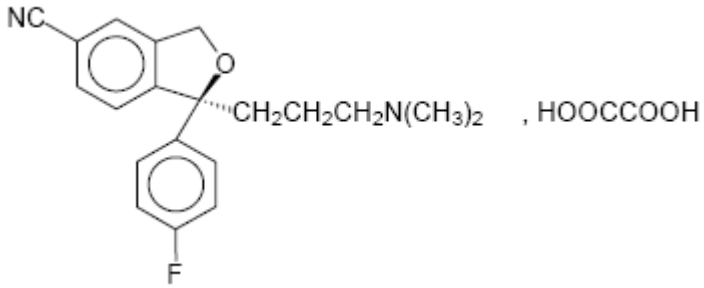
APO-ESCITALOPRAM TABLETS

NAME OF THE MEDICINE

Escitalopram oxalate.

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

Structural Formula:



Molecular Formula: $C_{20}H_{21}FN_2O.C_2H_2O_4$

Molecular Weight: 414.42

CAS Registry Number: 219861-08-2

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.

Each tablet contains 10 or 20 mg escitalopram (as oxalate). In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, colloidal anhydrous silica, purified talc, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 400 and titanium dioxide.

PHARMACOLOGY

Pharmacological Actions

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

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, α_1-, α_2-, β-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 5-fold less potent at inhibiting 5-HT reuptake than escitalopram *in vitro*. It is therefore unlikely to contribute significantly to the overall antidepressant effect.

Pharmacokinetics

Absorption

Data specific to escitalopram are unavailable. Absorption is expected to be almost complete and independent of food intake (mean T_{max} is 4 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 26 L/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 28–31% 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 ($t_{½\beta}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0.6 L/min.

Escitalopram and major metabolites are, like racemic citalopram, assumed to be eliminated both by the hepatic (metabolic) and 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 20 mg escitalopram 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 1 week. Average steady state concentrations of 50 nmol/L (range 20 – 125 nmol/L) are achieved at a daily dose of 10 mg.

Hepatic Impairment

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** and **DOSAGE AND ADMINISTRATION**).

Renal Impairment

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 < 20 mL/min).

Pharmacokinetics in 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. 10 mg is the recommended dose for elderly patients.

Gender

In a multiple-dose study of escitalopram (10 mg/day for 3 weeks) in 18 male (9 elderly and 9 young) and 18 female (9 elderly and 9 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

Escitalopram 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

Escitalopram 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 10–20 mg/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 1-week single-blind placebo lead-in period followed by an 8-week double-blind treatment period.

Patients were required to have depression with a minimum score of 22 on the Montgomery-Åsberg Depression Rating Scale (MADRS) at both the screening and baseline visits. The MADRS consists of 10 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 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 sub-groups of patients showed a trend towards greater improvement in patients with severe major depressive disorder (HAM-D > 25) receiving 20 mg/day as compared to 10 mg/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 8 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).

Escitalopram demonstrated efficacy in the treatment of anxiety symptoms associated with depression. In the three positive double-blind placebo-controlled studies, escitalopram was shown to be effective compared to placebo on the MADRS anxiety items; inner tension and sleep disturbances. Furthermore, in the one study where the Hamilton Anxiety Scale (HAM-A) and the anxiety factor of the Hamilton Depression Rating Scale (HAM-D scale) were used, results have shown that escitalopram was significantly better than placebo.

In a relapse prevention trial, 274 patients meeting (DSM-IV) criteria for major depressive disorder, who had responded during an initial 8-week open-label treatment phase with escitalopram 10 or 20 mg/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 ≥ 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% vs. 40%; hazard ratio = 0.56, $p = 0.013$).

Further evidence of long-term efficacy is provided in a 6-month study which compared escitalopram 10 mg/day to citalopram 20 mg/day over a 6-month treatment period. Analysis of the primary end-point (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.

Obsessive-Compulsive Disorder (OCD)

Escitalopram 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 + 24-week placebo-controlled relapse-prevention study.

