TRANSPARENCY COMMITTEE
Opinion
12 June 2013

SEROPLEX 5 mg, film-coated tablet
B/14 (CIP: 3400936428973)
B/28 (CIP: 3400935993519)

SEROPLEX 10 mg, film-coated tablet
B/28 (CIP: 3400935993748)

SEROPLEX 15 mg, film-coated tablet
B/28 (CIP: 3400935993977)

SEROPLEX 20 mg, film-coated tablet
B/28 (CIP: 3400935994110)

SEROPLEX 20 mg/ml oral drops, solution
B/1 (CIP: 3400938204599)

Applicant: LUNDBECK SAS

<table>
<thead>
<tr>
<th>INN</th>
<th>Escitalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (year):</td>
<td>N06AB10 (antidepressants)</td>
</tr>
</tbody>
</table>

Reason for the review

Renewal of inclusion
Re-assessment of actual benefit and of improvement in actual benefit at the request of the Transparency Committee in accordance with article R 163-21 of the French Social Security Code)

List concerned

National Health Insurance (French Social Security Code L.162-17)

Indications concerned

- Treatment of major depressive episodes (i.e. characteristic symptoms).
- Panic disorder with or without agoraphobia.
- Treatment of social anxiety disorder (social phobia).
- Treatment of generalised anxiety disorder.
- Treatment of obsessive compulsive disorder.
01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (mutual recognition)
SEROPLEX 5 mg, film-coated tablet 21/08/2002
SEROPLEX 10 mg, scored film-coated tablet 21/08/2002
SEROPLEX 20 mg/ml oral drops, solution 26/11/2007

Prescribing and dispensing conditions/ special status
List I

ATC Classification

<table>
<thead>
<tr>
<th>ATC Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>N06</td>
<td>Psychoanaleptics</td>
</tr>
<tr>
<td>N06A</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>N06AB</td>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>N06AB10</td>
<td>Escitalopram</td>
</tr>
</tbody>
</table>

02 BACKGROUND

Escitalopram (SEROPLEX) is an antidepressant of the selective serotonin reuptake inhibitor class marketed by Lundbeck. It is the S-enantiomer of citalopram (SEROPRAM).
SEROPLEX has been marketed in France since 2005. At present it is reimbursed in five indications, i.e. treatment of major depressive episodes, and four indications in anxiety disorders (treatment of panic disorder with or without agoraphobia, treatment of social anxiety disorder, treatment of generalised anxiety disorder, treatment of obsessive compulsive disorder).
The actual benefit (AB) of SEROPLEX is substantial for all the indications apart from social anxiety disorder, for which its actual benefit is moderate.
The Transparency Committee decided that there was a minor improvement in actual benefit (IAB level IV) in terms of efficacy compared with SEROPRAM in the indication “Treatment of major depressive episodes (i.e. characteristic symptoms)” (Opinion of 13 October 2004), and that there was no IAB in the other indications (Opinion of 13 October 2004 and Opinion of 19 March 2008).
In view of the new efficacy and safety data now available, the Committee wishes to re-assess the actual benefit and the improvement in actual benefit of SEROPLEX in its indications.

03 CHARACTERISTICS OF THE MEDICINAL PRODUCT

03.1 Therapeutic 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. ”

03.2 Dosage

See SPC.
04 THERAPEUTIC NEED

Major depressive episodes are characterised by a depressed mood or a loss of interest or pleasure in almost all daily activities. The term ‘anxiety disorders’ describes a group of disorders characterised by excessive or persistent anxiety. There are a number of forms of anxiety disorder (obsessive compulsive disorder, panic disorder with or without agoraphobia, simple or specific phobias, social phobia, generalised anxiety disorder, post-traumatic stress disorder). The various anxiety disorders very often overlap with each other and there is often comorbidity with other psychiatric disorders (particularly depressive disorders).

The most serious consequences of a major depressive episode are attempted suicide or suicide. Twenty-three antidepressants are currently marketed in France. They all have an indication for the treatment of “major depressive episodes (i.e. characteristic symptoms)”.

In the last decade or so, a number of antidepressants have been approved for use in anxiety disorders (see section 06).

