AUSTRALIAN PRODUCT INFORMATION

LOXALATE®

(escitalopram oxalate) tablets

1 NAME OF THE MEDICINE

Escitalopram oxalate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg, 10 mg or 20 mg of escitalopram (as oxalate) as the active ingredient.

Excipients with known effect: lactose and traces of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

LOXALATE (Escitalopram oxalate) 5 mg: 5.5 mm normal convex white film coated tablet debossed “EC” over 5 on one side and “G” on the other.

LOXALATE (Escitalopram oxalate) 10 mg: 9.5 mm x 5.5 mm oblong normal convex white film coated tablet debossed “EC/10” on one side and “G” on the other.

LOXALATE (Escitalopram oxalate) 20 mg: 12.5 mm x 7.5 mm oblong normal convex white film coated tablet debossed “EC/20” on one side and “G” on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of major depression.

Treatment of social anxiety disorder (social phobia).

Treatment of generalised anxiety disorder.

Treatment of obsessive-compulsive disorder.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

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

Major Depression

Usually 2 - 4 weeks are necessary for antidepressant response.

The recommended dose is 10 mg (one 10 mg tablet). 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.

When stopping SSRI therapy gradual dose reduction should be considered.

Social anxiety disorder

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. Social anxiety disorder is a disease with a chronic course and long-term treatment is therefore warranted to consolidate response and prevent relapse.

Generalised anxiety disorder

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. Generalised anxiety disorder is a disease with a chronic course and long-term treatment is therefore warranted to consolidate response and prevent relapse.

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 Section 5.2 PHARMACOKINETIC PROPERTIES and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reduced renal function

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 < 30 mL/min) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reduced hepatic function

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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 Section 5.2 PHARMACOKINETIC PROPERTIES and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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.

4.3 CONTRAINDICATIONS

Hypersensitivity to citalopram, escitalopram and any excipients in LOXALATE (see Section 6.1 LIST OF EXCIPIENTS).

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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Pimozide – Concomitant use in patients taking pimozide is contraindicated (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 to 16-week), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 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 (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 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 LOXALATE 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). SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

LOXALATE 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.

Serotonin syndrome

Caution is advisable if escitalopram is used concomitantly with medicinal products with serotonergic effects such as triptans (including sumatriptan), opioids (including tramadol), and tryptophan.

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

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 Section 5.3 PRECLINICAL SAFETY DATA).

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.

Sexual Dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs.

Angle-closure Glaucoma

Antidepressants including escitalopram may have an effect on pupil size resulting in mydriasis. This mydriatic effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma, especially in pre-disposed patients. Escitalopram should therefore be used with caution in patients with raised intraocular pressure and in those at risk of angle-closure glaucoma.

ECT (electroconvulsive therapy)

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 Section 4.2 DOSE AND METHOD OF 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.

Use in 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 Section 5.2 PHARMACOKINETIC PROPERTIES and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in 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 < 30 mL/min) and escitalopram should be used with caution in such patients (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the Elderly

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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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.

Effects on Laboratory Tests

See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

MAOIs

Coadministration with MAO inhibitors may cause serotonin syndrome (see Section 4.3 CONTRAINDICATIONS).

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 Section 4.3 CONTRAINDICATIONS).

Irreversible, selective MAO-B inhibitor (selegiline)

In combination with selegiline (irreversible MAO-B inhibitor), caution is required due to the risk of developing serotonin syndrome.

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 Cmax 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 Section 4.3 CONTRAINDICATIONS).

Serotonergic drugs

Co-administration with serotonergic drugs e.g. opioids (including tramadol), triptans (including 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 Poor metabolisers of CYP2C19 under Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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, fluconazole and ticlopidine) or cimetidine. A reduction in the dose of escitalopram may be necessary based on clinical judgement (see also Poor metabolisers of CYP2C19 under Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 twofold 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 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 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.

Haemorrhage

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 LOXALATE. Patients receiving oral anticoagulant therapy should receive careful coagulation monitoring when escitalopram is started or stopped (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Alcohol

The combination of SSRIs and alcohol is not advisable.

4.6 FERTILITY, PREGNANCY AND LACTATION

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

Pregnancy Category: C

Limited clinical data are available regarding exposure to escitalopram during pregnancy. SSRIs have had limited use in pregnancy without a reported increase in birth defects.

