

NEW MEDICINES ON THE MARKET

Evaluated information for the NHS

ESCITALOPRAM

Summary

- Escitalopram (*Ciprallex*[®]) was launched in June 2002 for the treatment of major depressive episodes and panic disorder with or without agoraphobia.
- It is the S-enantiomer of the antidepressant citalopram, a selective serotonin reuptake inhibitor (SSRI). Citalopram is a racemic mixture of R and S-enantiomers in a 1:1 ratio. Studies have demonstrated that the antidepressant activity of citalopram resides in the S-enantiomer.
- The efficacy of escitalopram in the treatment of depression has been assessed in three 8-week placebo-controlled trials that included a citalopram arm as an active control. Data pooled from these studies indicate that compared with placebo, escitalopram at doses of 10-20mg daily is effective and well tolerated. However none of the trials was of sufficient power to detect a difference between active treatments. An unpublished study suggests that escitalopram is of similar efficacy to venlafaxine XR.
- The evidence to support the claim that escitalopram has improved efficacy and a faster onset of action than citalopram in the treatment of depression is not compelling.
- There are no fully published studies of escitalopram in the treatment of panic disorder.
- The current cost of equivalent doses of Ciprallex[®], Cipramil[®] and generic citalopram is the same for the usual dose however the cost of generic citalopram is likely to drop when other generic versions become available. At the higher equivalent dose, Ciprallex[®] is more expensive. All are more expensive than generic fluoxetine.

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Approved Name:	Escitalopram
Brand Name (Manufacturer):	Cipralex® (Lundbeck)
Presentation:	10mg tablets
BNF Therapeutic Class:	Selective serotonin reuptake inhibitor (BNF 4.3.3)
Licensed Indications:	<ul style="list-style-type: none">• Treatment of major depressive episodes.• Treatment of panic disorder with or without agoraphobia
Dosage and Administration:	Major depressive episodes: 10mg once daily. The dose may be increased to a maximum of 20mg daily. Panic disorder: 5mg daily for the first week then increasing to 10mg daily. The dose may be further increased up to a maximum of 20mg daily.
Sector of Use:	Hospital [Y] Primary Care [Y]

Therapeutic Comment:	Escitalopram is the S-enantiomer of the SSRI citalopram. There is no good evidence to suggest that escitalopram offers any therapeutic advantages over citalopram.
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Cost and Course Details:	28 days treatment (MIMS November 2002) Escitalopram 10mg daily - £16.03 Escitalopram 20mg daily - £32.06
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Treatment Alternatives:	28 days treatment (Drug Tariff Nov 2002) Citalopram (Cipramil® or generic) 20 - 40mg daily - £16.03 - £27.10 Fluoxetine 20mg daily - £7.10 Paroxetine 20mg daily - £13.85 Sertraline 50mg daily - £16.20
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INTRODUCTION

About two thirds of adults will at some time experience depressed mood of sufficient severity to influence their activities. The lifetime risk for major depressive disorder is 15%. Recurrence is common, with 25% of patients having a recurrence within one year, increasing to 75% by 10 years. Depression may become chronic in up to 25% of patients.¹ Both tricyclic antidepressants and serotonin reuptake inhibitors (SSRIs) are suitable first-choice agents for most patients, and choice should ideally be based on individual patient factors such as previous response, likely tolerability, concomitant conditions and suicide risk.² Often, newer antidepressants are claimed to have an early onset of action. However, this is difficult to show in conventional studies, and no antidepressant currently available has been conclusively shown to have a more rapid onset than any other.²

The patent for citalopram (*Cipramil*®) in the UK expired in January 2002 and escitalopram (*Cipralextm*®), an isomer of citalopram was launched in June 2002. Lagap launched a generic version of citalopram in the UK in October 2002 and Lundbeck are currently suing Lagap for breach of newer patents for citalopram.³ Lundbeck recently won an injunction against a Swiss generic company in Denmark and was granted another against another two companies in Norway, arguing in all cases that they infringe the production process patent for Cipramil®.⁴

