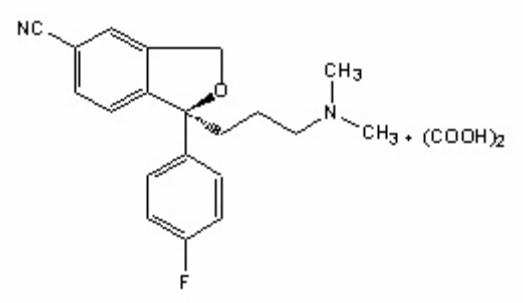
PRODUCT INFORMATION
ESITALO 10mg/20mg FILM COATED TABLETS

NAME OF THE MEDICINE

Escitalopram oxalate

Chemical Name: S(+)-1-[3(dimethylamino)propyl]-1- (4-fluorophenyl)-1,3-dihydroisobenzofuran-5- carbonitrile hydrogen oxalate



CAS Number: 219861-08-2

Empirical formula $C_{20}H_{21}FN_2O$, $C_2H_2O_4$ MW: 414.42

DESCRIPTION

Escitalopram is the active enantiomer (S-enantiomer) of citalopram. Escitalopram oxalate is a fine white to yellow, crystalline material.

Escitalopram oxalate is sparingly soluble in water, slightly soluble in acetone, soluble in ethanol and freely soluble in methanol. No polymorphic forms have been detected.

In addition to escitalopram oxalate, these tablets also contains lactose monohydrate, cellulose - microcrystalline, croscarmellose sodium, hypromellose, magnesium stearate, - silica – colloidal anhydrous, titanium dioxide, talc - purified, macrogol 6000.

PHARMACOLOGY

Pharmacodynamics:
Biochemical and behavioural studies have shown that escitalopram is a potent inhibitor of serotonin (5-HT) uptake *(in vitro* IC_{50} 2 nanomolar).

The antidepressant action of escitalopram is presumably linked to the potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibitory effect on the reuptake of 5-HT from the synaptic cleft.

Escitalopram is a highly selective serotonin reuptake inhibitor (SSRI). On the basis of *in vitro* studies, escitalopram had no, or minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

In contrast to many tricyclic antidepressants and some of the SSRIs, escitalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT_2, DA D_1 and DA D_2 receptors, $alpha_1$, $alpha_2$, beta-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine and opioid receptors. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity.

Escitalopram has high affinity for the primary binding site and an allosteric modulating effect on the serotonin transporter.

Allosteric modulation of the serotonin transporter enhances binding of escitalopram to the primary binding site, resulting in more complete serotonin reuptake inhibition.

Escitalopram is the S-enantiomer of the racemate (citalopram) and is the enantiomer to which the therapeutic activity is attributed. Pharmacological studies have shown that the R-enantiomer is not inert but counteracts the serotonin-enhancing properties of the S-enantiomer in citalopram.

In healthy volunteers and in patients escitalopram did not cause clinically significant changes in vital signs, ECGs or laboratory parameters.

S-demethylcitalopram, the main plasma metabolite, attains about 30% of parent compound levels after oral dosing and is about fivefold less potent at inhibiting 5-HT reuptake than escitalopram *in vitro.* It is therefore unlikely to contribute significantly to the overall antidepressant effect.

Pharmacokinetics:
In a bioavailability study, the mean Cmax and AUC values after a single oral dose of Esitalo 20mg was 20.03ng/mL and 670.09ng.h/mL.

Absorption. Data specific to escitalopram are unavailable. Absorption is expected to be almost complete and independent of food intake (mean T_{max} is four hours after multiple dosing). While the absolute bioavailability of escitalopram has not been studied, it is unlikely to differ significantly from that of racemic citalopram (about 80%).

Distribution. The apparent volume of distribution ($V_{d,beta}$ /F) after oral administration is about 12 to 26L/kg. The binding of escitalopram to human plasma proteins is independent of drug plasma levels and averages 55%.

Metabolism. Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent and metabolites are partly excreted as glucuronides. Unchanged escitalopram is the predominant compound in plasma. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28 to 31% and < 5% of the escitalopram concentration, respectively. Biotransformation of escitalopram to the demethylated metabolite is mediated by a combination of CYP2C19, CYP3A4 and CYP2D6.

Excretion. The elimination half-life ($t_{1/2beta}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0.6L/minute.

Escitalopram and major metabolites are, like racemic citalopram, assumed to be eliminated both by the hepatic (metabolic) and the renal routes with the major part of the dose excreted as metabolites in urine. Approximately 8.0% of escitalopram is eliminated unchanged in urine and 9.6% as the S-demethylcitalopram metabolite based on escitalopram 20mg data. Hepatic clearance is mainly by the P450 enzyme system.

The pharmacokinetics of escitalopram are linear over the clinical dosage range. Steady-state plasma levels are achieved in about one week. Average steady-state concentrations of 50 nanomole/L (range 20 to 125 nanomole/L) are achieved at a daily dose of 10mg.

Reduced hepatic function. In patients with mild or moderate hepatic impairment (Child-Pugh criteria A and B), the half-life of escitalopram was about twice as long and the exposure was about 60% higher than in subjects with normal liver function (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).

Reduced renal function. While there is no specific data, the use of escitalopram in reduced renal function may be extrapolated from that of racemic citalopram. Escitalopram is expected to be eliminated more slowly in patients with mild to moderate reduction of renal function with no major impact on the escitalopram concentrations in serum. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 20mL/minute).

Elderly patients (> 65 years). Escitalopram pharmacokinetics in subjects > 65 years of age were compared to younger subjects in a single dose and a multiple dose study. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, and C_{max} was unchanged. 10mg is the recommended dose for elderly patients.

Gender. In a multiple dose study of escitalopram (10mg/day for three weeks) in 18 male (nine elderly and nine young) and 18 female (nine elderly and nine young) subjects, there were no differences in AUC, C_{max} and half-life between the male and female subjects. No adjustment of dosage on the basis of gender is needed.

Polymorphism. It has been observed that poor metabolisers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolisers. No significant change in exposure was observed in poor metabolisers with respect to CYP2D6 (see DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

Esitalo should not be used for the treatment of major depression and obsessive compulsive disorder in children and adolescents under the age of 18 years since the safety and efficacy in this population have not been established.

Major depression.
Esitalo should not be used in the treatment of children and adolescents under the age of 18 years.

Two fixed dose studies and one flexible dose study have shown escitalopram in the dose range 10 to 20mg/day to be more efficacious than placebo in the treatment of depression. All three studies were randomised, double blind, parallel group, placebo controlled multicentre studies. Two of the studies included an active reference (citalopram). All three studies consisted of a one week single blind placebo lead-in period followed by an eight week double blind treatment period.