Neonates should be observed if maternal use of LOXALATE 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 (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Neonates exposed to LOXALATE, 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 SSRI's (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.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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 breastfeeding women, the decision to breast feed should always be made as an individual risk/benefit analysis.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Escitalopram does not impair intellectual function and psychomotor performance. However, adverse effects of escitalopram include visual disturbances (such as blurred vision) and dizziness which could affect the ability to drive or use machines (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

As with other psychoactive drugs, patients should be cautioned about their ability to drive a car and operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 the table below indicate adverse reactions where the incidence with escitalopram is statistically significantly different from placebo (P< 0.05).

System Organ Class & 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) *
dry mouth	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)

System Organ Class & Preferred Term	PLACEBO n (%)	ESCITALOPRAM n (%)
CENTRAL & 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) *

System Organ Class & Preferred Term	PLACEBO n (%)	ESCITALOPRAM n (%)
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 ≥ 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 groups and with an incidence rate in the 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 20 mg/day dose and 16.7 msec at the 60 mg/day dose of citalopram. The effect of escitalopram on the QT interval was similarly studied at doses of 10 mg/day and 30 mg/day. The change from baseline QTc (Fridericia correction) was 4.3 msec at the 10 mg/day dose and 10.7 msec with the above recommended dose of 30 mg/day. The QTc interval prolongation observed with 60 mg citalopram exceeded that observed with 30 mg escitalopram. It is probable that the R-enantiomer and its metabolites in racemic citalopram contribute to these effects.

Mydriasis and angle-closure glaucoma

Cases of mydriasis and angle-closure glaucoma have been reported in the post-marketing period (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 see Other Events Observed during the Premarketing Evaluation of escitalopram under Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

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 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 1/1000 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, tinnitus, otosalpingitis, ear disorder.

Heart Rate and Rhythm Disorders

Uncommon: bradycardia, tachycardia.

Liver and Biliary System Disorders

Uncommon: bilirubinaemia, hepatic enzymes increased.

Metabolic and Nutritional Disorders

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

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 & valve disorders

Uncommon: myocardial infarction, myocardial ischaemia, myocarditis, angina pectoris.

Neoplasm

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

Platelet, Bleeding & 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: flushing, cerebrovascular disorder, hot flushes [gs], ocular haemorrhage, peripheral ischaemia, vein disorder, varicose vein, vein distended.

Vision Disorders

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

White Cell and Reticuloendothelial System Disorder

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), hyperprolactinaemia (this event has been reported for the therapeutic class of SSRIs/SNRIs.).

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

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 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 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, suicidal ideation, suicidal behaviour, psychomotor restlessness, hepatitis.

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.

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. Postpartum haemorrhage has been reported for the therapeutic class of SSRIs/SNRIs (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Discontinuation symptoms seen when stopping treatment

Discontinuation of SSRIs/SNRIs (particularly when abrupt) commonly leads to discontinuation symptoms. 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 events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when escitalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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. Fatal cases of escitalopram overdose have rarely been reported with escitalopram alone; the majority of cases have involved overdose with concomitant medications. Doses between 400 and 800 mg of escitalopram alone have been taken without any severe symptoms.

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).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Biochemical and behavioural studies have shown that escitalopram is a potent inhibitor of serotonin (5-HT) - uptake (in vitro IC50 2nM).

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-HT1A, 5-HT2, DA D1 and DA D2 receptors, α1-, α2-, β-adrenoceptors, histamine H1, 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.

Clinical Trials

LOXALATE should not be used in the treatment of major depression, generalised anxiety disorder, social anxiety disorder and obsessive-compulsive in children and adolescents under the age of 18 years since the safety and efficacy in this population have not been established.

Major Depression

Two fixed-dose studies and one flexible-dose study has 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-Asberg 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 subgroups 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 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 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.

Generalised Anxiety Disorder (GAD)

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

The efficacy of escitalopram in the treatment of Generalised Anxiety Disorder was demonstrated in three 8-week placebo-controlled flexible-dose studies (10 to 20 mg per day) and one 12-week fixed-dose, active-reference (paroxetine 20 mg/day), study (5, 10 and 20 mg per day).

In the four studies, the mean HAM-A total scores at baseline ranged from 22.1 to 27.7 and the CGI-S scores were 4.2 or higher, indicating significant GAD symptomatology.

In all three placebo-controlled, flexible-dose studies, escitalopram was significantly better than placebo at endpoint on the primary efficacy measure (mean change from baseline to endpoint in HAM-A total score), and the results were supported by secondary efficacy measures.

