escitalopram, 5mg, 10mg, and 20mg tablets and 10mg/ml oral drops (Cipralex) No. (406/07)

Lundbeck Ltd

7 September 2007

The Scottish Medicines Consortium 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 not recommended for use within NHS Scotland for treatment of obsessive compulsive disorder.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of obsessive-compulsive disorder (OCD).

Dosing information

Initial dosage is 10mg once daily. Depending on the individual patient response, the dose may be increased to a maximum of 20mg daily.

Product availability date

July 2007

Summary of evidence on comparative efficacy

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site of the serotonin transporter, which has been shown to augment the efficiency of the inhibition of serotonin reuptake. Escitalopram is the S-enantiomer of the serotonin selective reuptake inhibitor (SSRI) citalopram, a racemic mixture of enantiomers.

A double-blind study recruited 466 patients between 18 and 65 years of age with a primary diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria, whose symptoms had been stable for at least 6 months. Patients were required to have a Yale-Brown Obsessive-Compulsive scale (Y-BOCS) total score at screening and baseline ≥20. The Y-BOCS is a 10-item scale with each item rated from 0 (no symptoms) to 4 (extreme symptoms), (total range 0-40) which provides a global measure of the severity and functional impact of symptoms of OCD that is not influenced by the type of obsessions or compulsions present. The study was placebo-controlled, with paroxetine used as an active reference. After screening, 458 patients were equally randomised to 24 weeks of treatment, on fixed doses of escitalopram 10 or 20mg/day, paroxetine 40mg/day or placebo. Patients randomised to escitalopram 20mg or paroxetine 40mg received up- and down-titration, at the beginning and end of the double-blind period. Efficacy and tolerability were assessed at baseline and after 1, 2, 4, 6, 8, 10, 16, 20 and 24 weeks. The primary endpoint was the mean change in Y-BOCS total score from baseline to week 12, based on the intent-to-treat population (ITT) and using last-observation-carried-forward (LOCF) method to impute missing data.

The trial was completed by 327 patients. At week 12 significantly greater improvement in Y-BOCS total score was achieved by the escitalopram 20mg and paroxetine 40mg groups, but not by the escitalopram 10mg group. The mean treatment changes relative to placebo were –1.97 [95% confidence interval (CI), –3.97 to 0.02] for escitalopram 10 mg, –3.21 [95% CI, –5.19 to –1.23] for escitalopram 20 mg and –2.47 [95% CI, –4.43 to –0.51] for paroxetine 40 mg daily. At week 24 both escitalopram 10 mg and 20 mg daily, and paroxetine 40 mg daily, significantly improved Y-BOCS total score and the Y-BOCS obsessive and compulsive subscores compared with placebo, as well as improvements in the National Institute of Mental Health obsessive–compulsive scale (NIMH-OCS) score, the clinical global impression of severity (CGI-S) score and the clinical global impression of improvement (CGI-I). Escitalopram 20mg had a consistently significantly higher remission rate than placebo from week 12.

A relapse prevention study started with a 16-week open label phase followed by a 24-week double-blind period. A total of 468 patients with similar inclusion criteria to the first study were recruited and received escitalopram 10-20mg daily flexible dosing until week 12 after which

the dose was fixed. The 320 treatment responders, defined as having ≥ 25% decrease from baseline in the Y-BOCS total score, were randomised equally to escitalopram (dose as in the open label study) or placebo. Of the 163 patients treated during the double-blind period, 30 (18%) received escitalopram 10 mg daily and 133 (82%) received escitalopram 20 mg daily. Efficacy and tolerability parameters were assessed 2, 4, 6, 8, and 12 weeks after randomisation and then every 4 weeks until the last dose of double-blind treatment (Week 24). The primary efficacy variable was the time to relapse (defined as either an increase in the Y-BOCS total score of ≥5 points from the time of randomisation, or an unsatisfactory treatment effect as judged by the investigator) from the start date of double-blind treatment.

Time to relapse was significantly improved in patients treated with escitalopram compared to placebo. Statistical significance was shown with both doses of escitalopram. The proportion of patients relapsing was significantly higher in the placebo group (52%, n=81/157) than in the escitalopram group (23%, n=38/163). The Y-BOCS relapse criterion accounted for almost all of the relapses (97%, n=116/119). During the double-blind period, significantly more patients responded to escitalopram than placebo from Week 20 (based on the Y-BOCS). The proportion of patients in remission (Y-BOCS score ≤ 10) was significantly greater for escitalopram-treated patients than for those who received placebo from Week 20.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

Escitalopram was well tolerated with a low incidence of adverse events. In the first study escitalopram had a similar tolerability profile to paroxetine. Adverse events reported in the escitalopram 10mg and 20mg groups and the paroxetine 40mg group were 71%, 75% and 80% respectively. There were no significant differences in adverse events between escitalopram 10 mg daily and placebo and the adverse events leading to withdrawals were similar between the active treatment groups.