Patients were required to have depression with a minimum score of 22 on the Montgomery-Asberg Depression Rating Scale (MADRS) at both the screening and baseline visits. The MADRS consists of ten items that measure core symptoms of depression, such as sadness, tension, pessimism and suicidal thoughts. Each item is rated on a scale of 0 (no abnormality) to 6 (severe). The populations studied were therefore defined as suffering from moderate to severe depression (mean MADRS score 29). A total of 591 patients received escitalopram in these studies.

All three studies showed escitalopram to be statistically significantly superior to placebo on the ITT LOCF (intention to treat/ last observation carried forward) analysis of the mean change from baseline in the MADRS total score ($p \leq 0.01$). The magnitude of the difference between escitalopram and placebo in the MADRS change score ranged from 2.7 to 4.6 (mean of these values: 3.6). The magnitude of the difference for citalopram ranged from 1.5 to 2.5 (mean of these values: 2.0). The magnitude of the difference is larger with escitalopram than with citalopram.

Escitalopram demonstrated a significant early difference compared to placebo from week 2 onwards on the MADRS (week 1 in observed cases analysis). Likewise, the Clinical Global Impression - Improvement items (CGI-I) differed significantly from placebo from week 1 onwards. These early differences were not seen with racemic citalopram.

In the study with two parallel escitalopram dose groups, analysis of subgroups of patients showed a trend towards greater improvement in patients with severe major depressive disorder (HAM-D > 25) receiving 20mg/day as compared to 10mg/day. The Hamilton Rating Scale for Depression (HAM-D) consists of 17 to 24 items reflecting core symptoms of depression. Each item is scored on a 3, 4 or 5 point scale with 0 reflecting no symptoms and higher scores reflecting increasing symptom severity.

In a fourth flexible dose study with a similar design, the primary analysis did not distinguish a significant drug/ placebo difference for either escitalopram or citalopram over eight weeks on the MADRS change score in the LOCF dataset. However, on the basis of the OC analysis, both

escitalopram and citalopram were significantly better than placebo ($p \leq 0.05$; difference between escitalopram and placebo: 2.9).

In a relapse prevention trial, 274 patients meeting (DSM-IV) criteria for major depressive disorder, who had responded during an initial eight week open label treatment phase with escitalopram 10 or 20mg/day, were randomised to continuation of escitalopram at the same dose, or to placebo, for up to 36 weeks of observation for relapse. Response during the open label phase was defined as a decrease of the MADRS total score to ≤ 12. Relapse during the double blind phase was defined as an increase of the MADRS total score to greater than or equal to 22, or discontinuation due to insufficient clinical response. Patients receiving continued escitalopram experienced a significantly longer time to relapse over the subsequent 36 weeks compared to those receiving placebo (26 versus 40%; hazard ratio = 0.56, p = 0.013).

Further evidence of long-term efficacy is provided in a six month study which compared escitalopram 10mg/day to citalopram 20mg/day over a six month treatment period. Analysis of the primary endpoint (the development of the MADRS total scores over 24 weeks) demonstrated escitalopram to be at least as efficacious as citalopram in the long-term treatment of depression. Secondary analyses showed that, while both treatments resulted in numerical improvements in ratings in the MADRS, HAM-A and the CGI, escitalopram was statistically superior to citalopram in several analyses, both during and at the end of the study.

Additional supportive evidence of the sustained efficacy of escitalopram treatment is demonstrated in an open label 12 month study. The efficacy of escitalopram was maintained throughout the study, as measured by the MADRS total score and CGI-S score. Patients showed continued improvement, with total MADRS scores falling from 14.2 at baseline to 5.8 at last assessment, and CGI-scores falling from 2.7 at baseline to 1.6 at last assessment.

A study in the elderly did not provide conclusive efficacy results for escitalopram, as the reference drug (fluoxetine) failed to differentiate from placebo. However, safety data from this study showed escitalopram to be well tolerated.

<u>Obsessive compulsive disorder (OCD)</u>
Esitalo should not be used in the treatment of children and adolescents under the age of 18 years.

Efficacy of escitalopram in the treatment of OCD was investigated in two clinical trials, a 24 week placebo controlled, fixed dose study (with efficacy assessments at week 12 and week 24) and a 16 plus 24 week placebo controlled relapse prevention study.

Patients included in these studies were male and female outpatients aged 18 to 65 years with a diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria and a predefined minimum score of 20 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Patients had actual baseline Y-BOCS scores of approximately 27, indicating significant OCD symptomatology. A structured clinical interview, the Mini International Neuropsychiatric Interview (MINI), was used to assist in the diagnosis and to exclude relevant psychiatric comorbidities. In order to avoid the confounding variable of significant concomitant depression, patients with more than mild depressive symptoms, i.e. a score of 22 or more on the

Montgomery-Asberg Depression Rating Scale (MADRS), were excluded. To ensure a relatively homogenous population with OCD, patients currently diagnosed with any other psychiatric disorders as per Axis I of DSM-IV-TR or any clinically significant unstable medical illness were also excluded.

Results at week 12 of the 24 week placebo controlled, fixed dose study are shown in Tables 5 and 6. In the short-term (12 weeks), escitalopram 20mg/day separated from placebo on the Y-BOCS total score. Please refer to table 1.

Escitalopram	**Table 1**
Long-term (24 weeks) fixed dose study	**Mean Change from Baseline to Week 12 in Y-BOCS Total Score (FAS, LOCF, ANCOVA) [95% CI]**
ESC10 to PBO	-1.97 [-3.97; 0.02]
ESC20 to PBO	-3.21* [_5.19; -1.23]

* $p \leq 0.01$; ESC10 = escitalopram 10mg; ECS20 = escitalopram 20mg; PBO = placebo

Furthermore, escitalopram 20mg/day was significantly more efficacious than placebo on the Y-BOCS subscale of rituals at week 12. Both escitalopram 10mg/day and escitalopram 20mg/day were significantly more efficacious than placebo on the Y-BOCS subscale of obsessions as well as on the NIMH-OCS total score, CGI-I score and CGI-S score. Please refer to table 2.

Escitalopram	**Table 2**				
Long-term (24 weeks) fixed-dose study	**Mean Change from Baseline to Week 12 (FAS, LOCF, ANCOVA) [95% CI]**				
	Y-BOCS Obsessional Subscore	**Y-BOCS Compulsive Subscore**	**NIMH-OCS Score**	**CGI-I Score**	**CGI-S Score**
ESC10 to PBO	-1.15* [-2.20; -0.10]	-1.01 [-2.04; 0.01]	-1.01** [-1.70; -0.33]	-0.36* [-0.66; -0.06]	-0.41* [-0.72; -0.09]
ESC20 to PBO	-2.05*** [-3.10; -1.01]	-1.34** [-2.37; -0.32]	-1.40*** [-2.08; -0.72]	-0.53*** [-0.83; -0.23]	-0.64*** [-0.95; -0.33]

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$; ESC10 = escitalopram 10mg; ECS20 = escitalopram 20mg; PBO = placebo

Results after 24 weeks showed that both escitalopram 10mg/day ($p < 0.05$) and escitalopram 20mg/day ($p < 0.01$) were significantly more efficacious than placebo as measured by the primary outcome measure, the Y-BOCS total score, as well as on the secondary subscales of Y-BOCS (obsessions and rituals) and the NIMH-OCS score (escitalopram 10mg/day ($p < 0.01$) and escitalopram 20mg/day ($p < 0.001$)).