In the fixed-dose study, over a 12-week period, escitalopram in doses of 10 and 20 mg/day was statistically significantly more effective than placebo on the primary measure of efficacy, with an effect size at least as high as that of the reference treatment paroxetine. The 5 mg dose of escitalopram was numerically, but not statistically significantly, superior to placebo. 10 mg escitalopram was statistically significantly superior to the reference treatment paroxetine (LOCF) based on the HAM-A and CGI-I.

Table 1

Study	Mean Treatment Difference in Change from Baseline in HAM-A Total Scores (LOCF) [95% CI]	
	8 weeks	**12 weeks**
Flexible-dose		
ESC to PBO	-1.6*[-3.2; -0.0]	-
Flexible-dose		
ESC to PBO	-1.48*[-2.83; -0.13]	-
Flexible-dose		
ESC to PBO	-3.49***[-4.93; -2.04]	-
Fixed-dose		
ESC5 to PBO	-	-1.29 [-3.13; 0.54]

Study	Mean Treatment Difference in Change from Baseline in HAM-A Total Scores (LOCF) [95% CI]	
	8 weeks	12 weeks
ESC10 to PBO	-	-2.56** [-4.40; -0.73]
ESC20 to PBO	-	-2.15* [-3.99; -0.31]
PAR20 to PBO	-	-0.51 [-2.33; 1.32]
ESC20 to PAR20	-	-1.65# [-3.49; 0.20]

*p≤0.05; **p≤0.01; ***p≤0.001; #p≤0.05 versus PAR

ESC = escitalopram; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PAR20 = paroxetine 20 mg; PBO = placebo

In the pooled analysis of these three placebo-controlled, flexible-dose studies of similar design, the mean change from baseline in HAM-A total score improved statistically significantly (LOCF) over time in the escitalopram group relative to the placebo group.

The separation from placebo was first observed at week 1 and continued through to the end of the study (week 8). The treatment difference to placebo at week 8 was –2.3 in favour of escitalopram (p≤0.01).

The results of the primary analysis (pooled data) were supported by secondary LOCF analyses (pooled data), where escitalopram was statistically significantly superior to placebo on the HAM-A psychic anxiety subscale score (p≤0.001), the HAM-A item 1 (anxious mood) score (p≤0.001), and the HAM-A item 2 (tension) score (p≤0.01). Escitalopram was also more effective than placebo on the CGI-S score (p≤0.01) and on the CGI-I score at week 8 (p≤0.001). The results on the HAD anxiety subscale, the HAM-A somatic subscale, the HAM-D anxiety scale, the Covi Anxiety Scale (OC), and the QoL (OC) also showed superior efficacy of escitalopram relative to placebo at week 8 (p≤0.05).

The long-term efficacy of escitalopram in the treatment of GAD is based on the results from the double-blind active comparator study, an open-label extension study and a double-blind, randomised, placebo-controlled relapse prevention study.

The active comparator study demonstrated numerically superior efficacy of escitalopram over paroxetine both on the primary efficacy measure (mean change from baseline in HAM-A total score) and on the secondary efficacy measures (mean change from baseline in HAM-A psychic anxiety, CGI-S, QoL, HAM-A somatic anxiety, HAM-A item 1 (anxious mood), HAM-A item 2 (tension), HAM-D anxiety and Covi scores, and mean CGI-I score) at week 24. For all but one (QoL) of the efficacy measures, a further improvement was seen from week 8 to week 24. In the primary efficacy analysis, the extra improvement in mean HAM-A total score over the last 16 weeks of treatment was 2.3 points for escitalopram compared with 1.6 points for paroxetine.

Further evidence of long-term efficacy is provided by an open-label extension study, which showed a beneficial effect of continued treatment with escitalopram. In this study, escitalopram treatment was associated with additional improvement beyond the response observed during the initial 8 weeks of treatment in the lead-in studies. The mean change in HAM-A total score from baseline (final visit of the lead-in study) to week 24 (LOCF) was -3.8, with greater improvement observed in patients who were switched from placebo in the lead-in study to escitalopram in the extension study (4.9 points versus 2.7 points for those previously treated with escitalopram). Similar positive results were seen in the analyses of secondary efficacy measures.

Escitalopram 20 mg/day significantly reduced the risk of relapse in a 24- to 76-week randomised continuation study in 373 patients who had responded during the initial 12-week open-label treatment.

Social Anxiety Disorder (SAD)

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

The efficacy of escitalopram in the treatment of SAD was demonstrated in three placebo-controlled clinical studies. A short-term, flexible-dose (10 to 20 mg/day) study, a long-term, fixed-dose (5, 10, and 20 mg/day), active-reference (paroxetine 20 mg/day) study, and a relapse prevention study.