Escitalopram is claimed to have an improved efficacy profile and a faster onset of action than its racemate in the treatment of depression. Single isomers of already approved racemic drugs were developed because in theory, the isomer that does not contribute to the therapeutic effects of the racemate may complicate the

clinical response to the racemate, and may give rise to unnecessary side effects.⁵

PHARMACOLOGY

Escitalopram is the S-enantiomer of the SSRI citalopram, which is a racemic mixture of R and S-enantiomers in a 1:1 ratio. Studies have demonstrated that the antidepressant activity of citalopram resides in the S-enantiomer.⁶ It has been postulated that the S-enantiomer may have an improved therapeutic profile because it is a more potent and more selective inhibitor of serotonin reuptake than citalopram in vitro. This has led to claims that removal of the unwanted R enantiomer will result in a drug that is twice as potent, has less complicated pharmacokinetics and an improved tolerability profile compared to citalopram.⁷ It has also been claimed that the R-isomer possesses yet to be described pharmacological activity that inhibits or impedes the therapeutic effects of the S-isomer.⁷

PHARMACOKINETICS

Refer to SPC.

EFFICACY

Escitalopram has been assessed in three placebo-controlled trials, with a citalopram arm as an active control. The data from these studies have been pooled.⁷ Each of the three was a randomised, multicentre study comparing the effect of eight weeks of double blind treatment with escitalopram (10-20mg daily) or citalopram (20-40mg daily) with placebo in outpatients with major depression (*DSM IV criteria*).

Patients were required to have a minimum score of 22 on the Montgomery Asberg Depression Rating Scale (MADRS). After the initial screening period, patients received one week of single blind placebo treatment

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followed by randomisation to eight weeks of double blind treatment with the active drugs or placebo. A fixed-dose design was employed in one trial; with patients in the active groups being force-titrated to their final dose (10 to 20mg of escitalopram or 40mg of citalopram daily) after one week of treatment with half the assigned dose. In the other two studies, a more flexible dose design was employed with initial doses of 10mg daily for escitalopram and 20mg daily for citalopram. The dose could be increased to a maximum of 20mg daily of escitalopram and 40mg daily of citalopram at week 4 or 6 in one trial but only at week 3 in the other. Both trials allowed a dose reduction to initial dose if adverse effects arose. Evaluations were conducted after 1, 2, 4, 6 and 8 weeks of double blind treatment. The mean change in MADRS score from baseline to end point was the primary efficacy outcome for all three trials. Efficacy was also assessed using the Clinical Global Impression of Improvement (CGI-I) scale.⁷

A total of 1321 patients (<1% over 65 years of age) were included in the pooled intention to treat population for the analysis of efficacy. Patients in the active treatment groups received a mean daily dose of 13.3mg of escitalopram or 28.9mg of citalopram. Both active treatments were reported to have significantly improved depressive symptoms compared with placebo. Escitalopram produced statistically significant improvements compared with placebo after 1 week of treatment and this was maintained at every study visit through to endpoint. Citalopram treatment was statistically superior to placebo at weeks 6 and 8.⁷

Table 1. Efficacy comparison of escitalopram and citalopram

Study week MADRS	Placebo	Escitalopram	Citalopram
1	-3.8	-4.7*#	-3.7
2	-6.6	-7.8*	-3.7
4	-9.4	-11.0*	-10.2
6	-10.3	-13.0*#	-12.0*
8	-11.2	-13.8*	-13.1*

* p<0.05 active treatments vs placebo

p<0.05 escitalopram vs citalopram

In addition, escitalopram was reported to be statistically significantly superior to citalopram treatment in improving MADRS scores at week 1. The proportion of patients considered to be MADRS responders (MADRS score improved by at least 50% from baseline) at week 8 were 59.3%, 53.4% and 41.2% in the escitalopram, citalopram and placebo groups respectively (p<0.001 for both active treatments vs placebo). Escitalopram treatment produced statistically significant improvement in the CGI-I compared with placebo from week 1 onwards, however statistical superiority was not achieved with citalopram until week 4⁷.