Please refer to table 3.

Escitalopram	**Table 3**
Long-term (24 weeks) fixed dose study	**Mean Change from Baseline to Week 24 in Y-BOCS Total Score (FAS, LOCF, ANCOVA) [95% CI]**
ESC10 to PBO	-2.56* [-4.93; 0.20]
ESC20 to PBO	-3.55** [_-5.90; -1.20]

ESC (10 or 20mg) vs PBO: * $p \leq 0.05$*; **$p \leq 0.01$; ESC10 = escitalopram 10mg; ECS20 = escitalopram 20mg; PBO = placebo

The beneficial efficacy of long-term treatment with escitalopram was also demonstrated by the analyses of responders and remitters in this study as shown in Tables 8 and 9. Please refer to table 4.

Escitalopram	**Table 4**	
Long-term (24 weeks), fixed dose study	**Responders (CGI-I ≤ 2) (LOCF) (%)**	
	12 weeks	**24 weeks**
Placebo	38.9	38.1
Escitalopram 10mg	50	58*
Escitalopram 20mg	57.9*	56.1*

ESC (10 or 20mg) vs PBO: * $p \leq 0.01$

Please refer to table 5.

Escitalopram	**Table 5**	
Long-term (24 weeks), fixed dose study	**Remitters (CGI-S ≤ 2) (LOCF) (%)**	
	12 weeks	**24 weeks**
Placebo	11.5	26.5
Escitalopram 10mg	24.1*	41.1*
Escitalopram 20mg	28.1**	38.6

ESC (10 or 20mg) vs PBO: *p ≤ 0.05; ** p ≤ 0.01

Maintenance of efficacy and prevention of relapse were investigated in the relapse prevention study. This 24 week relapse prevention study was preceded by a 16 week open label period with patients initially receiving escitalopram 10mg/day. In case of lack of efficacy (as judged by the investigator), the dose could be increased to a maximum of 20mg/day. If dose limiting adverse effects occurred, it was permissible to decrease the dose to 10mg/day. Thus the dose of escitalopram was flexible at 10 to 20mg/day from week 2 to 12. Subsequently, the dose was fixed at the dose received at the end of week 12 until week 16 to allow stabilisation of the patient on this dose. Responders to treatment were defined as patients with a decrease in Y-BOCS total score from baseline by greater than or equal to 25% at week 16, and remitters were defined as Y-BOCS ≤ to 10. See Table 10 for responder and remitter rates at the end of the 16 week open label phase. Please refer to table 6.

Escitalopram	**Table 6**	
Relapse-prevention study (16 week open-label, flexible-dose phase)	**Responders (Reduction of Y-BOCS ≥ 25%) (APTS I, LOCF) (%)**	**Remitters (Y-BOCS ≤ 10) (APTS I, LOCF) (%)**
Escitalopram 10 and 20mg	74.4	34.0

Responders at the end of the above 16 week open label treatment phase (escitalopram 10mg: 30 responders; escitalopram 20mg: 133 responders) entered the 24 week randomised, double blind placebo controlled relapse prevention phase. Both escitalopram 10mg/day (p = 0.014) and 20mg/day (p < 0.001) showed significantly fewer relapses as seen in Table 11. Please refer to table 7.

Escitalopram	**Table 7**			
Relapse-prevention study (24-week double-blind phase)		**n**	**Number of relapses**	**% relapsed**
10mg dose group	ESC10	30	3	10.00*
	PBO	20	7	35.00
20mg dose group	ESC20	133	35	26.32**
	PBO	137	74	54.01
10-20mg dose group	ESC	163	38	23.31**
	PBO	157	81	51.59

ESC (10 or 20mg) vs PBO: * $p \leq 0.05$*; **$p \leq 0.001$; ESC10 = escitalopram 10mg; ECS20 = escitalopram 20mg; ESC = escitalopram 10 & 20mg; PBO = placebo

INDICATIONS

- Treatment of major depression.
- Treatment of obsessive compulsive disorder.

CONTRAINDICATIONS

Hypersensitivity to citalopram, escitalopram and any excipients in Esitalo (see DESCRIPTION).

Monoamine oxidase inhibitors. Cases of serious reactions, such as potentially life-threatening serotonin syndrome (characterised by neuromuscular excitation, altered mental status and autonomic dysfunction) have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI) or the reversible MAOI (RIMA) moclobemide, and in patients who have recently discontinued an SSRI and have been started on an MAOI (see INTERACTIONS WITH OTHER MEDICINES).

The combination of escitalopram with the reversible non-selective MAO-inhibitor linezolid, is contraindicated due to the risk of onset of a serotonin syndrome with agitation, tremor, hyperthermia etc. (see INTERACTIONS WITH OTHER MEDICINES).

Escitalopram should not be used in combination with an MAOI or the reversible MAOI (RIMA), moclobemide, or within 14 days of discontinuing treatment with an irreversible MAOI, and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. Similarly, at least 14 days should elapse after discontinuing escitalopram treatment before starting an MAOI (RIMA). Cases of serious reactions, such as potentially life-threatening serotonin syndrome (characterised by neuromuscular excitation and altered mental status) have been reported in patients receiving SSRI in combination with a MAOI or the reversible MAOI (RIMA), moclobemide, and in patients who have recently discontinued an SSRI and have been started on a MAOI. (see INTERACTIONS WITH OTHER MEDICINES).

Pimozide. Concomitant use in patients taking pimozide is contraindicated (see INTERACTIONS WITH OTHER MEDICINES).

Escitalopram is contraindicated in patients with known QT-interval prolongation or congenital long QT syndrome.
Escitalopram is contraindicated together with medicinal products that are known to prolong the QT-interval (see INTERACTIONS WITH OTHER MEDICINES)

PRECAUTIONS

Clinical worsening and suicide risk. The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/ behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms are present.

Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Other psychiatric conditions for which escitalopram is prescribed, can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicidal related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at great risk of suicidal thoughts or suicidal attempts, and should receive careful monitoring during treatment.

Pooled analyses of 24 short-term (4 to 16 week), placebo controlled trials of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (four trials), or other psychiatric disorders (four trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (buproprion, mirtazapine, nefazodone, venlafaxine).