05 SUMMARY OF PREVIOUS ASSESSMENTS

<table>
<thead>
<tr>
<th>Date of opinion</th>
<th>13 October 2004 (inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications</td>
<td>Treatment of major depressive episodes (i.e. characteristic symptoms) Panic disorder with or without agoraphobia.</td>
</tr>
<tr>
<td>AB</td>
<td>Substantial</td>
</tr>
<tr>
<td>IAB</td>
<td>SEROPLEX provides minor (level IV) improvement in actual benefit in terms of efficacy compared with SEROPRAM in the indication “Treatment of major depressive episodes (i.e. characteristic symptoms)”.</td>
</tr>
<tr>
<td>Studies requested</td>
<td>Not applicable</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Date of opinion</th>
<th>19 March 2008, (inclusion on the list of medicines in an extension of indication)</th>
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<tbody>
<tr>
<td>Extension of Indication</td>
<td>Treatment of social anxiety disorder (social phobia)</td>
</tr>
<tr>
<td>AB</td>
<td>Moderate</td>
</tr>
<tr>
<td>IAB</td>
<td>In the indication of social anxiety disorder (social phobia), SEROPLEX does not provide any improvement in actual benefit (level V) compared with other drug therapies available.</td>
</tr>
<tr>
<td>Studies requested</td>
<td>A follow-up study under actual conditions of use of SEROPLEX in social anxiety disorder (social phobia).</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Date of opinion</th>
<th>19 March 2008, (inclusion on the list of medicines in an extension of indication)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extension of Indication</td>
<td>Treatment of generalised anxiety disorder</td>
</tr>
<tr>
<td>AB</td>
<td>Substantial</td>
</tr>
<tr>
<td>IAB</td>
<td>In the indication of generalised anxiety disorder, SEROPLEX does not provide any improvement in actual benefit (level V) compared with other drug therapies available.</td>
</tr>
<tr>
<td>Studies requested</td>
<td>A follow-up study under actual conditions of use of SEROPLEX in generalised anxiety disorder.</td>
</tr>
<tr>
<td>Date of opinion</td>
<td>19 March 2008, (inclusion on the list of medicines in an extension of indication)</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Extension of indication</td>
<td>Treatment of obsessive compulsive disorder.</td>
</tr>
<tr>
<td>AB</td>
<td>Substantial</td>
</tr>
<tr>
<td>IAB</td>
<td>In the indication of obsessive compulsive disorder, SEROPLEX does not provide any improvement in actual benefit <strong>level V</strong> compared with other drug therapies available.</td>
</tr>
<tr>
<td>Studies requested</td>
<td>Not applicable</td>
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</table>
The relevant comparators are selective serotonin reuptake inhibitor antidepressants (SSRIs), serotonin and noradrenalin reuptake inhibitor antidepressants (SNRIs) and the "other antidepressants" available in France in the same indications as escitalopram:

<table>
<thead>
<tr>
<th>INN</th>
<th>Medicinal product</th>
<th>MA holder</th>
<th>Generics</th>
<th>Indications</th>
<th>AB</th>
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<tr>
<td><strong>Selective serotonin reuptake inhibitors (SSRIs)</strong></td>
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<tr>
<td>citalopram</td>
<td>SEROPRAM</td>
<td>LUNDBECK</td>
<td>x</td>
<td>MDE, panic disorder</td>
<td>substantial</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>PROZAC</td>
<td>LILLY</td>
<td>x</td>
<td>MDE, OCD</td>
<td>substantial</td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>FLOXYFRAL</td>
<td>ABBOTT</td>
<td>x</td>
<td>MDE, OCD</td>
<td>substantial</td>
</tr>
<tr>
<td>paroxetine</td>
<td>DEROXAT, DIVARIUS</td>
<td>GLAXOSMITHKLINE</td>
<td>x</td>
<td>MDE, panic disorder, GAD, SAD, OCD, PTSD</td>
<td>substantial except for SAD (moderate)</td>
</tr>
<tr>
<td>sertraline</td>
<td>ZOLOFT</td>
<td>PFIZER</td>
<td>x</td>
<td>MDE, panic disorder, SAD, OCD, PTSD</td>
<td>substantial except for SAD (moderate)</td>
</tr>
</tbody>
</table>

| **Serotonin and noradrenaline reuptake inhibitors (SNRIs)**             |                    |          |                                 |           |
| duloxetine             | CYMBALTA          | LILLY    | x         | MDE, SAD, GAD, OCD, PTSD        | substantial |
| milnacipran           | IXEL              | PIERRE FABRE | x         | MDE, SAD, GAD, OCD, PTSD        | substantial |
| venlafaxine           | EFFEXOR, EFFEXOR XR | WYETH PHARMACEUTICALS | x         | MDE, panic disorder, GAD, SAD, OCD | substantial except for SAD (moderate) |

| **“Other” antidepressants**                             |                    |          |                                 |           |
| agomelatine       | VALDOXAN          | SERVIER  | x         | MDE                             | substantial |
| mianserin         | Generic versions of ATHYMIL† | -- | x         | MDE                             | substantial |
| mirtazapine       | NORSET            | SCHERING PLOUGH | x         | MDE                             | substantial |

