiety is characterised by a progression to disability and/or a deterioration in quality of life.

The efficacy/safety ratio is high.
This medicinal product is used for symptomatic treatment.

There are alternative pharmacological and non-pharmacological therapies.

Public health benefit: the public health burden represented by generalised anxiety is high taking into account the incidence of this disorder and its repercussions.

The therapeutic need is covered by existing therapies (other antidepressants and behavioural and cognitive therapy in particular). Although additional therapies for disabling forms of generalised anxiety disorder are useful, they cannot be considered as a public health priority.

Based on clinical data, and taking into account the existence of these other therapies (paroxetine in particular), the proprietary medicine SEROPLEX is not expected to impact morbidity and mortality or quality of life.

It may be difficult to extrapolate the trial data to clinical practice because of the difficulty in detecting the disorder (in particular in general medicine) and because adherence to treatment is lower under real-life conditions than during a clinical trial.

Consequently, given our current knowledge and taking into account other therapies available at this time, the proprietary drug SEROPLEX is not expected to have a public health benefit in this indication.

The actual benefit of these proprietary drugs in this indication is substantial.

4.2 Improvement in actual benefit

In the indication "Generalised Anxiety Disorder", SEROPLEX does not improve actual benefit (IAB level V) with respect to other available medicinal products.

4.3 Therapeutic use[10,11,12]

Different treatments have been shown to be effective in most anxiety disorders: psychotherapy, in particular cognitive and behavioural psychotherapy, antidepressants and the combination of these two treatment modalities.

Patient information and education, in particular about dietary and lifestyle changes (no alcohol, reduction in coffee consumption and smoking, regular physical exercise) are considered as first-line treatment (professional agreement).
Antidepressants have a preferential action on the mental symptoms of anxiety.
Escitalopram is an alternative pharmacological therapy to other medicinal products with an MA in the treatment of generalised anxiety disorders: paroxetine, buspirone and venlafaxine.
The time to action onset of antidepressants is from 1 to 3 weeks. The complete response is obtained after several weeks of treatment. The duration of treatment must be at least 6 months (expert consensus).

4.4 Target Population

The target population of SEROPLEX is difficult to estimate as there are insufficient data on:
- the number of persons requiring pharmacotherapy for anxiety.
- the overlap between populations in the five indications.

According to the AFSSAPS 2006 guidelines[10], in Western countries, the estimated annual prevalence rate of generalised anxiety disorder is 4% in the general population (3% in men and 6% in women).
According to INSEE, the French general population concerned by the indication was 46,656 525, on 1 January 2008.
Hence, the target population of SEROPLEX in the indication "generalised anxiety disorder" is approximately 1,900,000.

[10] French clinical practice guidelines. Management of an isolated depressive episode in adult outpatients. ANAES May 2002.
[11] Diagnosis and management of adult outpatients with generalised anxiety disorder. ANAES 2001
[12] Benefit-risk management of antidepressant medications in the treatment of depression and anxiety disorders in the Adult. Afssaps. recommendations October 2006.

4.5 Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication “Generalised anxiety disorder”.

The Transparency Committee draws the Economic Committee for Health Products’ attention to fact that the dossier for this extension of indication (MA 2005) was only submitted in 2007.

The Transparency Committee requests to perform a follow-up study of SEROPLEX under real-life conditions of use in generalized anxiety. This must describe in particular:

- The characteristics of treated patients (sex, age, severity, comorbidity, prior therapies including behavioural and cognitive therapies etc.),
- The characteristics of prescribers (general practitioners, hospital or private specialists),
- Treatment procedures (dosages, duration of treatment, concomitant therapy: pharmacotherapies, behavioural and cognitive therapies etc.),
- Frequency of treatment discontinuation and reasons for discontinuation,
- Clinical course in treated patients.

The study duration must be justified by an independent scientific committee.