Pooled analyses of short-term studies of antidepressant medications have also shown an increased risk of suicidal thinking and behaviour, known as suicidality, in young adults aged 18 to 24 years during initial treatment (generally the first one to two months). Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the

age of 24 years, and there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or nonpsychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms to health care providers immediately. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for Esitalo should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Akathisia/psychomotor restlessness. The use of SSRIs/SNRIs has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Haemorrhage. Bleeding abnormalities of the skin and mucous membranes have been reported with the use of SSRIs (including purpura, ecchymoses, haematoma, epistaxis, vaginal bleeding and gastrointestinal bleeding). Esitalo should therefore be used with caution in patients concomitantly treated with oral anticoagulants, medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products (NSAIDs), which may increase bleeding tendency ticlopidine and dipyridamole) as well as in patients with a past history of abnormal bleeding or those with predisposing conditions. Pharmacological gastroprotection should be considered for high risk patients.

Hyponatraemia. Probably due to inappropriate antidiuretic hormone secretion (SIADH), hyponatraemia has been reported as a rare adverse reaction with the use of SSRIs. Caution should be exercised in patients at risk, such as the elderly, or patients with cirrhosis or if used in combination with other medications which may cause hyponatraemia.

Seizures. Escitalopram should be discontinued if a patient who develops seizures for the first time or if there is an increase in seizure frequency (in patients previous with a previous diagnosis of

epilepsy). SSRIs should be avoided in patients with unstable epilepsy, and patients with controlled epilepsy should be closely monitored. (see Preclinical safety, below).

Diabetes. In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Mania. A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

SSRIs should be used with caution in patients with a history of mania/hypomania. SSRIs should be discontinued in any patient entering a manic phase.

Electroconvulsive therapy (ECT). There is limited published clinical experience of concurrent administration of SSRIs and ECT, therefore caution is advisable.

Discontinuation. Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt.

The risk of discontinuation symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity.

They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose.

Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 - 3 months or more). It is therefore advised that escitalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see DOSAGE AND ADMINISTRATION).

Cardiac disease. Escitalopram has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Like other SSRIs, escitalopram causes a small decrease in heart rate. Consequently, caution should be observed when escitalopram is initiated in patients with pre-existing slow heart rate.

QT interval prolongation. Escitalopram has been found to cause a dose-dependent prolongation of the QT-interval. Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period, predominantly in patients of

female gender, with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases (see CONTRAINDICATIONS, INTERACTIONS WITH OTHER MEDICINES, ADVERSE EFFECTS and OVERDOSAGE).
Caution is advised in patients with significant bradycardia; or in patients with recent acute myocardial infarction or uncompensated heart failure.
Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant arrhythmias and should be corrected before treatment with escitalopram is started.
If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.
If signs of cardiac arrhythmia occur during treatment with escitalopram, the treatment should be withdrawn and an ECG should be performed.

Preclinical safety. High doses of escitalopram, which resulted in plasma C_{max} for escitalopram and metabolites at least eightfold greater than anticipated clinically, have been associated with convulsions, ECG abnormalities and cardiovascular changes in experimental animals. Of the cardiovascular changes, cardiotoxicity (including congestive heart failure) was observed in comparative toxicological studies in rats following oral escitalopram or citalopram administration for 4 to 13 weeks and appears to correlate with peak plasma concentrations although its exact mechanism is not clear. Clinical experience with citalopram, and the clinical trial experience with escitalopram, do not indicate that these findings have a clinical correlate.

Renal insufficiency. Escitalopram is extensively metabolised and excretion of unchanged drug in the urine is a minor route of elimination. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 20mL/minute) and escitalopram should be used with caution in such patients (see DOSAGE AND ADMINISTRATION).

Hepatic insufficiency. In subjects with hepatic impairment, clearance of escitalopram was decreased and plasma concentrations were increased. The dose of escitalopram in hepatically impaired patients should therefore be reduced (see Pharmacodynamics, Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Use in the elderly. (greater than or equal to 65 years.)
Escitalopram AUC and half-life were increased in subjects greater than or equal to 65 years of age compared to younger subjects in a single dose and a multiple dose pharmacokinetic study. The dose of escitalopram in elderly patients should therefore be reduced (see DOSAGE AND ADMINISTRATION).

Carcinogenesis, mutagenesis, impairment of fertility
Carcinogenicity. No carcinogenicity studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

Citalopram did not show any carcinogenic activity in long-term oral studies using mice and rats at doses up to 240 and 80mg/kg/day, respectively.

Genotoxicity
No genotoxicity studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

In assays of genotoxic activity, citalopram showed no evidence of mutagenic or clastogenic activity.

Effects on fertility
No fertility studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

In rats, female fertility was unaffected by oral treatment with citalopram doses which achieved plasma drug concentrations slightly in excess of those expected in humans, but effects on male rat fertility have not been tested with adequate oral doses.

Animal data have shown that some SSRIs induce a reduction of fertility index and pregnancy index, reduction in number in implantation and abnormal sperm. No animal data related to this aspect are available for escitalopram.

Animal data have shown that some SSRIs may affect sperm quality.

Use in pregnancy (Category C)
Limited clinical data are available regarding exposure to escitalopram during pregnancy.

Neonates should be observed if maternal use of Esitalo continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy. If escitalopram is used until or shortly before birth, discontinuation effects on the neonate are possible. Neonates exposed to escitalopram, other SSRIs or SNRIs (serotonin norepinephrine reuptake inhibitors) late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. In the majority of cases the complications begin immediately or soon (less than 24 hours) after delivery.

Epidemiological studies have shown that the use of SSRI's (including escitalopram) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of persistent pulmonary hypertension of the neonate (PPHN). The risk of PPHN among infants born to women who used SSRIs late in pregnancy was estimated to be 4 to 5 times higher the rate of 1 to 2 per 1000 pregnancies observed in the general population.

Oral treatment of rats with escitalopram during organogenesis at maternotoxic doses led to increased postimplantation loss and reduced fetal weight at systemic exposure levels (based on

AUC) approximately elevenfold that anticipated clinically, with no effects seen at sixfold. No teratogenicity was evident in this study at relative systemic exposure levels of approximately 15 (based on AUC).

There were no perinatal or postnatal effects of escitalopram following oral dosing of pregnant rats (conception through to weaning) at systemic exposure levels (based on AUC) approximately twofold that anticipated clinically. However, the number of stillbirths was increased and the size, weight and postnatal survival of offspring were decreased at a relative systemic exposure level approximately 5.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed and only after careful consideration of the risk/benefit.

Australian categorisation definition of Category C:
Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Use in lactation.
It is expected that escitalopram, like citalopram, will be excreted into human milk. Consequently, breast-feeding is not recommended during treatment.