These data suggest that escitalopram may have a faster onset of action than citalopram, however the study was only powered to assess the change in MADRS score at week 8 from baseline and not differences between the two active treatment arms.

Escitalopram has also been compared with venlafaxine in an 8-week double blind study in which 293 patients with major depressive disorder (MADRS >18 at baseline) were randomised to either 10 to 20mg of escitalopram or 75 to 150mg of venlafaxine XR daily. The dose of either product could be doubled after 2 or 4 weeks of treatment if the response was considered inadequate by the investigator. The mean daily dose at week 8 was 12.1mg for escitalopram and 95.2mg per day for venlafaxine XR. Patients completing the double

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blind treatment entered a 1-week single-blind run-out period to evaluate possible withdrawal symptoms using the Discontinuation Emergent Signs and Symptoms (DESS) scale.⁸

There was no significant difference between the two drugs in the change in mean MADRS total score from baseline (~29) to week 8 (<9), which was the primary efficacy endpoint. A significantly larger proportion of escitalopram treated patients than venlafaxine treated patients were reported to have achieved a sustained response by week 6 ($p<0.05$) and sustained remission at weeks 2, 3, 4 and 6. The sustained response was reported to have been achieved 4.6 days faster ($p<0.05$) and sustained remission 6.6 days faster ($p<0.001$) for escitalopram treated patients than for venlafaxine treated patients.⁸ This study has not yet been fully published.

There have been no published studies of escitalopram in panic disorder. Unpublished data from a 12-week study in 237 patients suggest that it significantly improved symptoms and quality of life compared with placebo.⁹ Citalopram and paroxetine are the other SSRI's currently licensed for the treatment of panic disorder.

ADVERSE EFFECTS

In the largest of the placebo-controlled trials, discontinuations due to adverse events occurred in

2.5% of placebo, 4.2% of escitalopram 10mg/day, 10.4% of escitalopram 20mg and 8.8% of citalopram 40mg treated patients. There was a significant difference in the discontinuation rates due to adverse events between the placebo and the escitalopram 20mg and citalopram 40mg groups ($P\leq 0.05$). There was no statistically significant difference in these rates between the escitalopram 20mg and the citalopram 40mg groups. The overall incidence of adverse effects did not differ between the escitalopram 10mg group compared with placebo and also did not differ for the escitalopram 20mg compared with the citalopram 40mg group. Adverse events that occurred in at least 10% of patients in any active treatment group and which were more prevalent than in the placebo group are listed in Table 2 below.⁵

In the venlafaxine trial, 11% of patients on this drug and 8% on escitalopram withdrew due to adverse effects. A total of 69% on escitalopram and 76% on venlafaxine reported treatment emergent adverse effects during the double blind phase, nausea being the most commonly reported problem in both groups. Nausea, constipation and increased sweating occurred with a statistically significantly higher incidence in the venlafaxine group ($p<0.05$). Twice as many patients on venlafaxine were reported to have had an increase in Discontinuation Emergent Signs and Symptoms (DESS) score of 4 or higher ($p<0.01$), although the absolute data to support this statement is not available.⁹

Table 2. Most frequent adverse effects (% of patients)

Adverse event	Placebo (n=122)	Citalopram 40mg (n=125)	Escitalpram 10mg (n=119)	Escitalopram 20mg (n=125)
Nausea	6	22	21	14
Diarrhoea	7	11	10	14
Insomnia	3	11	10	14
Dry mouth	7	10	10	9
Ejaculatory disorders	0	4	9	12

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CONTRAINDICATIONS AND PRECAUTIONS

Escitalopram is an inhibitor of CYP2D6 and caution is advised with the co-administration of products that are mainly metabolised by this enzyme, and that have a narrow therapeutic index e.g. flecainide, propafenone and metoprolol and some CNS drugs such as tricyclic antidepressants or antipsychotics. As the metabolism of escitalopram is mainly mediated by CYP2C19, co-administration of products that inhibit this enzyme (e.g. omeprazole) can result in elevated plasma concentrations of escitalopram.¹⁰

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