4.5.1 Packaging:

These are not appropriate for the prescription conditions.
The Committee points out that in its deliberation of 20 July 2005, it recommended for treatments lasting for one month, a harmonisation of the package size to 30 days and consequently 90-day packs for treatments lasting three months.

4.5.2 Reimbursement rate

65 %.

HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

OPINION

19 march 2008

SEROPLEX 5 mg, tablet
Pack of 14 tablets (CIP: 364 289-7)
Pack of 100 tablets (CIP: 563 706-7)

SEROPLEX 10 mg, film-coated tablet
Pack of 28 tablets (CIP: 359 937-4)
Pack of 100 tablets (CIP: 563 707-3)

SEROPLEX 20 mg, film-coated tablet
Pack of 28 tablets (CIP: 359 941-1)
Pack of 100 tablets (CIP: 563 710-4)

Applicant: Lundbeck SAS

Escitalopram

List I
ATC Code: N06AB10

Date of Marketing Authorisation (MA) and its variations:
21 August 2002: 5-mg, 10-mg and 20-mg tablets
3 June 2004: extension of indication “treatment of social anxiety disorder (social phobia)”
21 November 2005: extension of indication “treatment of generalised anxiety disorder”
13 July 2007: extension of indication “treatment of obsessive-compulsive disorder”

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication “treatment of obsessive-compulsive disorder”:

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient

Escitalopram

1.2 Indications

“Treatment of major depressive episodes (i.e. characteristic symptoms),
Treatment of panic disorder with or without agoraphobia,
Treatment of “social anxiety” disorder (social phobia)
Treatment of generalised anxiety disorder

Treatment of obsessive-compulsive disorder”

1.3 Dosage

“The safety of dosages higher than 20 mg per day has not been demonstrated. Escitalopram is administered in a single daily dose during or between meals.

Obsessive-compulsive disorders: the starting dose is 10 mg once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg per day. As obsessive-compulsive disorder (OCD) is a disease with a chronic course, patients must be treated for a sufficient period to ensure disappearance of symptoms. The benefit of treatment and the dosage must be reassessed at regular intervals.

Persons aged over 65 years: a starting dose corresponding to half the usually recommended dosage and a lower maximum dosage must be considered.

Children and adolescents (< 18 years): Escitalopram is not recommended in children and adolescents under the age of 18 years.

Reduced renal function: No dose adjustment is required in patients with mild to moderate renal impairment. Caution is advised in patients with severely reduced renal function (Cl_{CR} less than 30 ml/min).

Reduced hepatic function: An initial dose of 5 mg daily for the first two weeks of treatment is recommended in patients with mild or moderate hepatic impairment. Depending on individual patient response, the dose may be increased to 10 mg per day. Caution and extra vigilant dose titration is advised in patients with severely reduced hepatic function.

Poor metabolisers of CYP2C19: For patients who are known to be poor metabolisers of the isoenzyme CYP2C19, an initial dose of 5 mg daily during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg per day.

Discontinuation symptoms seen when stopping treatment: Abrupt discontinuation should be avoided. When stopping escitalopram treatment, the dose should be gradually reduced over a period of at least one to two weeks in order to limit the risk of discontinuation reactions. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, resuming the previously prescribed dose may be considered. Subsequently, the doctor may continue decreasing the dose, but at a more gradual rate.

2. SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification

N	: Nervous system
N06	: Psychoanaleptics
N06A	: Antidepressants
N06AB	: Selective serotonin reuptake inhibitors (SSRI)
N06AB10	: Escitalopram

2.2 Medicines in the same therapeutic category

Selective serotonin reuptake inhibitors indicated in the “Treatment of obsessive-compulsive disorder”:

- Fluoxetine: PROZAC 20 mg scored dispersible tablet, PROZAC 20 mg capsule, PROZAC 20 mg/5 ml oral solution and its generic versions
- Fluvoxamine: FLOXYFRAL 50 mg, 100 mg, tablets and its generic versions
- Paroxetine: DEROXAT 20 mg tablet, DEROXAT 20 mg/ml oral solution and its generic versions, DIVARIUS 20 mg tablet.
- Sertraline: ZOLOFT 50 mg capsule (in adults and children from 6 to 17 years) and its generic versions.