Paediatric use (children and adolescents, 18 years).
Escitalopram should not be used in the treatment of children and adolescents under the age of 18 years. Suicide related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Effect on ability to drive or operate machinery.
Escitalopram does not impair intellectual function and psychomotor performance. However, as with other psychoactive drugs, patients should be cautioned about their ability to drive a car and operate machinery.

INTERACTIONS WITH OTHER MEDICINES

Monoamine oxidase inhibitors (MAOIs). Coadministration with MAOIs may cause serotonin syndrome (see CONTRAINDICATIONS).

Serotonin syndrome
Development of serotonin syndrome may occur in association with treatment with SSRIs and SNRIs, particularly when given in combination with MAOIs or other serotonergic agents.

Symptoms and signs of serotonin syndrome include rapid onset of neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Treatment with escitalopram should be discontinued if such events occur and supportive symptomatic treatment initiated.

Reversible, selective MAO-A inhibitor (moclobemide)
Due to the risk of serotonin syndrome, the combination of escitalopram with a MAO-A inhibitor such as moclobemide is contraindicated (see CONTRAINDICATIONS). If the combination proves necessary, it should be started at the minimum recommended dosage and clinical monitoring should be reinforced.

Reversible, non-selective MAO-inhibitor (linezolid)
The antibiotic linezolid is a reversible non-selective MAO-inhibitor and should not be given to patients treated with escitalopram. If the combination proves necessary, it should be given with minimum dosages and under close clinical monitoring (see CONTRAINDICATIONS).

Irreversible, selective MAO-B inhibitor (selegiline)
In combination with selegiline (irreversible MAO-B inhibitor), caution is required due to the risk of developing a serotonin syndrome. Selegiline doses up to 10mg/day have been safely co-administered with racemic citalopram.

Pimozide. Coadministration of a single dose of pimozide 2mg to subjects treated with racemic citalopram 40mg/day for eleven days caused an increase in AUC and C_{max} of pimozide, although not consistently throughout the study. The coadministration of pimozide and citalopram resulted in a mean increase in the QTc interval of approximately 10 milliseconds. Due to the interaction with citalopram noted at a low dose of pimozide, concomitant administration of escitalopram and pimozide is contraindicated (see CONTRAINDICATIONS).

Serotonergic drugs. Coadministration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to an enhancement of serotonergic effects. Similarly, *Hypericum perforatum* (St John's wort) should be avoided, as adverse interactions have been reported with a range of drugs including antidepressants.

Lithium and tryptophan. There have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore concomitant use of SSRIs with these drugs should be undertaken with caution.

Medicines affecting the central nervous system. Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Medicines lowering the seizure threshold. SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g. antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes, butyrophenones), mefloquine, bupropion and tramadol).

QT interval prolongation. Pharmacokinetic and pharmacodynamic studies of escitalopram combined with other medicinal products that prolong the QT interval have not been performed. An additive effect of escitalopram and these medicinal products cannot be excluded. Therefore, co-administration of escitalopram with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarian treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine), is contraindicated.

Hepatic enzymes. Escitalopram has a low potential for clinically significant drug interactions. *In vitro* studies have shown that the biotransformation of escitalopram to its demethylated metabolites depends on three parallel pathways (cytochrome P450 (CYP) 2C19, 3A4 and 2D6). Escitalopram is a very weak inhibitor of isoenzymes CYP1A2, 2C9, 2C19, 2E1 and 3A4, and a weak inhibitor of 2D6.

Effects of other drugs on escitalopram in vivo. The pharmacokinetics of escitalopram was not changed by coadministration with ritonavir (CYP3A4 inhibitor). Furthermore coadministration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of racemic citalopram.

Coadministration of escitalopram with omeprazole (a CYP2C19 inhibitor) resulted in a moderate (approximately 50%) increase in plasma concentrations of escitalopram and a small but statistically significant increase (31%) in the terminal half-life of escitalopram (see also DOSAGE AND ADMINISTRATION, Poor metabolisers of CYP2C19).

Coadministration of escitalopram with cimetidine (moderately potent general enzyme inhibitor) resulted in a moderate (approximately 70%) increase in the plasma concentrations of escitalopram.

Thus, caution should be exercised at the upper end of the dose range of escitalopram when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluoxetine, fluvoxamine, lansoprazole and ticlopidine) or cimetidine. A reduction in the dose of escitalopram may be necessary based on clinical judgment (see also DOSAGE AND ADMINISTRATION, Poor metabolisers of CYP2C19).

Effects of escitalopram on other drugs in vivo. Escitalopram is an inhibitor of the enzyme CYP2D6. Caution is recommended when escitalopram is coadministered with medicinal products that are mainly metabolised by this enzyme, and that have a narrow therapeutic index, e.g. flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting medicinal products that are mainly metabolised by CYP2D6, e.g. antidepressants such as desipramine, clomipramine and nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.

Coadministration with desipramine (a CYP2D6 substrate) resulted in a twofold increase in plasma levels of desipramine. Therefore, caution is advised when escitalopram and desipramine are coadministered. A similar increase in plasma levels of desipramine, after administration of imipramine, was seen when given together with racemic citalopram.

Coadministration with metoprolol (a CYP2D6 substrate) resulted in a twofold increase in the plasma levels of metoprolol. However, the combination had no clinically significant effects on blood pressure and heart rate.

The pharmacokinetics of ritonavir (CYP3A4 inhibitor) was not changed by coadministration with escitalopram.

Furthermore, pharmacokinetic interaction studies with racemic citalopram have demonstrated no clinically important interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), warfarin (CYP3A4 and CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor), lithium and digoxin.

Medicines that interfere with haemostasis (nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, warfarin). Serotonin release by platelets plays an important role in haemostasis. There is an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of abnormal bleeding. Concurrent use of an NSAID, aspirin or warfarin potentiates this risk. Thus, patients should be cautioned about using such medicines concurrently with Esitalo.

Alcohol. The combination of SSRIs and alcohol is not advisable.

ADVERSE EFFECTS

Adverse effects observed with escitalopram are in general mild and transient. They are most frequent during the first one or two weeks of treatment and usually decrease in intensity and frequency with continued treatment and generally do not lead to a cessation of therapy. Data from short-term placebo controlled studies are presented below. The safety data from the long-term studies showed a similar profile.

Treatment Emergent Adverse Events with an Incidence of ≥ 1% in placebo-controlled trials

Figures marked with * in Table 8 indicate adverse reactions (incidence with escitalopram statistically significantly different from placebo ($p < 0.05$)). Please refer to table 12.

