National PBM Drug Monograph
Escitalopram (Lexapro®)
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Escitalopram is the S-enantiomer of the SSRI citalopram and is responsible for inhibition of 5-HT reuptake. It has been proposed that by eliminating the R-enantiomer portion of citalopram, that safety and efficacy may be improved. Escitalopram was approved in August 2002 for the treatment of major depressive disorder.

The use of escitalopram in the treatment of panic disorder, generalized anxiety disorder, and social anxiety disorder have been presented as posters at the 22nd National Conference of the Anxiety Disorders Association of America (March 21-24, Austin, Tx) and have not been included in this review.

PHARMACOKINETICS

	Escitalopram	**Citalopram**
Tmax (single-dose)	5 ± 1.5hrs	≈ 4hrs
Oral bioavailability	Data unavailable	80%
Volume of distribution	Data unavailable	12L/kg
T1/2	27-32hrs	≈ 35hrs
Protein binding	56%	80%
Metabolism	CYP3A4, CYP2C19 S-demethylcitalopram S-Didemethylcitalopram	CYP3A4, CYP2C19 Demethylcitalopram Didemethylcitalopram Citalopram-N-oxide Deaminated propionic acid derivative
Serum concentration of metabolites	[S-DCT] –1/3 of that of escital [S-DDCT]- not detectable	[DCT] – ½ of citalopram [DDCT] –1/10 of citalopram
Potency of metabolites	Escit 7X more potent than S-DCT 27X more potent than S-DDCT	Citalopram 8x more potent than its metabolites
Fraction recovered in urine	Escitalopram 8% S-DCT 10%	Citalopram 10% DCT 5%
Absorption	Not affected by food	Not affected by food
Effect on CYP450 enzymes	Does not appear to inhibit CYP 3A4, 1A2, 2C9, 2C19, and 2E1. It has a modest inhibitory effect on 2D6	Does not appear to inhibit CYP 3A4, 2C9, and 2E1. It is a weak inhibitor of 1A2, 2D6, and 2C19

Information obtained from product package insert

Escitalopram and its metabolites of have no or very low affinity for serotonergic (1-7), alpha-adrenergic, beta-adrenergic, dopamine (1-5), histamine (1-3), muscarinic (1-5), and benzodiazepine receptors. Citalopram has no or very low affinity for 5-HT_{1A}, 5-HT_{2A}, alpha-1, alpha-2, beta-adrenergic, histamine-1, GABA, muscarinic, and benzodiazepine receptors.

EFFICACY IN MAJOR DEPRESSIVE DISORDER

There are two published 8-week trials with escitalopram, both of which are fixed-dose trials. Wade et al compared escitalopram 10mg to placebo and Burke et al. compared escitalopram 10 and 20mg, citalopram 40mg, to placebo. There are also 2 flexible-dose trials comparing escitalopram, citalopram, and placebo whose combined results are presented in a poster. There are no published long-term trials evaluating continuation or maintenance therapy; however, there are 2 studies presented as posters that will be briefly addressed. Unfortunately, the transcripts from the FDA Advisory Committee were not posted on the FDA website for additional information.

Fixed-dose comparator studies

In Burke et al., all active treatment groups showed improvement in all efficacy endpoints when compared to placebo. There was no significant difference between either dose of escitalopram and citalopram 40mg (refer to table 1). After 2 weeks, improvement with all active treatments compared to placebo was observed.

Wade et al. also showed favorable results with escitalopram 10mg compared to placebo as measured by MADRS change from baseline score, the % of responders (patients with 50% improvement in MADRS), the % of remitters (MADRS score ≤ 12), and the CGI-I score (refer to table 1). There was no significant difference compared to placebo, for the final MADRS or CGI-S scores.

Flexible-dose comparator studies

There are 2 similarly designed randomized, double-blind trials comparing escitalopram, citalopram, and placebo in outpatients with major depression. The combined results for these 2 studies are presented in a poster. Patients with ongoing major depression and a MADRS score ≥ 22 entered a single-blind placebo run-in followed by 8 weeks of double-blind treatment. Escitalopram was started at 10mg daily and could be adjusted up to 20mg daily. Citalopram was started at 20mg daily and could be adjusted up to 40mg. The average daily dose of escitalopram was 12.6mg and for citalopram was 25.5mg.