MDE: major depressive episode; OCD: obsessive compulsive disorder; GAD: generalised anxiety disorder; SAD: social anxiety disorder; PTSD: post-traumatic stress disorder

Other antidepressants available in France for the treatment of major depressive episodes:

<table>
<thead>
<tr>
<th>INN</th>
<th>Medicinal product</th>
<th>MA holder</th>
<th>Generics</th>
<th>Indications</th>
<th>AB</th>
</tr>
</thead>
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<td><strong>Imipramine antidepressants</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clomipramine</td>
<td>ANAFRANIL</td>
<td>DEFIAnte FARMACEUTICA SA</td>
<td>x</td>
<td>MDE</td>
<td>substantial</td>
</tr>
<tr>
<td>amoxapine</td>
<td>DEFANYL</td>
<td>EI SAI</td>
<td></td>
<td>MDE</td>
<td>substantial</td>
</tr>
<tr>
<td>amitriptyline</td>
<td>ELAVIL, LAROXYL</td>
<td>TEOFARMA/ MERCK SHARP &amp; DOHME CHIBRET</td>
<td></td>
<td>MDE</td>
<td>substantial</td>
</tr>
<tr>
<td>maprotiline</td>
<td>LUDIOMIL</td>
<td>AMDIPHARM</td>
<td></td>
<td>MDE</td>
<td>substantial</td>
</tr>
<tr>
<td>dosulepin</td>
<td>PROTHIADEM</td>
<td>TEOFARMA</td>
<td></td>
<td>MDE</td>
<td>substantial</td>
</tr>
<tr>
<td>doxepin</td>
<td>QUITAXON</td>
<td>NEPALM</td>
<td></td>
<td>MDE</td>
<td>substantial</td>
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<tr>
<td>trimipramine</td>
<td>SURMONTIL</td>
<td>SANOFI AVENTIS</td>
<td></td>
<td>MDE</td>
<td>substantial</td>
</tr>
<tr>
<td>imipramine</td>
<td>TOFRANIL</td>
<td>AMDIPHARM</td>
<td></td>
<td>MDE</td>
<td>substantial</td>
</tr>
<tr>
<td><strong>Selective MAO-A inhibitors</strong></td>
<td></td>
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<tr>
<td>moclobemide</td>
<td>MOCLAMINE</td>
<td>BIOCODEX</td>
<td></td>
<td>MDE</td>
<td>substantial</td>
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<tr>
<td><strong>Non-selective IMAOI</strong></td>
<td></td>
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<tr>
<td>iproniazid</td>
<td>MARSILID</td>
<td>ALKOPHARMA</td>
<td></td>
<td>MDE</td>
<td>substantial</td>
</tr>
<tr>
<td><strong>“Other” antidepressants</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tianeptine*</td>
<td>STABLON</td>
<td>SERVIER</td>
<td></td>
<td>MDE</td>
<td>substantial</td>
</tr>
</tbody>
</table>

† ATHYMIL was withdrawn from the market in 2011; *classed as a narcotic (controlled prescription, prescription restricted to 28 days)
MDE: major depressive episode
07 ANALYSIS OF THE NEW DATA AVAILABLE

07.1 Efficacy

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

Since the last Transparency Committee Opinion of 19 March 2008, four meta-analyses have been found that evaluated the efficacy and safety of escitalopram in the treatment of major depressive episodes in adults.

- Cipriani et al. in a 2009 Cochrane meta-analysis compared the efficacy and safety of escitalopram with that of other antidepressants in the acute treatment of a major depressive episode.¹
- In 2009, Cipriani et al. compared the efficacy and acceptability of twelve second generation antidepressants (including escitalopram) in the acute treatment of a major depressive episode.²
- In 2011, Gartlehner et al. compared the efficacy and safety of thirteen second generation antidepressants (including escitalopram) in the treatment of a major depressive episode.³,⁴
- In 2010, NICE re-evaluated the relative efficacy and safety of antidepressants during their updating of the clinical guideline on depression.⁵

The company submitted the results of eleven additional studies, ten of which had been published: ⁶,⁷,⁸,⁹,¹⁰,¹¹,¹²,¹³,¹⁴,¹⁵ and one of which was unpublished [Alexopoulos, 2004]. All the studies were included in the meta-analyses mentioned above.