Escitalopram **Table 8**

Treatment-emergent adverse events with an incidence of ≥ 1% in placebo-controlled trials

System Organ Class and Preferred Term	Placebo n (%)	Escitalopram n (%)
Patients Treated	1795	2632
Patients with Treatment Emergent Adverse Event	1135 (63.2)	1891 (71.8)
Gastrointestinal System Disorders		
nausea	151 (8.4)	481 (18.3)*
diarrhoea	91 (5.1)	207 (7.9)*
mouth dry	74 (4.1)	152 (5.8)*
constipation	42 (2.3)	71 (2.7)
abdominal pain	47 (2.6)	68 (2.6)
vomiting	29 (1.6)	54 (2.1)
dyspepsia	30 (1.7)	33 (1.3)
flatulence	15 (0.8)	31 (1.2)
Central And Peripheral Nervous System Disorders		
headache	305 (17.0)	506 (19.2)
dizziness	64 (3.6)	147 (5.6)*
paraesthesia	13 (0.7)	35 (1.3)
migraine	17 (0.9)	23 (0.8)
tremor	15 (0.8)	33 (1.3)
Psychiatric Disorders		
insomnia	82 (4.6)	245 (9.3)*
somnolence	62 (3.5)	217 (8.2)*
anorexia	12 (0.7)	56 (2.1)*
libido decreased	21 (1.2)	102 (3.9)*
anxiety	44 (2.5)	77 (2.9)
appetite decreased	8 (0.5)	35 (1.3)*
agitation	6 (0.3)	33 (1.3)*
nervousness	13 (0.7)	25 (1.0)
dreaming abnormal	18 (1.0)	41 (1.6)
impotence [gs]	4 (0.6)	22 (2.2)*
Respiratory System Disorders		
upper respiratory tract infection	91 (5.1)	96 (3.6)
coughing	18 (1.1)	24 (0.9)
rhinitis	81 (4.8)	146 (5.5)
sinusitis	24 (1.3)	46 (1.7)
pharyngitis	44 (2.5)	57 (2.2)
yawning	3 (0.2)	58 (2.2)*
bronchitis	31 (1.7)*	26 (0.9)
Body As A Whole - General Disorders		
influenza-like symptoms	65 (3.6)	87 (3.3)
fatigue	62 (3.5)	230 (8.7)*
back pain	61 (3.4)	74 (2.8)
Skin And Appendages Disorders		
sweating increased	27 (1.5)	145 (5.5)*
Musculoskeletal System Disorders		
arthralgia	22 (1.2)	27 (1.0)
Reproductive Disorders, Female		
anorgasmia [gs]	3 (0.3)	47 (2.9)*
Metabolic And Nutritional Disorders		
weight increase	20 (1.1)	45 (1.7)
Reproductive Disorders, Male		
ejaculation disorder [gs]	3 (0.5)	48 (4.7)*
ejaculation failure [gs]	1 (0.2)	27 (2.7)*
Cardiovascular Disorders		
hypertension	24 (1.3)*	13 (0.5)
Heart Rate And Rhythm Disorders		
palpitation	15 (0.8)	30 (1.1)
Secondary Terms		
inflicted injury (unintended injury)	22 (1.2)	23 (0.8)

* = Statistically significant difference escitalopram vs placebo ($p < 0.05$); [gs] = gender specific

Adverse Events in Relation to Dose

The potential dose dependency of common adverse events (defined as an incidence rate of greater than or equal to 5% in either the escitalopram 10 or 20mg groups) was examined on the basis of the combined incidence of adverse events in two fixed dose trials. The overall incidence rates of adverse events in escitalopram 10mg treated patients (66%) was similar to that of the placebo treated patients (61%), while the incidence rate in escitalopram 20mg/day treated patients was greater (86%). Common adverse events that occurred in the escitalopram 20mg/day group with an incidence approximately twice that of the escitalopram 10mg/day group and approximately twice that of the placebo group are shown in Table 9. Please refer to table 9.

Escitalopram	**Table 9**		
Incidence of common adverse events* in patients with major depression receiving placebo, 10mg/day escitalopram, or 20mg/day escitalopram			
Adverse Event	**Placebo (n=311)**	**10mg/day escitalopram (n=310)**	**20mg/day escitalopram (n=125)**
Insomnia	4%	7%	14%
Diarrhoea	5%	6%	14%
Dry mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating increased	<1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

*adverse events with an incidence rate of at least 5% in either escitalopram group and with an incidence rate in the 20mg/day escitalopram group that was approximately twice that of the 10mg/day escitalopram group and the placebo group.

Vital sign changes. Escitalopram and placebo groups were compared with respect to mean change from baseline in vital signs (pulse, systolic blood pressure and diastolic blood pressure), and to the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with escitalopram treatment.

ECG changes. Cases of QT prolongation have been reported during the post-marketing period with both citalopram and escitalopram. Citalopram can cause dose-dependent QT interval prolongation. In an ECG study, the observed change from baseline QTc (Fridericia correction) was 7.5 msec at the 20mg/day dose and 16.7 msec at the 60mg/day dose of citalopram. The effect of escitalopram on the QT interval was similarly studied at doses of 10mg/day and 30mg/day. The change from baseline QTc (Fridericia correction) was 4.3 msec at the 10mg/day dose and 10.7 msec with the above recommended dose of 30mg/day. The QTc interval prolongation observed with 60mg citalopram exceeded that observed with 30mg escitalopram. It is probable that the R-enantiomer and its metabolites in racemic citalopram contribute to these effects.

Weight changes. Patients treated with escitalopram in controlled trials did not differ from placebo treated patients with regard to clinically important change in bodyweight.

Laboratory changes. In clinical studies, there were no signals of clinically important changes in either various serum chemistry, haematology and urinalysis parameters associated with escitalopram treatment compared to placebo or in the incidence of patients meeting the criteria for potentially clinically significant changes from baseline in these variables.

For abnormal laboratory changes registered as either uncommon events or serious adverse events from ongoing trials and observed during (but not necessarily caused by) treatment with escitalopram, please see Other events observed during the premarketing evaluation of escitalopram, below.

Other events observed during the premarketing evaluation of escitalopram.
Following is a list of WHO terms that reflect adverse events occurring at an incidence of < 1% and serious adverse events from ongoing trials. All reported events are included except those already listed in the table or elsewhere in the Adverse Effects section, and those occurring in only one patient. It is important to emphasise that, although the events reported occurred during treatment with Esitalo, they were not necessarily caused by it.

Events are further categorised by body system and are listed below. Uncommon adverse events are those occurring in less than 1/100 patients but at least 1/1,000 patients.

Application site disorders. Uncommon: otitis externa, cellulitis.

Body as a whole. Uncommon: allergy, aggravated allergy, allergic reactions, asthenia, carpal tunnel syndrome, chest pain, chest tightness, fever, hernia, leg pain, limb pain, neck pain, oedema, oedema of extremities, peripheral oedema, rigors, malaise, syncope, scar.