Mean baseline MADRS scores (average 28.8) and CGI-S scores (4.3) were similar between groups. The percent completing the trial was 86% for escitalopram, 89% for citalopram, and 87% for placebo. At study end, the MADRS decreased by -15, -14, -12.5 (estimated from graph) for the escitalopram, citalopram, and placebo groups respectively. The change in MADRS for both active treatments was considered significant compared to placebo. At week 4, the change in MADRS was significant only for escitalopram. The percent of patients who were considered treatment responders was 60.1% for escitalopram and 53.6% for citalopram, and 45.5% for placebo and was considered significant for the 2 active treatments. The CGI-S score also decreased in a fashion similar to that of the MADRS.

Quality of Life

Burke et al. evaluated quality of life. Patient functioning was assessed using the Center for Epidemiological Studies-Depression Scale (CES-D) and the 16-item Quality of Life Questionnaire (QOL), which is derived from the Quality of Life Enjoyment and Satisfaction Questionnaire. For QOL, higher numbers represent better quality of life. The placebo-adjusted change in QOL was 2.4 for the 10mg ($p=0.04$) dose and 4.8 for the 20mg ($p< 0.01$). The placebo-adjusted change in CES-D was –2.7 ($p=0.02$) and –6.8 ($p< 0.01$) for the 10 and 20mg doses respectively.

Long-term trials

There are 2 poster presentations, assessing long-term therapy. The first study assessed efficacy and the second tolerability. Patients who previously completed an 8-week trial of escitalopram, citalopram, or placebo were included. Patients then entered an 8-week open-label flexible phase of escitalopram 10-20mg. Those defined as responders (MADRS ≤ 12), were randomized to receive escitalopram or placebo for 36 weeks in a double-blind fashion. The baseline MADRS score for those randomized to placebo and escitalopram was 6.2 ± 0.4 and 7.2 ± 0.3 respectively. Patients continued to take the same number of tablets as in the open-label phase. The primary outcome was time to depression relapse defined as MADRS ≥ 22 or discontinuation due to lack of efficacy. The cumulative rate of relapse was 26% for those receiving escitalopram and 40% for those receiving placebo (hazard ratio =0.56; $p=0.013$). The time to relapse was significantly longer with escitalopram.

The second study evaluated long-term tolerability. Patients completing an 8-week trial of escitalopram, citalopram, or placebo were eligible to enter a 12-month, open-label trial of escitalopram. All patients began with a 10mg dose, which could be increased to a maximum of 20mg at 2 weeks at the discretion of the investigator's clinical judgment. The primary analysis was time to withdrawal due to an adverse event using a Kaplan-Meier plot. Of the 590 patients treated, 9% withdrew due to an adverse event. Time to withdrawal for all adverse events was higher during the first 100 days, followed by a subsequent decrease. The most common reasons for withdrawal were weight and nausea.

Table 1. Published clinical trials

<table>
<tr><th>Study</th><th>Inclusion</th><th>Dosing</th><th>Demographics</th><th>Results</th></tr>
<tr>
<td>Burke 2002
R, DB, PC, PR, MC
Escitalopram 10mg vs. 20mg vs citalopram 40mg vs. placebo
8 weeks
n=491
ITT/LOCF analysis</td>
<td>18-65y/o
Outpatients with major depression (DSM-IV) ≥ 4 weeks
MADSR ≥ 22
Score ≥ 2 on item 1 of HAM-D</td>
<td>Fixed-dose trial
1-week placebo lead-in

Escitalopram 10mg
Escitalopram 20mg (titrated)
Citalopram 40mg (titrated)
Placebo

No concomitant psychotropic meds were allowed except for zoldipem for insomnia not to exceed 3 doses/week</td>
<td>Age (yrs) – E10 40.7 ± 12.3; E20 39.6 ± 12; C40 40 ± 11.5; PL 40.1 ± 10.6