Patients included in these studies were male and female outpatients aged 18–65 years with a diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria and a pre-defined minimum score of 20 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Patients had actual baseline Y-BOCS scores of approx. 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-Åsberg 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 1 and 2. In the short-term (12 weeks), 20 mg/day escitalopram separated from placebo on the Y-BOCS total score.

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 ≤ 0.01

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Furthermore, escitalopram 20 mg/day was significantly more efficacious than placebo on the Y-BOCS subscale of rituals at week 12. Both escitalopram 10 mg/day and escitalopram 20 mg/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.

Table 2

Long-term (24 weeks) fixed-dose study	Mean Change from Baseline to Week 12 (FAS, LOCF, ANCOVA) [95% CI]				
	Y-BOCS Obsessional Sub-score	Y-BOCS Compulsive Sub-score	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 ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Results after 24 weeks showed that both escitalopram 10 mg/day ($p < 0.05$) and escitalopram 20 mg/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 10 mg/day ($p < 0.01$) and escitalopram 20 mg/day ($p < 0.001$)).

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 20 mg) vs. PBO: * p ≤ 0.05; ** p ≤ 0.01

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; 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 4 and 5.

Table 4

Long-term (24 weeks) fixed-dose study	Responders (CGI-I ≤ 2) (LOCF) (%)	
	12 weeks	24 weeks
PBO	38.9	38.1
ESC10	50	58**
ESC20	57.9**	56.1**

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

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Table 5

Long-term (24 weeks) fixed-dose study	Remitters (CGI-S ≤ 2) (LOCF) (%)	
	12 weeks	24 weeks
PBO	11.5	26.5
ESC10	24.1*	41.1*
ESC20	28.1**	38.6

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

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

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 10 mg/day. In case of lack of efficacy (as judged by the investigator), the dose could be increased to a maximum of 20 mg/day. If dose-limiting adverse effects occurred, it was permissible to decrease the dose to 10 mg/day. Thus the dose of escitalopram was flexible at 10–20 mg/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 ≥ 25% at week 16 and remitters were defined as Y-BOCS ≤ 10. See Table 6 for responder and remitter rates at the end of the 16-week open-label phase.

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) (%)
ESC	74.4	34.0

ESC = escitalopram 10 & 20 mg

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

Table 7

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

Relapse-prevention study (24-week double-blind phase)		n	Number of relapses	% relapsed
	PBO	157	81	51.59

ESC (10 or 20 mg) vs. PBO: * $p \leq 0.05$; ** $p \leq 0.001$

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; ESC = escitalopram 10 & 20 mg; PBO = placebo

INDICATIONS

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

CONTRAINDICATIONS

Hypersensitivity to citalopram, escitalopram and any excipients in the tablets (see **DESCRIPTION**).

Monoamine Oxidase Inhibitors

Escitalopram should not be used in combination with monoamine oxidase inhibitors (MAOI) or the reversible MAOI (RIMA), moclobemide, or within 14 days of discontinuing treatment with a MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. Similarly, at least 14 days should be allowed after stopping escitalopram before starting a MAOI or RIMA. 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 a MAOI (see **INTERACTIONS WITH OTHER MEDICINES).**

Pimozide

Concomitant use in patients taking pimozide is contraindicated (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.

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

Pooled analyses of 24 short-term (4 – 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 (4 trials) or other psychiatric disorders (4 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 (bupropion, 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 non-psychiatric. 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 or caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non-psychiatric) 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 escitalopram 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). Escitalopram 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), 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. Especially elderly patients seem to be a risk group.

Seizures

The drug should be discontinued in any patient who develops seizures. SSRIs should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. SSRIs should be discontinued if there is an increase in seizure frequency (see **PRECAUTIONS**, **Pre-Clinical Safety**).

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.

ECT (Electroconvulsive Therapy)

There is limited published clinical experience of concurrent administration of SSRIs and ECT, therefore caution is advised.

Effect on Ability to Drive and Use Machines

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.

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.

Hepatic Impairment

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 **PHARMACOLOGY, Pharmacokinetics** and **DOSAGE AND ADMINISTRATION**).