Cardiovascular disorders, general. Uncommon: hypertension aggravated, hypotension, hypertension, abnormal ECG.

Central and peripheral nervous system disorders. Uncommon: ataxia, dysaesthesia, dysequilibrium, dysgeusia, dystonia, hyperkinesia, hyperreflexia, hypertonia, hypoaesthesia, leg cramps, lightheadedness, muscle contractions, nerve root lesion, neuralgia, neuropathy, paralysis, sedation, tetany, tics, twitching, vertigo.

Gastrointestinal system disorders. Uncommon: abdominal cramp, abdominal discomfort, belching, bloating, change in bowel habit, colitis, colitis ulcerative, enteritis, epigastric discomfort, gastritis, gastroesophageal reflux, haemorrhoids, heartburn, increased stool frequency, irritable bowel syndrome, melaena, periodontal destruction, rectal haemorrhage, tooth disorder, toothache, ulcerative stomatitis.

Hearing and vestibular disorders. Uncommon: deafness, earache, ear disorder, otosalpingitis, tinnitus.

Heart rate and rhythm disorders. Uncommon: bradycardia, tachycardia.

Liver and biliary system disorders. Uncommon: bilirubinaemia, hepatic enzymes increased.

Metabolic and nutritional disorders. Uncommon: abnormal glucose tolerance, diabetes mellitus, gout, hypercholesterolaemia, hyperglycaemia, hyperlipaemia, thirst, weight decrease, xerophthalmia.

Musculoskeletal system disorders. Uncommon: arthritis, arthropathy, arthrosis, bursitis, costochondritis, fascitis plantar, fibromyalgia, ischial neuralgia, jaw stiffness, muscle cramp, muscle spasms, muscle stiffness, muscle tightness, muscle weakness, myalgia, myopathy, osteoporosis, pain neck/shoulder, tendinitis, tenosynovitis.

Myocardial, endocardial and pericardial and valve disorders. Uncommon: myocardial infarction, myocardial ischaemia, myocarditis, angina pectoris.

Neoplasm. Uncommon: female breast neoplasm, ovarian cyst, uterine fibroid.

Platelet, bleeding and clotting disorders. Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes, including purpura, epistaxis, haematomas, vaginal bleeding and gastrointestinal bleeding.

Poison specific terms. Uncommon: sting.

Psychiatric disorders. Uncommon: aggressive reaction, amnesia, apathy, bruxism, carbohydrate craving, concentration impairment, confusion, depersonalisation, depression, depression aggravated, emotional lability, excitability, feeling unreal, forgetfulness, hallucination, hypomania, increased appetite, irritability, jitteriness, lethargy, loss of libido, obsessive-compulsive disorder, panic reaction, paroniria, restlessness aggravated, sleep disorder, snoring, suicide attempt, thinking abnormal.

Red blood cell disorders. Uncommon: anaemia hypochromic, anaemia.

Reproductive disorders/ female. Uncommon: amenorrhoea, atrophic vaginitis, breast pain, genital infection, intermenstrual bleeding, menopausal symptoms, menorrhagia, menstrual cramps, menstrual disorder, premenstrual tension, postmenopausal bleeding, sexual function abnormality, unintended pregnancy, dysmenorrhoea, vaginal haemorrhage, vaginal candidiasis, vaginitis.

Reproductive disorders/ male. Uncommon: ejaculation delayed, prostatic disorder.

Resistance mechanism disorders. Uncommon: moniliasis genital, abscess, infection, herpes simplex, herpes zoster, infection bacterial, infection parasitic, infection (tuberculosis), moniliasis.

Respiratory system disorders. Uncommon: asthma, dyspnoea, laryngitis, nasal congestion, nasopharyngitis, pneumonia, respiratory tract infection, shortness of breath, sinus congestion, sinus headache, sleep apnoea, tracheitis, throat tightness.

Skin and appendages disorders. Uncommon: acne, alopecia, dermatitis, dermatitis fungal, dermatitis lichenoid, dry skin, eczema, erythematous rash, furunculosis, onychomycosis, pruritus, psoriasis aggravated, rash, rash pustular, skin disorder, urticaria, verruca.

Secondary terms. Uncommon: accidental injury, bite, burn, fall, fractured neck of femur, alcohol problem, traumatic haematoma, cyst, food poisoning, lumbar disc lesion, surgical intervention.

Other special senses disorders. Uncommon: dry eyes, eye irritation, taste alteration, taste perversion, visual disturbance, ear infection NOS (not otherwise specified), vision blurred.

Urinary system disorders. Uncommon: cystitis, dysuria, facial oedema, micturition frequency, micturition disorder, nocturia, polyuria, pyelonephritis, renal calculus, urinary frequency, urinary incontinence, urinary tract infection.

Vascular (extracardiac) disorders. Uncommon: cerebrovascular disorder, flushing, hot flush [gs], ocular haemorrhage, peripheral ischaemia, varicose vein, vein disorder, vein distended.

Vision disorders. Uncommon: accommodation abnormal, blepharospasm, eye infection, eye pain, mydriasis, vision abnormal, vision blurred, visual disturbance.

White cell and reticuloendothelial system disorders. Uncommon: leucopenia.

In addition the following adverse reactions have been reported with racemic citalopram (all of which have also been reported for other SSRIs).

Disorders of metabolism and nutrition. Hyponatraemia, inappropriate ADH secretion (both especially in elderly women).

Neurological disorders. Convulsions, convulsions grand mal and extrapyramidal disorder, serotonin syndrome (typically characterised by a rapid onset of changes in mental state, with confusion, mania, agitation, hyperactivity, shivering, fever, tremor, ocular movements, myoclonus, hyperreflexia, and incoordination).

Skin disorders. Ecchymoses, angioedema.

Furthermore a number of adverse reactions have been listed for other SSRIs. Although these are not listed as adverse reactions for escitalopram or citalopram, it cannot be excluded that these adverse reactions may occur with escitalopram. These SSRI class reactions are listed below.

Cardiovascular disorders. Orthostatic hypotension.

Hepatobiliary disorders. Abnormal liver function tests.

Neurological disorders. Movement disorders.

Psychiatric disorders. Mania, panic attacks.

Renal and urinary disorders. Urinary retention.

Reproductive disorders. Galactorrhoea.

Other events observed during the postmarketing evaluation of escitalopram.
Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported in association with escitalopram treatment in at least three patients (unless otherwise noted) and not described elsewhere in the Adverse Effects section.

Stomatitis, drug interaction NOS, feeling abnormal, hypersensitivity NOS, nonaccidental overdose, injury NOS, psychotic disorder.