⁷ Yevtushenko V. et al. Efficacy and Tolerability of Escitalopram Versus Citalopram in Major Depressive Disorder: A 6-Week, Multicenter, Prospective, Randomized, Double-Blind, Active-Controlled study in Adult Outpatients. Clinical Therapeutics. 2007, vol 29, no.11:2319-2332.
7.1.1.1 Cochrane Review 20091

a) Methodology
Cipriani et al. compared the efficacy and safety of escitalopram with that of other antidepressants in the treatment of major depression in adults. Randomised trials comparing escitalopram with another antidepressant in the treatment of major depression were included. The primary endpoint was the percentage of responders during the acute stage of treatment (six to twelve weeks). Responders were patients with at least a 50% reduction in score on the Hamilton scale or the Montgomery-Asberg Depression Rating Scale (MADRS), or patients who were "improved" or "very much improved" on a clinical global impression scale (CGI).

b) Results
A total of 22 randomised studies were included in the meta-analysis, i.e. fourteen studies comparing escitalopram with another SSRI (including six studies versus citalopram) and eight studies versus other second generation antidepressants (venlafaxine, bupropion, duloxetine). No studies versus tricyclic antidepressants or MAOI were included. Escitalopram was more effective than citalopram for percentage of responders in the acute stage of treatment (six studies; 1 823 patients; odds ratio [OR] = 0.67 [95% CI 0.50 to 0.89]). A difference was also found in favour of escitalopram compared with citalopram for percentage remission and symptom relief during the acute stage of treatment (six studies; 1 823 patients; OR = 0.57 [95% CI 0.36 to 0.90]; symptom relief: five studies; 1 392 patients; standardised mean difference - 0.17 [95% CI -0.30 to 0.04]).

There was no difference in efficacy between escitalopram and the other antidepressants included in the analysis. There was only one statistical difference in favour of escitalopram compared with fluoxetine for symptom relief (secondary endpoint) (three studies; 759 patients; standardised mean difference - 0.17 [95% CI -0.32 to -0.03]). There was no difference between escitalopram and the other antidepressants for percentage of premature drop-outs from the study, except in comparison with duloxetine, the results being in favour of escitalopram (three studies; 1 120 patients; OR = 0.62 [95% CI 0.38 to 0.99]).

7.1.1.2 Cipriani et al., 20092

a) Methodology
Cipriani et al. compared twelve second generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline and venlafaxine) in acute therapy for major depression in adults. Randomised studies comparing second generation antidepressants in acute therapy (six to twelve weeks) for major depression were included. Any placebo groups were excluded. A meta-analysis of direct comparison studies and a Bayesian network meta-analysis were performed. Two criteria were evaluated:
• the percentage of responders (efficacy endpoint): patients with a decrease of at least 50% in score on the Hamilton or MADRS depression scales, or patients who had "improved" or "very much improved" on the CGI scale;
• the percentage of premature drop-outs (acceptability endpoint)
b) Results

A total of 117 randomised studies were included with a total of 25 928 patients. Nineteen studies\textsuperscript{16} compared escitalopram with another antidepressant: bupropion (three studies), citalopram (five studies), duloxetine (three studies), fluoxetine (two studies), paroxetine (two studies), sertraline (two studies), venlafaxine (two studies).

- Results of direct comparisons with escitalopram
  Escitalopram was more effective than citalopram for percentage of responders (five studies; 1 604 patients; OR = 1.47 [95% CI 1.15 to 1.90]). Escitalopram was not more effective than the other six antidepressants with which it was compared (bupropion, duloxetine, fluoxetine, paroxetine, sertraline, venlafaxine).

- Results of the network meta-analysis
  In the Bayesian network meta-analysis, the twelve antidepressants were compared two by two for percentage of responders and percentage of premature drop-outs.
  Four antidepressants (mirtazapine, venlafaxine, sertraline and escitalopram) were more effective than five other antidepressants (duloxetine, fluoxetine, fluvoxamine, paroxetine and reboxetine) for percentage of responders. There was no difference in efficacy between escitalopram and citalopram.
  Premature drop-out was less common with escitalopram, sertraline, citalopram and bupropion than with the other antidepressants.

The authors concluded that there were clinically significant differences in terms of efficacy and acceptability between the second generation antidepressants in favour of escitalopram and sertraline. They considered sertraline to be the best option for starting treatment of moderate to severe depression in adults in view of its added value in terms of efficacy, safety and cost.

7.1.1.3 Gartlehner et al., 2011\textsuperscript{4}

a) Methodology

Gartlehner et al. studied the efficacy and safety of thirteen second generation antidepressants (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone and venlafaxine) as acute therapy for major depression. The authors searched for randomised studies comparing two antidepressants for at least six weeks in the treatment of major depression and for placebo-controlled studies for the indirect comparisons. A Bayesian network meta-analysis was performed when fewer than three direct comparison studies were available.

Efficacy endpoints in the acute stage of treatment (six to twelve weeks) were percentage of responders (reduction of at least 50% in the score on the Hamilton and MADRS depression scales) and mean difference in symptom relief.