MADRS- E10 28 ± 4.9; E20 28.9 ± 4.6; C40 29.2 ± 4.5; PL 29.5 ± 5

HAM-D – E10 24.3 ± 6.2; E20 25.8 ± 5.7; C40 25.9 ± 5.9; PL 25.8 ± 5.9

CGI-S – E10 4.2 ± 0.5; E20 4.3 ± 0.6; C40 4.3 ± 0.6; PL 4.2 ± 0.5

69-73% with recurrent disease
60-70% female

Mean ± SD</td>
<td>
<table>
<tr><th></th><th>E10</th><th>E20</th><th>C40</th><th>PL</th></tr>
<tr><td>Δ MADRS</td><td>-12.8 ± 0.8*</td><td>-13.9 ± 0.8*</td><td>-12 ± 0.9*</td><td>-9.4 ± 0.9</td></tr>
<tr><td>Δ HAM-D</td><td>-10.2 ± 0.7*</td><td>-11.7 ± 0.8*</td><td>-9.9 ± 0.9*</td><td>-7.6 ± 0.8</td></tr>
<tr><td>Δ CGI-S</td><td>-1.3 ± 0.1*</td><td>-1.4 ± 0.1*</td><td>-1.2 ± 0.1*</td><td>-0.8 ± 0.1</td></tr>
<tr><td>CGI-I</td><td>2.5 ± 0.1*</td><td>2.4 ± 0.1*</td><td>2.6 ± 0.1*</td><td>3.0 ± 0.1*</td></tr>
<tr><td>Δ HAM-A</td><td>-1.1* (PL-adjusted)</td><td>-2.6* (PL-adjusted)</td><td>Not done</td><td></td></tr>
<tr><td>% pts w/ 50% imp in MADRS</td><td>50%*</td><td>51.2%*</td><td>45.6%*</td><td>27.7%*</td></tr>
<tr><td>d/c due to LOE</td><td>2.5%</td><td>0</td><td>0.8%</td><td>4.9%</td></tr>
<tr><td>d/c due to AE</td><td>4.2%</td><td>10.4%*</td><td>8.8%*</td><td>2.5%</td></tr>
<tr><td>Tx-emergent AEs</td><td>79%</td><td>85.6%*</td><td>86.4%*</td><td>70.5%</td></tr>
</table>
*Significant versus placebo
Mean ± SEM
</td>
</tr>
<tr>
<td>Wade 2002
R, DB, PC, PR, MC
Escitalopram 10mg vs. placebo
8 weeks
n=380
ITT/LOCF analysis</td>
<td>18-65y/o
Outpatients with major depression (DSM-IV)
MADSR ≥ 22 and ≤ 40</td>
<td>Fixed-dose trial
1 week placebo lead-in

Escitalopram 10mg
Placebo</td>
<td>Age (yrs) – escitalopram 41 ± 11; PL 40 ± 12

MADRS – escitalopram 29.2 ± 4.2; PL 28.7 ± 3.7
% w/ MADRS 22-29 – escitalopram 57.4%; PL 59.8%
% w/ MADRS 30-40 – escitalopram 42.6%; PL 40.2%

CGI-S – escitalopram 4.38 ± 0.66; PL 4.37 ± 0.6

Approximately 75% female

Mean ± SD</td>
<td>
<table>
<tr><th></th><th>Escitalopram</th><th>Placebo</th></tr>
<tr><td>Δ MADRS</td><td>-16.3*</td><td>-13.6</td></tr>
<tr><td>MADRS</td><td>14.3 ± 9.1</td><td>16.7 ± 9.1</td></tr>
<tr><td>% pts w/ 50% improvement in MADRS</td><td>55%*</td><td>42%</td></tr>
<tr><td>% w/ MADRS score ≤ 12</td><td>48%*</td><td>36%</td></tr>
<tr><td>CGI-S</td><td>2.74 ± 1.24</td><td>2.97 ± 1.2</td></tr>
<tr><td>CGI-I</td><td>2.26 ± 1.18*</td><td>2.58 ± 1.24</td></tr>
<tr><td>d/c due to LOE</td><td>3.7%</td><td>6.9%</td></tr>
<tr><td>d/c due to AE</td><td>4.7%</td><td>1.1%</td></tr>
</table>
Mean ± SD except for the 1° outcome of change from baseline for MADRS where the treatment difference was 2.7 ± SE
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</tr>
</table>