2.3 Medicines with a similar therapeutic aim

- Clomipramine: ANAFRANIL 10 mg, 25 mg, 75 mg tablets, 25 mg/2 ml solution for injection and its generic versions.

3. ANALYSIS OF AVAILABLE DATA

The applicant submitted 2 clinical studies evaluated by EMEA:

- A placebo-controlled study, with a paroxetine active comparator arm, which evaluated the efficacy and safety of escitalopram in subjects with OCD (study 10205);
- A placebo-controlled study which evaluated the efficacy of escitalopram in the prevention of relapses in patients with OCD (study 10193).

3.1 Study 10205

This was a randomised, double-blind study *versus* placebo with a paroxetine 40 mg/day active comparator arm, to evaluate the efficacy of escitalopram 10 mg/day or 20 mg/day in outpatients with OCD over a 12-week treatment period.
Inclusion criteria: patients had to have OCD according to DSM-IV criteria with a total score on the Yale – Brown scale[13] (Y-BOCS) ≥ 20, and a diagnosis of OCD for at least one year which had been stable for at least 6 months;
Patients with OCD associated with depression were excluded from the study (Montgomery and Asberg depression rating scale (MADRS) score ≥22).
Primary endpoint: Change in Y-BOCS score between baseline and week 12 of treatment.
Secondary efficacy endpoints were:

- Change in Y-BOCS score between baseline and week 24 of treatment;
- Percentage of patients in whom a 25% reduction in the Y-BOCS score was observed at 12 and 24 weeks of treatment.

Efficacy results:

Table 1: Results of study 10205

	Placebo N = 113	**ESC 10 mg/day N = 112**	**ESC 20 mg/day N = 114**	***PXT 40 mg/day N = 116***
Mean baseline Y-BOCS score	27.7 ± 4.2	26.6 ± 3.7	26.6 ± 3.9	*27.3 ± 4.0*
Mean change in Y-BOCS score at 12 W	- 7.45 ± 0.74	- 9.43 ± 0.74 p = 0.052	- 10.66 ± 0.74 p = 0.002	*- 9.92 ± 0.72* *p = 0.014*
Mean change in Y-BOCS score at 24 W	- 8.03 ± 0.88	- 10.59 ± 0.88 p = 0.034	- 11,58 ± 0.88 p = 0.003	*- 11,51 ± 0.86* *p = 0.003*
25 % Responders at 12 W*	57.7 %	77.2 % p = 0.005	80 % p = 0.001	*76.7 %* *p = 0.008*
25 % Responders at 24 W*	65.4 %	80.7 % p = 0.033	82 % p = 0.021	*86.3 %* *p = 0.003*

* LOCF: *Last Observation Carried Forward*

The mean reduction in the Y-BOCS score at 12 weeks of treatment was significantly higher in patients receiving escitalopram 20 mg/day and paroxetine 40 mg/day than in the placebo-treated group. The significance threshold was not reached in the escitalopram 10 mg/day group.
The mean reduction in Y-BOCS score at 24 weeks of treatment was significantly higher in patients receiving escitalopram 10 mg/day and 20 mg/day and paroxetine 40 mg/day than in the placebo-treated group.

[13] Yale-Brown Scale: 10 questions scored from 0 to 4, total score between 0 and 40: 5 categories according to results: from 0 to 7 (a few mild symptoms or no OCD), from 8 to 15 (mild OCD), from 16 to 23 (moderate OCD), from 24 to 31 (severe OCD) and from 32 to 40 (extreme OCD). Above 15: Treatment probably required.

The percentage of responders at 12 weeks of treatment, defined by a 25% reduction in the Y-BOCS score, was significantly higher in all the treatment groups in comparison with the placebo-treated group.
The percentage of responders at 24 weeks of treatment was significantly higher in all the treatment groups than in the placebo-treated group.