Renal Impairment

Escitalopram is extensively metabolised and excretion of unchanged drug in 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 < 20 mL/min) and escitalopram should be used with caution in such patients (see DOSAGE AND ADMINISTRATION).

Pre-Clinical Safety

High doses of escitalopram, which resulted in plasma C_{max} for escitalopram and metabolites at least 8-fold 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 experiences with citalopram and the clinical trial experience with escitalopram, do not indicate that these findings have a clinical correlate.

Effects on Fertility

No fertility studies were performed with escitalopram. However, other non-clinical studies suggest that the effects of escitalopram can be directly predicted from those of 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.

Newborns should be observed if maternal use of escitalopram continues into the later stages of pregnancy, particularly in the third trimester. If escitalopram is used until or shortly before birth, discontinuation effects in the newborn are possible. Abrupt discontinuation should be avoided during pregnancy.

Newborns exposed to escitalopram, other SSRIs (Selective Serotonin Reuptake Inhibitors) 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 (< 24 hours) after delivery.

Epidemiological studies have shown that the use of SSRIs (including escitalopram) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of persistent pulmonary hypertension of the newborn (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 than 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 post-implantation loss and reduced foetal weight at systemic exposure levels (based on AUC) ca. 11-fold that anticipated clinically, with no effects seen at 6-fold. No teratogenicity was evident in this study at relative systemic exposure levels of ca. 15 (based on AUC).

There were no peri/postnatal effects of escitalopram following oral dosing of pregnant rats (conception through to weaning) at systemic exposure levels (based on AUC) ca. 2-fold 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 ca. 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.

Use in Lactation

It is expected that escitalopram, like citalopram, will be excreted into human breast milk. Studies in nursing mothers have shown that the mean combined dose of citalopram and demethylcitalopram transmitted to infants via breast milk (expressed as a percentage of the weight-adjusted maternal dose) is 4.4–5.1% (below the notional 10% level of concern).

Plasma concentrations of these drugs in infants were very low or absent and there were no adverse effects. Whilst the citalopram data support the safety of use of escitalopram in breast-feeding women, the decision to breast-feed should always be made as an individual risk/benefit analysis.

Paediatric Use

The efficacy and safety of escitalopram has not been established in children and adolescents less than 18 years of age. Consequently, escitalopram should not be used in children and adolescents less than 18 years of age.

Use in the Elderly (> 65 years)

Escitalopram AUC and half-life were increased in subjects ≥ 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**).

Carcinogenicity

No carcinogenicity studies were performed with escitalopram. However, other non-clinical 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 80 mg/kg/day, respectively.

Genotoxicity

No genotoxicity studies were performed with escitalopram. However, other non-clinical 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.

INTERACTIONS WITH OTHER MEDICINES

MAOIs

Co-administration with MAO inhibitors 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.

Pimozide

Co-administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and C_{max} of pimozide, although not consistently

throughout the study. The co-administration of pimozide and citalopram resulted in a mean increase in the QTc interval of approximately 10 msec. 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

Co-administration 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].

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 isoenzyme 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 co-administration with ritonavir (CYP3A4 inhibitor). Furthermore, co-administration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of racemic citalopram.

Co-administration 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**).

Co-administration 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 judgement (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 co-administered 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.

Co-administration with desipramine (a CYP2D6 substrate) resulted in a two-fold increase in plasma levels of desipramine. Therefore, caution is advised when escitalopram and desipramine are co-administered. A similar increase in plasma levels of desipramine, after administration of imipramine, was seen when given together with racemic citalopram.

Co-administration with metoprolol (a CYP2D6 substrate) resulted in a two-fold increase in 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 co-administration 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 (NSAIDs, Aspirin, Warfarin, etc)

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 escitalopram.

Alcohol

The combination of SSRIs and alcohol is not advisable.

ADVERSE EFFECTS

Adverse reactions 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 below table indicate adverse reactions where incidence with escitalopram is statistically significantly different from placebo ($p < 0.05$).