CGI-S= AE= adverse event, Clinical Global Impression-Severity, CGI-I= Clinical Global Impression-Improvement, DB= double-blind, E10= escitalopram 10mg, E20= escitalopram 20mg, C40= citalopram 40mg, HAM-D= Hamilton Rating Scale for Depression, HAM-A= Hamilton Rating Scale for Anxiety, ITT= intent-to-treat, LOCF= last observation carried forward, LOE= lack of efficacy, MADRS= Montgomery-Ashberg Depression Rating Scale, MC= multicenter, PR= parallel, PC= placebo-controlled, R= randomized

ADVERSE EVENTS
Adverse events occurring in at least 10% of patients and greater than that observed in the placebo group were nausea, diarrhea, insomnia, and dry mouth. These adverse events were considered as mild in severity for the majority. The percentage of events occurring in the escitalopram groups was similar to citalopram.

Table 2. Adverse events

	Escitalopram 10	Escitalopram 20	Citalopram 40	Placebo
Nausea	21%	14%	22%	6%
Diarrhea	10%	14%	11%	7%
Insomnia	10	14%	11%	3%
Dry mouth	10%	9%	10%	7%

In the Wade study, the only adverse events with an incidence of >5%, that was significantly greater than placebo was nausea (8.9% vs. 3.7%).

The percent of males experiencing ejaculatory disorders were 9%, 12%, 4%, and 0% for escitalopram 10mg, 20mg, citalopram 40mg, and placebo. It is interesting to note that the percent with escitalopram was greater than citalopram. Loss of libido was reported in 2-3% of patients receiving any active treatment. In the Wade study ejaculation disorder occurred in 3 men (6%) taking escitalopram and 0 taking placebo.

DOSING
The recommended dose is 10mg taken once daily. In the study by Burke, greater efficacy was not seen with the 20mg dose. No dosage adjustment is needed for mild-moderate renal impairment; however, caution should be used in those with severe impairment. The 10mg daily dose is recommended for hepatically impaired patients and the elderly.

COST/AVAILABILITY
Citalopram is scheduled to lose exclusivity in January 2004 barring any litigation. Forest plans on stopping the promotion and sampling of Celexa. Beginning January 2003, the price of Celexa will increase from $1.07 to $1.14.

Escitalopram 5mg unscored film-coated tablets 10mg scored film-coated tablets 20mg scored film-coated tablets	 - $1.11 $1.11	 Available in bottles of 30, 100, 1000 and 10x10 unit dose
Citalopram 10mg unscored film-coated tablets 20mg scored film-coated tablets 40mg scored film-coated tablets	 - $1.14 $1.14	 Bottles of 100, 10x10 unit dose, 10mg/ml oral solution 240ml

REFERENCES
Wade A, Lemming OM, Hedegaard KB. Escitalopram 10mg/day is effective and well tolerated I a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol 2002; 17:95-102.

Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. J Clin Psychiatry 2002; 63:331-336.

Rapaport MH, Bose A, Zheng H, et al. Escitalopram prevents relapse of depressive episodes. *Presented at the XII World Congress of Psychiatry, August 24-29, 2002, Yokohama, Japan.*

Wade A, Despiegel N, Reines EH, et al. Depression in primary care patients: escitalopram is safe and well tolerated in long-term treatment. *Presented at the XXIII CINP Congress, June 23-27, 2002, Montreal, Canada.*

Trivedi M, Lepola U. Flexible-dose experience with escitalopram in the treatment of major depressive disorder. *Presented at the annual meeting of The College of Neuropsychopharmacology, December 9-13, Waikiloa Village, Hawaii.*

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