Gartlehner et al. also compared antidepressants in prevention of relapse.

b) Results

- Acute therapy
  A total of seventy-eight comparisons were made. A difference in efficacy was observed for five comparisons (escitalopram > citalopram, escitalopram > duloxetine, escitalopram > fluoxetine, sertraline > fluoxetine, venlafaxine > sertraline).

Fifteen studies\textsuperscript{17} comparing escitalopram with another second generation antidepressant were

\textsuperscript{16} The studies selected were identical to those included in the Cochrane meta-analysis, apart from two studies which had not been published at the time the meta-analysis was performed (Yevtushenko et al., 2007 and Mao et al., 2008).

\textsuperscript{17} All the studies selected were also included in the Cochrane meta-analysis. Four studies included in the Cochrane meta-analysis were not included in this meta-analysis, i.e. two studies versus fluoxetine (Kennedy 2005, and SCT-MD-09 [unpublished]).
included, i.e. ten studies versus another SSRI (including five studies versus citalopram) and five studies versus other second generation antidepressants (venlafaxine, duloxetine).

Only the comparison versus citalopram was analysed as a direct comparison; the other eleven comparisons were analysed using a mixed approach (Bayesian network meta-analysis).

Escitalopram was more effective than citalopram for percentage of responders (six studies; \( n = 1 \ 802; \ OR = 1.47 \ [95\% \ CI \ 1.07 \ to \ 2.01] \)). The authors state that this relative difference for percentage of responders represents a modest absolute difference. A mean of 62\% of the patients who received escitalopram and 56\% of the patients who received citalopram were responders.

In the Bayesian network meta-analysis, escitalopram was more effective than duloxetine (\( OR = 0.74 \ [credible \ interval \ (CRI) \ 0.56 \ to \ 0.98] \)) and fluoxetine (\( OR = 0.66 \ [CRI \ 0.49 \ to \ 0.89] \)) for percentage of responders. There was no difference for percentage of responders for the other eight comparisons involving escitalopram.

- Prevention of recurrence
  
  Six randomised studies comparing two antidepressants for prevention of recurrence between five months and four years and one 52-week observational study were included in this analysis. Two of the randomised studies included an escitalopram arm.

  There was no difference between the antidepressants compared for prevention of relapse.

The authors concluded that there was no particular difference in efficacy between the second generation antidepressants. According to these authors, current data do not make it possible to recommend one second generation antidepressant rather than any other.

### 7.1.1.4 NICE, 20105

**a) Methodology**

In 2010, NICE reviewed the efficacy and relative safety of antidepressants while they were updating their guidelines on depression.

A search was performed for randomised studies evaluating the efficacy of escitalopram in the treatment of major depression.

**b) Results**

- Results of direct comparisons with escitalopram

A total of twenty-one studies\(^{18}\) comparing escitalopram with other antidepressants were included: fourteen studies versus other SSRI (including six studies versus citalopram) and seven studies versus other second generation antidepressants.

Escitalopram was compared with the other antidepressants as a group, and then with each antidepressant individually.

Escitalopram was more effective than the group of other antidepressants for response to treatment (19 studies; \( n = 5 \ 832; \ 37.7\% \ versus \ 41.4\%; \ RR = 0.9 \ [95\% \ CI \ 0.85 \ to \ 0.96] \)). There was also a difference in favour of escitalopram for percentage remission, symptom relief and percentage of premature drop-outs (17 studies; \( n = 5 \ 206; \ 46.3\% \ versus \ 49.7\%; \ RR = 0.93 \ [95\% \ CI \ 0.88 \ to \ 0.98] \); symptom relief: 11 studies; \( n = 3 \ 009; \ standardised \ mean \ difference = -0.1 \ [95\% \ CI \ -0.17 \ to \ -0.02] \); premature drop-outs: 17 studies; \( n = 4 \ 839; \ 63.9\% \ versus \ 64.4\%; \ RR = 0.94 \ [95\% \ CI \ 0.91 \ to \ 0.98] \)).

Observed effect sizes were small.

In the two-by-two comparisons, there was no difference in efficacy between escitalopram and the other antidepressants apart from citalopram. Escitalopram was more effective than citalopram for all the efficacy endpoints: response to treatment (5 studies; \( n = 1 \ 594; \ 40.2\% \ versus \ 45.6\%; \ RR = 0.85 \ [95\% \ CI \ 0.76 \ to \ 0.95] \)); remission (3 studies; \( n = 968; \ 44.9\% \ versus \ 48.7\%; \ RR = 0.92 \ [95\% \ CI \ 0.8 \ to \ 1.06] \)) and symptom relief (4 studies; \( n = 1 \ 143; \ standardised \ mean \ difference = -0.2 \ [95\% \ CI \ -0.34 \ to \ -0.06] \)).