In addition, although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to be temporally associated with racemic citalopram treatment subsequent to the marketing of racemic citalopram and were not observed during the premarketing evaluation of escitalopram or citalopram: acute renal failure, akathisia, anaphylaxis, choreoathetosis, delirium, dyskinesia, epidermal necrolysis, erythema multiforme, gastrointestinal haemorrhage, haemolytic anaemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinaemia, prothrombin decreased, QT prolonged, rhabdomyolysis, spontaneous abortion, thrombocytopenia, thrombosis, Torsades de pointes, ventricular arrhythmia and withdrawal syndrome.

The following other adverse events have also been reported:

Frequencies are defined as: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1000 to < 1/100), Rare (≥ 1/10,000 to < 1/1000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

Immune system disorders. Rare: anaphylactic reactions.

Metabolism and nutrition disorders.
Common: decreased appetite, increased appetite, weight increased.
Not known: anorexia[2].

Psychiatric disorders.
Common: anxiety, restlessness, abnormal dreams, (female and male) libido decreased, (female) anorgasmia.
Uncommon: agitation, nervousness.
Rare: aggression.
Not known: suicidal ideation and suicidal behaviour[1].

Nervous system disorders.
Common: insomnia, somnolence, dizziness, paraesthesia, tremor.

Rare: serotonin syndrome (typically characterised by a rapid onset of changes in mental state with confusion, mania, agitation, hyperactivity, shivering, fever, tremor, ocular movements, myoclonus, hyperreflexia and incoordination).

Cardiac disorders. Not known: Ventricular arrhythmia including torsade de pointes.

Respiratory, thoracic and mediastinal disorders.
Common: sinusitis, yawning.
Uncommon: epistaxis.

Gastrointestinal disorders.
Very common: nausea.
Common: diarrhoea, constipation, vomiting, dry mouth.
Uncommon: gastrointestinal haemorrhages (including rectal haemorrhage).

Hepatobiliary disorders. Not known: hepatitis.

Skin and subcutaneous tissue disorders. Common: sweating increased.

Musculoskeletal and connective tissue disorders. Common: arthralgia, myalgia.

Reproductive system and breast disorders.
Common: (male) ejaculation disorder, impotence.
Uncommon: (female) metrorrhagia.

General disorders and administration site conditions. Common: fatigue, pyrexia.

[1]Cases of suicidal ideation and suicidal behaviours have been reported during escitalopram therapy or early after treatment discontinuation (see PRECAUTIONS).

[2]These events have been reported for the therapeutic class of SSRIs.

QT interval prolongation
Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases (see CONTRAINDICATIONS, PRECAUTIONS, INTERACTIONS WITH OTHER MEDICINES and OVERDOSAGE).

Class effect

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

DOSAGE AND ADMINISTRATION

Adults
Escitalopram is administered as a single oral dose and may be taken with or without food.

Major depression. The recommended dose is 10mg (one 10mg tablet) once daily. Depending on individual patient response, the dose may be increased to a maximum of 20mg (one 20mg tablet) daily.

Usually two to four weeks are necessary for antidepressant response, although the onset of therapeutic effect may be seen earlier. The treatment of a single episode of depression requires treatment over the acute and the medium term. After the symptoms resolve during acute treatment, a period of consolidation of the response is required. Therefore, treatment of a depressive episode should be continued for a minimum of six months.

Obsessive compulsive disorder. The recommended starting dose is 10mg (one 10mg tablet) once daily. Depending on individual patient response, the dose may be increased to 20mg (one 20mg tablet) daily.

Long-term treatment has been studied for a maximum of 40 weeks. Patients responding to a 16 week open label treatment phase were randomised to a 24 week placebo controlled relapse prevention phase, receiving escitalopram 10 or 20mg daily. As OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom free. This period may be several months or even longer.

Elderly patients (greater than or equal to 65 years of age).
A longer half-life and a decreased clearance have been demonstrated in the elderly. 10mg (one 10mg tablet) is the recommended maximum maintenance dose in the elderly (see Pharmacodynamics, Pharmacokinetics and PRECAUTIONS).

Children and adolescents (< 18 years of age).
Safety and efficacy have not been established in this population. Escitalopram should not be used in children and adolescents under 18 years of age (see PRECAUTIONS).

Renal insufficiency.
Dosage adjustment is not necessary in patients with mild or moderate renal impairment. No information is available on the treatment of patients with severely reduced renal function (creatinine clearance < 20mL/minute) (see PRECAUTIONS).

Hepatic insufficiency.
An initial dose of 5mg (half a 10mg tablet) daily for the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10mg (one 10mg tablet) daily (see PRECAUTIONS).

Poor metabolisers of CYP2C19.
For patients who are known to be poor metabolisers with respect to CYP2C19, an initial dose of 5mg (half a 10mg tablet) daily during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10mg (one 10mg tablet) daily (see Pharmacodynamics, Pharmacokinetics and INTERACTIONS WITH OTHER MEDICINES).

Discontinuation.
Significant numbers of discontinuation symptoms may occur with abrupt discontinuation of escitalopram. To minimise discontinuation reactions, tapered discontinuation over at least one to two weeks is recommended. If unacceptable discontinuation symptoms occur following a decrease in the dose or upon discontinuation of treatment then resuming the previously prescribed dose may be considered. Subsequently, the dose may be decreased but at a more gradual rate.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

Symptoms
Toxicity. Clinical data on escitalopram overdose are limited and many cases involve concomitant overdoses of other drugs. In the majority of cases mild or no symptoms have been reported. Doses between 400 and 800mg of escitalopram alone have been taken without any severe symptoms. No fatalities or sequelae were reported in the few cases with a higher dose (one patient survived ingestion of either 2,400 or 4,800mg).

Signs
Symptoms seen in reported overdose of escitalopram include symptoms mainly related to the central nervous system (ranging from dizziness, tremor and agitation to rare cases of serotonin syndrome, convulsion and coma), the gastrointestinal system (nausea/ vomiting), and the cardiovascular system (hypotension, tachycardia, arrhythmia and ECG changes (including QT prolongation)), and electrolyte/fluid balance conditions.

Treatment
In general, the main therapy for all overdoses is supportive and symptomatic care.

There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. The use of activated charcoal should be considered. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering

activated charcoal via a nasogastric tube, once the airway is protected. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.
ECG monitoring is advisable in case of overdose, in patients with congestive heart failure/bradyarrhythmias, in patients using concomitant medications that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment.

PRESENTATION AND STORAGE CONDITIONS

Esitalo 10mg tablets - oval, white, with breaking notch on one side, film coated.

Al/Al Blister packs of 28 tablets.

Esitalo 20mg tablets – round, white, with cross breaking notch on both sides, film-coated.

Al/Al Blister packs of 28 tablets.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
MACQUARIE PARK, NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG): 23/10/2008

DATE OF MOST RECENT AMENDMENT: 03/11/2016