This trial was designed to compare each treatment group with placebo and not to directly compare the escitalopram and paroxetine groups. The paroxetine group allowed an internal validation of the trial.

Safety results:
Possibly treatment-related adverse events were observed in:

- 70.8 % of patients in the escitalopram 10 mg/day group,
- 75.4 % of patients in the escitalopram 20 mg/day group,
- 80.3 % of patients in the paroxetine 40 mg/day group,
- 64 % of patients in the placebo group.

The most common adverse reactions were as follows:

- Placebo group: headache, insomnia and nausea
- Incidences of nausea, fatigue and reduction in libido were higher in the escitalopram 20 mg and paroxetine 40 mg groups than in the placebo group.
- Incidences of ejaculation disorders in the escitalopram 20 mg group and hyperhidrosis in the paroxetine 40 mg group were higher than in the placebo group.

3.2 Study 10193

This was a randomised double-blind study *versus* placebo with the objective of evaluating the efficacy of escitalopram 10 mg/day or 20 mg/day in the prevention of relapses in outpatients with OCD during a 24-week treatment period.
The patients had been previously treated by open-label escitalopram 10 mg/day or 20 mg/day for 16 weeks. Patients were then randomly assigned to receive either active or placebo in a double-blind manner.
Inclusion criteria: Patients had to have OCD according to DSM-IV criteria, with a baseline Y-BOCS score ≥ 20 and OCD for at least 1 year with stable symptoms for at least 6 months. The Y-BOCS score had to have fallen by at least 25% at the end of the open-label period.
Patients in whom OCD was associated with depression were excluded from the study (Montgomery and Asberg depression rating scale (MADRS) score ≥ 22).
Primary endpoint: Time to relapse. Relapse was defined by an increase in the Y-BOCS score ≥ 5 or by loss of efficacy, as judged by the investigator.
Efficacy results: The study included 468 patients in the open-label phase and 320 of them were included in the double-blind phase (escitalopram group n = 163, placebo group n = 157).
The time to relapse of patients treated by escitalopram (0.83 years, i.e. approximately 10 months) was significantly longer than in patients treated by placebo (median time to relapse: 0.27 year, i.e. approximately 3 months) ($p < 0.001$).
The relapse rate of patients treated by escitalopram was significantly lower than for patients treated by placebo: 23 % *versus* 52 % ($p < 0.001$).
The patients included in the double-blind phase *versus* placebo had previously received escitalopram treatment open-label. Patients not responding during this open-label period were excluded from the study so all patients included in the double-blind phase were responders to escitalopram.
The Transparency Committee regrets the absence of a direct comparison between escitalopram and paroxetine.

Safety results:
In the escitalopram group, 70 patients (42.7%) had a possibly treatment-related adverse event, *versus* 82 patients (51.9%) in the placebo group.
During the double-blind period, none of the possibly treatment-related adverse events with an incidence ≥ 2% was significantly more frequent in the escitalopram group than in the placebo group.

3.3 Conclusion:

Study 10205 showed the efficacy of escitalopram 20 mg/day *versus* placebo on the change in Y-BOCS score after 12 weeks of treatment in patients with OCD: - 10.66 in the escitalopram 20 mg/day group *versus* -7.45 in the placebo group (p=0.002). The threshold of statistical significance *versus* placebo was not reached in the escitalopram 10 mg/day group after 12 weeks of treatment. The Transparency Committee noted that this threshold was reached after 24 weeks of treatment (secondary efficacy endpoint).
The Transparency Committee regrets the absence of a direct comparison with paroxetine. Although the paroxetine arm of this study was an active comparator arm it did not allow a direct comparison between the two active treatments.