Observed effect sizes were small.

---

\(^{18}\) The studies selected were the same as those included in the Cochrane meta-analysis with one exception; an unpublished study (SCT-MD-35) was not included in the NICE meta-analysis.
According to the authors of the NICE report, the review of clinical data for escitalopram showed a small advantage for this product over the other antidepressants, but they did not consider this advantage to be clinically important. The authors of the NICE report concluded that the global efficacy of the antidepressants is similar, and that the choice of antidepressant should be based mainly on the side effects profile, patient preference, history of treatment, risk of withdrawal symptoms and toxicity after overdose.

### 7.1.2 Anxiety disorder

Since the last opinion issued by the Transparency Committee, one meta-analysis has been published: NICE evaluated the efficacy of antidepressants in the management of generalised anxiety disorder in adults.\(^{19}\)

Twenty-nine placebo-controlled studies were included. The principal antidepressants evaluated were venlafaxine, duloxetine, escitalopram, sertraline and paroxetine.

Symptom relief was greater than that of placebo for all five antidepressants: the weighted mean difference compared with placebo for the Hamilton anxiety rating scale was between -0.50 (venlafaxine) and -0.23 (paroxetine). For escitalopram it was -0.33 (95% CI -0.47 to -0.19; 4 studies; \(n = 1\ 512\)).

Six studies comparing the antidepressants with each other were included: two studies comparing escitalopram with paroxetine, one study of sertraline versus paroxetine, one study of escitalopram versus venlafaxine and two studies of duloxetine versus venlafaxine.

Escitalopram was better than paroxetine for symptom relief (2 studies; \(n = 523\); weighted mean difference - 0.32 [CI 95% -0.50 to -0.14]).

The authors concluded that SSRI and SNRI antidepressants are more effective than placebo in the treatment of generalised anxiety disorder and that the evidence is insufficient to allow any conclusions to be drawn on difference in efficacy between antidepressants.

No new data have been found for other anxiety disorders (panic disorder with or without agoraphobia, social anxiety disorder, obsessive compulsive disorder).

The company provided the results of a published study of treatment of generalised anxiety disorder.\(^{20}\) This study was included in the NICE meta-analysis.


07.2 Safety/Adverse effects

7.2.1 Gartlehner et al. literature review, 2011

Gartlehner et al., 2011 evaluated the safety of second generation antidepressants. They considered randomised studies and observational studies with a population of at least one thousand patients and at least twelve weeks' follow-up. A total of 143 studies were included, 92 of which were randomised studies comparing two antidepressants. A mean of 63% of patients experienced at least one adverse event. The most commonly-reported events were: diarrhoea, dizziness, dry mouth, fatigue, headache, nausea, sexual dysfunction, sweating, tremor, and weight gain. The authors concluded that second generation antidepressants cause similar adverse events, but that specific adverse events occur at different frequencies between them.

Thirteen studies evaluated the risk of suicidal thoughts or behaviour. The available data did not reveal any difference between second generation antidepressants for this risk.

7.2.2 Amendments to the Marketing Authorisation since 2008

Since the Transparency Committee Opinion of 19 March 2008, a number of additions and clarifications have been made to the escitalopram SPC, concerning the safety of SSRIs.

<table>
<thead>
<tr>
<th>Date</th>
<th>Amendments to the Marketing Authorisation</th>
</tr>
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<tbody>
<tr>
<td>22/08/2008</td>
<td>Addition of a warning about the increased risk of suicide in young adults less than 25 years old treated with antidepressants (Section 4.4).</td>
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<td>Addition of the following undesirable effects: suicidal ideation, suicidal behaviour (frequency not known) (section 4.8).</td>
</tr>
<tr>
<td>17/10/2011</td>
<td>Addition of a statement on the risk of persistent pulmonary hypertension of the newborn: “Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.” (section 4.6).</td>
</tr>
<tr>
<td></td>
<td>Addition of the following undesirable effects: decreased appetite, psychomotor restlessness/akathisia, QT interval prolongation (frequency not known) (section 4.8).</td>
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<tr>
<td></td>
<td>Addition of a statement on the increased fracture risk in elderly subjects receiving SSRIs or tricyclic antidepressants (section 4.8).</td>
</tr>
<tr>
<td>24/04/2012</td>
<td>Addition of contraindication in patients with acquired or congenital QT interval prolongation or in combination with other medicinal products known to prolong the QT interval (section 4.3).</td>
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<tr>
<td></td>
<td>Addition of details of the risk of dose-dependent prolongation of the QT interval. (sections 4.4, 4.5, 4.8, 4.9, 5.1).</td>
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<tr>
<td></td>
<td>Addition of the following undesirable effects: ventricular arrhythmia including torsade de pointes (frequency not known) (section 4.8).</td>
</tr>
<tr>
<td>26/11/2012</td>
<td>Addition of a statement on sperm quality: “Animal data have shown that citalopram may affect sperm quality. Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.” (section 4.6).</td>
</tr>
</tbody>
</table>

