# Scottish Medicines Consortium

## escitalopram 5mg, 10mg and 20mg tablets (Cipralex®) No. 253/06

## Lundbeck Limited

7 April 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**escitalopram (Cipralex®)** is accepted for use within NHSScotland for the treatment of generalised anxiety disorder in situations where pharmacological therapy is appropriate. Escitalopram shows similar efficacy to the other selective serotonin re-uptake inhibitor licensed for the treatment of generalised anxiety disorder.

Overleaf is the detailed advice on this product.

**Chairman**
**Scottish Medicines Consortium**

**Escitalopram 5mg, 10mg and 20mg tablets (Cipralex®)**

## Indication
Treatment of generalised anxiety disorder.

## Dosing information
Initially 10mg daily increased to a maximum of 20mg daily according to response.

## UK launch date
November 2005

## Comparator medications

The National Institute for Health and Clinical Excellence (NICE) clinical guideline on anxiety states that a selective serotonin re-uptake inhibitor (SSRI) is considered the first choice in pharmacological therapy for generalised anxiety disorder (GAD). Paroxetine and escitalopram are the only drugs from this class with a licence for GAD. The following alternative drugs have also been effective: benzodiazepines (short-term), the antihistamine, (hydroxyzine) and the serotonin and noradrenaline re-uptake inhibitor, venlafaxine (only the extended-release formulation is licensed for GAD under specialist advice). The evidence for buspirone in GAD is reported to be equivocal.

## Cost of relevant comparators

| Drug | Daily Dose Range | Cost for 28 days | Cost per year |
|---|---|---|---|
| **Escitalopram** | **10-20mg daily** | **£15-£25** | **£194-£328** |
| Paroxetine | 20-50mg daily | £9-47 (generic*)<br>£12-34 (Seroxat®) | £115-£616 (generic*)<br>£160-£442 (Seroxat®) |
| Hydroxyzine | 50-100mg four times daily | £10-20 | £127-£254 |
| Venlafaxine XL® | 75mg daily | £23 | £304 |
| Buspirone | 15-45mg daily (in divided doses) | £45-£107 | £587-£1390 |

Costs from eVadis accessed on 1/2/06; * generic costs are taken from the Scottish Drug Tariff

## Summary of evidence on comparative efficacy

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines GAD as at least 6 months of excessive anxiety and/or worry (occurring on more days than not) with at least three of the following symptoms: restlessness, fatigue, difficulty concentrating, irritability, muscle tension and disturbed sleep. It is accompanied by dysfunction in everyday life. Escitalopram is the S-enantiomer of racemic citalopram. It is an SSRI now licensed for the treatment of GAD.

The efficacy data to support the use of escitalopram in the management of GAD come from the results of seven studies. The primary endpoint in most of these studies was the change from baseline in the Hamilton Rating Scale for Anxiety (HAMA) total score. This scale includes 14 items each scored on a 5-point scale (0-4) to give a total maximum score of 56. Other endpoints included subscales of HAMA and response rates defined by a $\geq$ 50% reduction in the HAMA total score or a Clinical Global Impression of Improvement of much improved or very much improved (CGI-I $\leq$ 2).

Only two studies included an active comparator, paroxetine. In the first study, patients were randomised and received fixed daily doses of study drug for 12 weeks: escitalopram 5mg (n=134), escitalopram 10mg (n=136), escitalopram 20mg (n=133), paroxetine 20mg (n=139) or placebo (n=139). Published results are currently only available in abstract form. The primary endpoint of change in mean HAMA total score found that escitalopram 10mg and 20mg were superior to placebo at week 12. Paroxetine was significantly different from placebo at week 10 only ($p<0.05$). Escitalopram 10mg was reported to be significantly superior to paroxetine 20mg at week 12 ($p<0.05$). Response rates based on CGI-I $\leq$ 2 were reported to be higher significantly with escitalopram 10mg and 20mg compared with placebo and with escitalopram 10mg than paroxetine 20mg ($p<0.05$).

In the other comparative study, patients were randomised to receive 24 weeks of treatment with escitalopram (10mg daily for the first 4 weeks, thereafter 10-20mg daily, n=60) or paroxetine (20mg daily for the first 2 weeks, then increased as necessary by 10mg every 14 days to a maximum of 50mg, n=61). This was followed by a 2-week, down-titration phase, when doses were reduced in increments of 10mg to a final daily dose of 10mg in each group. After 24 weeks there was no significant difference between treatments in the mean change in the HAMA total score (-15.3 versus –13.3, with escitalopram and paroxetine, respectively, p=0.13). The proportion of responders (defined as CGI-I $\leq$ 2) did not differ significantly between treatments (78% with escitalopram and 62% with paroxetine at week 24).