In the second study, during the double-blind phase, none of the adverse events had a significantly higher incidence in the escitalopram-treated groups than in the placebo group.

Summary of clinical effectiveness issues

Apart from the use of paroxetine as an active reference in the first pivotal trial, escitalopram has not been compared to any other SSRI or to clomipramine. Fluoxetine, citalopram and clomipramine are currently used in clinical practice in Scotland.

Co-morbidity between OCD, anxiety disorders, and affective disorders is common. In the clinical studies patients had lower co-morbidity and therefore may not be reflective of patients in the general population.

Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis comparing escitalopram to paroxetine as a choice of SSRIs after fluoxetine and sertraline. The strategies compared starting a patient on 10mg and titrating to 20mg escitalopram with starting on 20mg of paroxetine and titrating, possibly to the maximum dose of 60mg. Clinical equivalence between the two strategies was assumed. While escitalopram may involve a higher drug cost per day, the assumption of a need for up to three additional consultations with a GP or psychiatrist during titration with paroxetine makes the overall cost of escitalopram lower. Costs and savings were estimated for seven months following treatment on the basis that this is the average treatment duration for OCD in the UK. At this point, the manufacturer estimated the cost of the escitalopram 'package' (including consultation costs) to be £184 compared to £254 for the paroxetine 'package'.

The main issues are:

- The clinical data for the 'head-to-head' trial do not relate to the position the manufacturer proposes.
- The evidence for clinical equivalence was based on a fixed dose of 10mg per day of escitalopram compared to 40mg of paroxetine over 24 weeks. In the economic evaluation it is assumed this can be applied to a starting dose of 10mg of escitalopram versus 20mg of paroxetine, both with titration, and lasting for seven months (roughly 30 weeks). There was no direct evidence to support this.
- The economic evaluation assumed treatment would continue for seven months – if treatment lasts for longer than this the advantage of escitalopram would be reduced and disappears if treatment goes much beyond one year. The NICE guideline recommends treatment for 12 months.

It seems likely that a sensitivity analysis that combined changes in titration rates, duration of treatment and costs of a consultation would undermine the claim that the product is cost saving. The economic case is not sufficiently robust to allow acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) guidelines on Obsessive-Compulsive Disorder: core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder- Guideline No. 31, published November 2005. Expected review date is November 2009.

NICE advise that there are unlikely to be any clinically important differences between SSRI's and clomipramine for efficacy and for adverse effects in OCD although SSRI's may be better tolerated.

NICE advise close monitoring especially when initiating SSRI treatment and around dose changes. SSRIs may increase the risk of suicidal ideas and self-harm in people with depression and in younger people and it is currently unclear whether there is an increased risk for people with OCD.

NICE recommend that patients should also be warned about, and monitored for, relapse and discontinuation/withdrawal symptoms when stopping or reducing SSRIs and advise that the dose should be tapered gradually over several weeks according to the persons needs.

Additional information: comparators

Fluoxetine, fluvoxamine, paroxetine and sertraline are all licensed in the UK for treatment of OCD. Clomipramine is licensed for obsessional states.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
escitalopram	**10-20mg daily orally**	**194 - 328**
fluvoxamine	After titration100-300mg daily orally	181-542
clomipramine	After titration 100-250mg daily orally	159-397
paroxetine	After titration 40-60mg daily orally	174-243
fluoxetine	20-60mg daily orally	25-74*
sertraline	50-200mg daily orally	45 - 53
Citalopram**	After titration 40mg daily orally	56

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 25.06.07. *This assumes using 3x20mg capsules for the 60mg dose. If a 60mg capsule is prescribed the corresponding cost is £578 per year. **Citalopram is used off-label.

Additional information: budget impact

The manufacturer presented a net budget impact that included the cost of consultations. On this basis, the overall saving predicted is between £2k and £4k in year 1, rising to between £15k and £30k in year 5. The manufacturer subsequently supplied figures for the impact in terms of medicines expenditure alone; this ranged from £1k-£2k in year 1 to £8k-£16k in year 5 depending on assumptions about numbers of patients. Given assumptions about the number of OCD patients being treated and the share for paroxetine, between 256 and 516 patients were eligible; escitalopram was expected to be used for 10% of this group in year one rising to 85% by year 5. Treatment duration was assumed to be 208 days. The budget impact estimate did not consider any role for citalopram as it is not licensed in this indication.

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 17 August 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/*

The undernoted references were supplied with the submission.

Stein DJ, Andersen EW, Tonnoir B, Fineberg N. Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study. Curr Med Res Opin 2007; 23: 701–711.

Fineberg NA, Tonnoir B, Lemming O, Stein DJ. Escitalopram prevents relapse of obsessive-compulsive disorder. Eur Neuropsychopharmacol 2007; 17: 430–439.