Study 10193 showed that the efficacy of escitalopram was maintained in OCD patients treated for 24 weeks and initially responding to this treatment with a significantly longer time to relapse than in placebo-treated patients who also initially responded to escitalopram. The relapse rate of patients treated by escitalopram was significantly lower than for patients treated by placebo: 23 % *versus* 52%.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit

Obsessive-compulsive disorder is characterised by recurrent obsessions or compulsions which are sufficiently severe to cause patients to experience suffering or disability. This disorder may significantly interfere with the subject's usual activities, his/her professional occupation, usual activities, social relations, or relations with others.

These proprietary medicines are used for symptomatic treatment of obsessive-compulsive disorder.

The efficacy/safety ratio of these proprietary drugs after 24 weeks of treatment is high.

There are alternative pharmacotherapies.

Public health benefit: The public health burden represented by OCD is high taking into account the incidence of this disorder and its repercussions.

The therapeutic need is covered by existing therapies (other antidepressants and behavioural and cognitive therapy in particular). Although other additional therapies for disabling forms of this disorder are useful, they cannot be considered as a public health priority.

Based on clinical data (only *versus* placebo) and taking into account the existence of these other therapies shows that the proprietary medicine SEROPLEX is not expected to impact morbidity and mortality or quality of life.

Consequently, given our current knowledge and taking into account other therapies available at this time, the proprietary drug SEROPLEX is not expected to have a public health benefit in this indication.

The actual benefit of these proprietary drugs in this indication is substantial.

4.2 Improvement in actual benefit

In the indication "Obsessive-compulsive disorder", SEROPLEX does not improve actual benefit (IAB level V) compared to other available pharmacotherapies.

4.3 Therapeutic use[14,15]

Different treatments have been shown to be effective in most anxiety disorders: psychotherapy, in particular cognitive and behavioural psychotherapy, antidepressants and the combination of these two treatment modalities.

Antidepressants are more effective against obsessive thoughts than compulsions.

14 Benefit-risk management of antidepressant medications in the treatment of depression and anxiety disorders in adults Afssaps. Recommendations October 2006

15 HAS May 2005, resistant obsessive-compulsive disorder (OCD): management and use of functional neurosurgery.

Escitalopram is an alternative pharmacological therapy to other antidepressants with an MA in the treatment of OCD: clomipramine, fluoxetine, fluvoxamine, paroxetine and sertraline.
Selective serotonin reuptake inhibitors are recommended as first-line treatment (grade A).
Clomipramine is recommended for second-line therapy because of its tolerability (grade A).
Effective dosages for the treatment of OCD may be higher than those used in depressive disorders.
The time to action onset of antidepressants is longer (about 4 to 8 weeks) in OCD than in depression. Likewise, a longer treatment time (10 to 12 weeks) is required to obtain the maximum therapeutic response. Hence treatment must be continued for at least 3 months before concluding that it is ineffective.

Treatment duration must be sufficiently prolonged, often longer than one year. This length of treatment is all the longer as this disorder is chronic and relapses often occur on discontinuation of treatment.
Comorbidity with a major depressive episode and the existence of a personality disorder are risk factors for failure of antidepressant treatment in OCD.

4.4 Target Population

The target population of SEROPLEX is difficult to estimate as insufficient data are available about:
- the number of persons requiring pharmacotherapy for anxiety.
- the overlapping of populations in the five indications.

According to the AFSSAPS 2006 recommendations[14], the prevalence of OCD is between 1.9 % and 3.2% in the general population.
According to INSEE, the French general population aged over 18 years concerned by the indication was 46,656,525 on 1 January 2008.
Hence the target population of SEROPLEX in the indication “obsessive-compulsive disorder” is between approximately 900,000 and 1,490,000 patients.

4.5 Transparency Committee recommendations

The Transparency Committee recommended inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication “Obsessive-compulsive disorder”.

4.5.1 Packaging

These are not appropriate for the prescription conditions.
The Committee underlines that in accordance with its deliberation dated 20 July 2005, it recommends, for treatments lasting for one month, a harmonisation of the package size to 30 days and consequently 90-day packs for treatments lasting three months.

4.5.2 Reimbursement rate: 65 %