## Summary of evidence on comparative safety

There were no new safety issues associated with escitalopram in this new indication. In the fully published comparison with paroxetine, treatment–emergent adverse events were reported in 77% of escitalopram-treated and 89% of paroxetine-treated patients. Significantly more patients withdrew due to adverse events with paroxetine than escitalopram (23% versus 6.6% respectively, p=0.02). The incidences of sexual adverse events (ejaculation disorder, anorgasmia, and decreased libido), constipation and insomnia were more frequent in the paroxetine group. Diarrhoea and upper respiratory tract infections were more common with escitalopram. In patients who completed 24 weeks of double-blind treatment, mean weight increased by 3.5 lbs with escitalopram and 5.5 lbs with paroxetine. A $\geq$ 7% increase in weight from baseline was reported by 18% of paroxetine and 8.3% of escitalopram patients. During

the two week down titration period, paraesthesia was reported in 6.5% and dizziness in 9.7% of paroxetine-treated patients and none of the escitalopram-treated patients.

## Summary of clinical effectiveness issues

The studies conducted demonstrate efficacy of escitalopram in patient populations relatively free from co-morbid conditions. In practice many patients with GAD also suffer other mood or anxiety disorders including depression, panic disorder, social phobia and specific phobias. The treatment effects seen in studies may be better than those expected in a more complicated general population.

In the escitalopram dose-finding study, the dose of paroxetine was fixed at 20mg daily. This is the lowest recommended dose (range: 20-50mg) and may have limited its relative efficacy. Paroxetine was found to be significantly different from placebo only at week 10. The claims in the submission that escitalopram is superior to paroxetine and faster acting are based on this study. The other comparison with paroxetine indicated similar efficacy but was limited by small patient numbers and a lack of placebo-control. The submission also claims improved tolerability over paroxetine which is only numerically supported by the incidence of treatment-emergent adverse events from the 24-week comparison and significantly fewer patients withdrawing from escitalopram than paroxetine treatment due to adverse effects. The tolerability profiles in the dose-ranging study were similar between escitalopram and paroxetine.

The down-titration of the paroxetine dose in the 24-week study was faster than the withdrawal rate recommended of several week or months according to the patient's needs. In clinical trials, paroxetine was reduced at a rate of 10mg once weekly. During this down titration period, the incidence of paraesthesia and dizziness in the paroxetine-treated patients may not reflect its use in practice.

## Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis of escitalopram versus paroxetine for treating patients with moderate to severe GAD with venlafaxine as the third line option when both SSRIs have failed. The main data source was the clinical trial comparing escitalopram with paroxetine supplemented by longer-term data on sustained response from a second escitalopram trial and a similar paroxetine study taken from the literature. The analysis predicts using escitalopram rather than paroxetine will be slightly cheaper and will yield slightly more QALYs.

The strengths of the design of the economic study are that the correct comparator is used, the choice and structure of the model used are appropriate, and the analysis is taken from both an NHS Scotland and societal perspective.

The main strengths in the handling of the clinical evidence are that a direct comparison trial was used in the economic evaluation, and the calculation of QALYs was attempted. Resource use and costs were generally handled appropriately, although no costs were included for treating adverse events and the number of out-patient clinic visits assumed seems high.

## Patient and public involvement

A Patient Interest Group Submission was not made.

## Budget impact

The gross budget impact of the direct costs of escitalopram is £236,000 in year 1 rising to £1.18 million in year 5. Compared to paroxetine, this would produce a net saving of £32,000 in year 1 rising to £162,000 in year 5. It is estimated that 514 patients will switch to escitalopram in year 1 rising to 2,600 in year 5.

## Guidelines and protocols

NICE Clinical Guideline No. 22. Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care (December 2004) recommends that any of the following types of interventions should be offered for the longer-term care of individuals with generalised anxiety disorder and the preference of the person with generalised anxiety disorder should be taken into account. The interventions which have evidence for the longest duration of effect, in descending order, are: psychological therapy, pharmacological therapy (antidepressant medication), and self-help.

## Additional information

The Scottish Medicines Consortium (SMC) issued advice in November 2002 for escitalopram for major depressive episodes not recommending it for use. Following a resubmission, this advice was changed to recommended in March 2003.

***Advice context:***

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*

*This assessment is based on data submitted by the applicant company up to and including 21 March 2006.*

*Drug prices are those available at the time the papers were issued to SMC for consideration.*

*The undernoted references were supplied with the submission.*

*The National Institute of Health and Clinical Excellence (NICE). Clinical Guideline No. 22. Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. December 2004.*

*Goodman WK, Bose A, Wang Q, Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. J Affect Disord 2005**;** 87(2–3): 161–167.*

*Davidson JRT, Bose A, Wang Q. Safety and efficacy of escitalopram in the long-term treatment of generalised anxiety disorder. J Clin Psychiatry 2005; 60: 1441-1446.*

*Allgulander C, Florea I, Huusom AKT. Prevention of relapse in generalized anxiety disorder by escitalopram treamtent. Int J Neuropsychopharmacol 2005; 9**:** 1–11.*

*Bielski RJ, Bose A, Chang CC. A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. Ann Clin Psychiatry 2005; 17(2): 65–69.*