SYSTEM ORGAN CLASS AND PREFERRED TERM	PLACEBO		ESCITALOPRAM	
	n	(%)	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	(6.3)	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)*

SYSTEM ORGAN CLASS AND PREFERRED TERM	PLACEBO		ESCITALOPRAM	
	n	(%)	n	(%)
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				
Palpitations	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 ≥ 5% in either the 10 mg or 20 mg escitalopram 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 10 mg escitalopram treated patients (66%) was similar to that of the placebo treated patients (61%), while the incidence rate in 20 mg/day escitalopram treated patients was greater (86%). Common adverse events that occurred in the 20 mg/day escitalopram group with an incidence approximately twice that of the 10 mg/day escitalopram group and approximately twice that of the placebo group are shown below.

Incidence of common adverse events* in patients with major depression receiving placebo, 10 mg/day escitalopram or 20 mg/day escitalopram			
ADVERSE EVENT	**PLACEBO (n = 311)**	**10 mg/day Escitalopram (n = 310)**	**20 mg/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 20 mg/day escitalopram group that was approximately twice that of the 10 mg/day escitalopram group and the placebo group.

Vital Sign Changes

Escitalopram and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure and diastolic blood pressure) and (2) 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 body weight.

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 refer to “Other Events Observed During the Pre-Marketing Evaluation of Escitalopram”.

Other Events Observed During the Pre-Marketing 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 escitalopram, 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, disequilibrium, 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.

Myo-, Endo- 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.

Special Senses Other, Disorders

Uncommon: dry eyes, eye irritation, taste alteration, taste perversion, visual disturbance, ear infection NOS, 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 inco-ordination).

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:	postural 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 Post-Marketing 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 3 patients (unless otherwise noted) and not described elsewhere in the **ADVERSE EFFECTS** section:

Stomatitis, drug interaction NOS, feeling abnormal, hypersensitivity NOS, non-accidental 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 pre-marketing 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.

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

Usually 2 – 4 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 6 months.

Obsessive-Compulsive Disorder

The recommended starting dose is 10 mg (one 10 mg tablet) once daily. Depending on individual patient response, the dose may be increased to 20 mg (one 20 mg 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 10 or 20 mg escitalopram 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 (> 65 years of age)

A longer half-life and a decreased clearance have been demonstrated in the elderly. 10 mg (one 10 mg tablet) is the recommended maximum maintenance dose in the elderly (see **PHARMACOLOGY, Pharmacokinetics** and **PRECAUTIONS**).

Paediatric Use

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**).

Hepatic Impairment

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

Renal Impairment

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 < 20 mL/min) (see **PRECAUTIONS**).

Poor Metabolisers of CYP2C19

For patients who are known to be poor metabolisers with respect to CYP2C19, an initial dose of 5 mg (half a 10 mg tablet) daily during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg (one 10 mg tablet) (see **PHARMACOLOGY**, **Pharmacokinetics** and **PRECAUTIONS, Interactions with Other Medicines**).

Discontinuation

Significant numbers of discontinuation symptoms may occur with abrupt discontinuation of escitalopram. To minimise discontinuation reactions, tapered discontinuation over a period of 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

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

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 800 mg 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 4,800 mg).

Symptoms

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), the cardiovascular system (hypotension, tachycardia, arrhythmia and ECG changes (including QT prolongation) and electrolyte/fluid balance conditions.

Treatment

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

APO-Escitalopram tablets are intended for oral administration.
Each tablet contains 10 mg or 20 mg escitalopram (as oxalate) as the active ingredient.

10 mg tablets: White to off-white, oval, biconvex, film-coated tablets with “C4” embossed on one side and a notch break-line on the other side.
Blister pack (PVC/PVdC/Al) of 28 tablets – AUST R 213721.

20 mg tablets: White to off-white oval, biconvex, film-coated tablets with “C3” embossed on one side and a notch break-line on the other side.
Blister pack (PVC/PVdC/Al) of 28 tablets – AUST R 213722.

* Not all strengths may be available.

Storage

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 –Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 11 July 2013

DATE OF MOST RECENT AMENDMENT: 03 December 2015