07.3 Usage/prescription data

According to IMS data (moving annual total Winter 2012), an estimated 5 637 392 prescriptions have been issued for escitalopram tablets and oral solution.
07.4 Summary & discussion

7.4.1 Major depressive episodes

Since 2008, four meta-analyses have evaluated the comparative efficacy of escitalopram in the treatment of major depressive disorder in adults.1,2,3,4

Short-term therapy:
The meta-analyses included between 15 and 22 studies comparing escitalopram with other antidepressants for six to twelve weeks. Citalopram was the comparator antidepressant in six studies.
In the direct comparison meta-analyses, escitalopram was
- more effective than citalopram for percentage of treatment responders (reduction of 50% or more in score on the Hamilton and MADRS depression rating scales, or improvement on the CGI scale). The difference in efficacy between the two medicinal products was considered by Gartlehner et al. and by the NICE report authors to be modest.
- Escitalopram was not different from the other antidepressants with which it was compared.
In the Cipriani et al. network meta-analysis (direct + indirect comparisons), four antidepressants, mirtazapine, venlafaxine, sertraline and escitalopram were more effective than five others (duloxetine, fluoxetine, fluvoxamine, paroxetine and reboxetine) for percentage of treatment responders. There was no difference in efficacy between escitalopram and citalopram. The authors concluded that there was a clinically significant difference in terms of efficacy and acceptability between the antidepressants in favour of escitalopram and sertraline.
Gartlehner et al. carried out a network meta-analysis using a similar approach to that of Cipriani et al. The authors concluded that there was no notable difference in efficacy between the antidepressants studied (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone and venlafaxine).

Prevention of relapse:
There are few longer-term efficacy data on prevention of recurrence. Gartlehner et al. found six studies comparing the efficacy of second generation antidepressants in preventing recurrence, two of these studies including an escitalopram arm. There was no difference in efficacy between the antidepressants.

According to Gartlehner et al., the data are insufficient to allow recommendation of any one second generation antidepressant rather than any other. According to NICE, as the global efficacy of the antidepressants is similar, the choice of antidepressant should be based mainly on the side effects profile, patient preference, history of treatment, risk of withdrawal symptoms and toxicity after overdose.

The safety profile of escitalopram is no different from that of other SSRIs. The events reported most frequently in the studies are diarrhoea, dizziness, dry mouth, fatigue, headache, nausea, sexual dysfunction, sweating, tremor, and weight gain.

7.4.2 Anxiety disorder

Since the previous Transparency Committee Opinion concerning generalised anxiety disorder, a NICE meta-analysis has become available that considered six studies comparing various antidepressants, including escitalopram, versus paroxetine (two studies) and versus venlafaxine (one study). Escitalopram was more effective than paroxetine in relieving symptoms. The authors conclude that the data are insufficient to allow any conclusion on a difference in efficacy between the antidepressants to be drawn.

No new data have been found concerning other anxiety disorders (panic disorder with or without agoraphobia, social anxiety disorder, obsessive compulsive disorder).
08 THERAPEUTIC USE

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

Antidepressants are the standard drug therapy for moderate to severe major depressive episodes. The National Medicines and Health Products Safety Agency (ANSM, formerly AFSSAPS) 2006 guidelines\textsuperscript{21} for moderate to severe depressive episodes managed in an outpatient setting recommend that unless there are special reasons against this, an SSRI (the class that includes escitalopram), an SNRI or one of the “other antidepressant” class drugs should be prescribed as first-line therapy. Within these three classes of product, no one antidepressant is recommended more strongly than the others. NICE recommends a generic SSRI as first-line therapy, and does not recommend any individual SSRI rather than any other.\textsuperscript{5} Drug therapy is only one aspect of the management of subjects with depressive disorders, and should only be considered in conjunction with psychotherapy. Antidepressants are not indicated in depressive syndromes that do not satisfy the criteria for a major depressive episode.

Escitalopram remains a first-line option for treating moderate to severe major depressive episodes.

08.2 Anxiety disorder

The National Medicines and Health Products Safety Agency (ANSM, formerly AFSSAPS) 2006 guidelines\textsuperscript{21} state that anxiety disorder should be managed with cognitive behavioural therapy (CBT) and/or antidepressants. Isolated symptoms of anxiety or symptoms that are not characteristic of anxiety disorder, simple phobia or agoraphobia alone are not indications for antidepressant therapy. None of the antidepressants with a Marketing Authorisation for anxiety disorder (see section 06) is recommended rather than any other.

Escitalopram remains an option as drug therapy for panic disorder with or without agoraphobia, social anxiety disorder, generalised anxiety disorder and obsessive-compulsive disorder.

\textsuperscript{21} Bon usage des médicaments antidepressants dans le traitement des troubles depressifs et des troubles anxieux de l’adulte. AFSSAPS, October 2006.
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

09.1 Re-assessment of actual benefit

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

Major depressive episodes are characterised by a depressed mood or a loss of interest or pleasure in almost all daily activities. The level of functional deterioration associated with major depressive episodes varies, but even in mild cases there is distress and/or impairment of their social or working life. The most serious consequences of a major depressive episode are attempted suicide or suicide.

Like other SSRIs, escitalopram is a first-line symptomatic therapy for major depressive episodes. The efficacy/adverse effects ratio for escitalopram is high. Alternative drug therapies are the other antidepressants indicated for the treatment of major depressive episodes.

Taking account of these points, the Committee considers that the actual benefit of SEROPLEX tablets and oral solution remains substantial for major depressive episodes (i.e. characteristic symptoms).

9.1.2 Obsessive compulsive disorder

Obsessive compulsive disorder is characterised by recurrent obsessions or compulsions that are sufficiently severe as to interfere significantly with the subject's normal activities, working life and social life.

Escitalopram is a symptomatic therapy for obsessive compulsive disorder. The efficacy/adverse effects ratio for escitalopram is high. Alternative drug therapies are the other antidepressants indicated for the treatment of obsessive compulsive disorder.

Taking account of these points, the Committee considers that the actual benefit of SEROPLEX tablets and oral solution remains substantial for obsessive compulsive disorder.

9.1.3 Panic disorder with or without agoraphobia

Panic disorder is characterised by recurrent and unexpected panic attacks followed by persistent fear, lasting at least a month, of having another panic attack, worries about the possible implications or consequences of these panic attacks, or significant behavioural changes related to these attacks. This disorder can interfere significantly with the subject's normal activities, working life and social life.

Escitalopram is a preventive therapy for panic disorder with or without agoraphobia. The efficacy/adverse effects ratio for escitalopram is high. Alternative drug therapies are the other antidepressants indicated for the treatment of panic disorder with or without agoraphobia.

Taking account of these points, the Committee considers that the actual benefit of SEROPLEX tablets and oral solution remains substantial for the prevention of panic attacks with or without agoraphobia.
9.1.4 Social anxiety disorder (social phobia)

Social anxiety disorder (social phobia) is a marked and persistent fear of social or performance situations in which the person may feel embarrassed. Avoidance behaviours are common and may be very incapacitating. Social anxiety disorder is limited to two or three everyday situations; when it affects most normal social situations it becomes generalised social anxiety disorder. It is a real disability, accompanied by considerable distress.

Escitalopram is a symptomatic treatment for social anxiety disorder.

*Taking account of these points, the Committee considers that the actual benefit of SEROPLEX tablets and oral solution remains moderate for social anxiety disorder (social phobia).*

9.1.5 Generalised anxiety disorder

Generalised anxiety disorder is characterised by excessive anxiety and worry, occurring more days than not for a period of at least six months, about a certain number of events or activities. This disorder can interfere significantly with the subject's normal activities, working life and social life.

Escitalopram is a symptomatic treatment for generalised anxiety disorder.

*Taking account of these points, the Committee considers that the actual benefit of SEROPLEX tablets and oral solution remains substantial for generalised anxiety disorder.*

09.2 Re-assessment of Improvement in Actual Benefit

Taking account of the short-term and long-term data comparing escitalopram to other SSRIs, SNRIs and ‘other antidepressants’, SEROPLEX does not provide any improvement in actual benefit (IAB level V, non-existent) compared with these antidepressants in the management of major depressive episodes (i.e. characteristic symptoms).

The improvement in actual benefit of SEROPLEX in the other indications (treatment of panic disorder with or without agoraphobia, treatment of social anxiety disorder, treatment of generalised anxiety disorder, treatment of obsessive compulsive disorder) is unchanged: SEROPLEX does not provide any improvement in actual benefit (IAB level V, non-existent) compared with the other available drug therapies.

09.3 Transparency Committee Recommendations

The Committee recommends continued inclusion on the list of medicines reimbursed by National Health Insurance in the indications in the Marketing Authorisation.

- **Proposed reimbursement rate:** 65%
- **Packaging**
  Appropriate for the prescription conditions.