Approximately two-thirds of patients in the studies were markedly or severely ill (score of 5 or 6 on the CGI-S) and one-third were moderately ill (score of 4 or less on the CGI-S). The mean baseline LSAS total score ranged from 92 to 96 in the three studies.

In the short-term, flexible-dose study, over a 12-week period, escitalopram was statistically significantly better than placebo on the primary, and almost all the secondary measures of efficacy (see Table 2).

In the placebo-controlled, active-reference study, escitalopram was effective both in the short- and in the long-term (see Table 2), with an effect size at least as high as that of the reference treatment paroxetine (escitalopram 20 mg/day was significantly superior to the reference treatment paroxetine 20 mg/day from week 16 and onwards (OC)). Thus, continued treatment with escitalopram improves treatment response. At week 24 of the study, all three doses of escitalopram also produced significant improvements in the LSAS subscale scores for fear/anxiety and avoidance, the CGI-I score (except for the 10 mg dose of escitalopram), the CGI-S score, and the SDS subscale scores for work, social life, and family life.

Table 2

Study	**Mean Treatment Difference in Change from Baseline in LSAS Total Scores (LOCF) [95% CI]**	
	12 weeks	**24 weeks**
Short-term, flexible-dose		
ESC to PBO	-7.29** [-12.37; -2.21]	-
Long-term, fixed-dose		
ESC5 to PBO	-9.18*** [-14.40; -3.95]	-10.46*** [-16.27; -4.66]
ESC10 to PBO	-5.07 **** [-10.32; 0.18]	-7.45** [-13.29; -1.62]
ESC20 to PBO	-10.31*** [-15.56; -5.06]	-15.09*** [-20.92; -9.25]
PAR20 to PBO	-9.83*** [-15.04; -4.61]	-11.82*** [-17.62; -6.03]
ESC20 to PAR20	-	-3.26 [-9.07; 2.54]

*p≤0.05; **p≤0.01; ***p≤0.001; ****p=0.059

ESC = escitalopram; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PAR20 = paroxetine 20 mg; PBO = placebo

The beneficial effect of long-term treatment with escitalopram was also reflected in the analyses of responders and remitters in this study. The analyses showed a further increase both in the proportion of responders and in the proportion of remitters from week 12 to week 24, especially in the escitalopram 20 mg group. At week 24, a statistically significantly greater proportion of responders and remitters were seen in all three escitalopram dose groups (except for the proportion of responders in the 10 mg group) than in the placebo group (p≤0.01) (see Tables 3 and 4).

Table 3

Long-term, fixed-dose study	**Responders (CGI-I ≤ 2) (LOCF) (%)**	
	12 weeks	**24 weeks**
PBO	41	50
ESC5	61***	67**

Long-term, fixed-dose study	Responders (CGI-I ≤ 2) (LOCF) (%)	
	12 weeks	24 weeks
ESC10	55*	58
ESC20	62***	70***
*p≤0.05; **p≤0.01; ***p≤0.001 ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo		

Table 4

Long-term, fixed-dose study	Remitters (CGI-S ≤ 2) (LOCF) (%)	
	12 weeks	24 weeks
PBO	13	19
ESC5	29***	39***
ESC10	24*	37***
ESC20	27**	46***
*p≤0.05; **p≤0.01; ***p≤0.001 ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo		

In the relapse prevention study, the primary efficacy analysis showed a statistically significantly superior effect of escitalopram relative to placebo on the time to relapse of SAD (log-rank test, p≤0.001). Furthermore, patients treated with escitalopram had fewer protocol-defined relapses than those treated with placebo. In addition, patients treated with escitalopram showed a further improvement in mean LSAS total score during the double-blind period, while patients treated with placebo showed deterioration. Escitalopram was also statistically significantly superior to placebo at week 24 on all the secondary efficacy measures in this study: the LSAS total score, the LSAS subscale scores for fear/anxiety and avoidance, the CGI-S score, and the SDS subscale scores for work, social life, and family life (p≤0.001).

Obsessive-Compulsive Disorder (OCD)

LOXALATE 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 5 and 6. In the short-term (12 weeks), 20 mg/day escitalopram separated from placebo on the Y-BOCS total score.

Table 5

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 6

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≤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 7

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 8 and 9.

Table 8

Long-term, 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≤0.01 ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo		

Table 9

Long-term, 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 10 for responder and remitter rates at the end of the 16-week open-label phase.

Table 10

Relapse prevention study (16-week open-label, flexible-dose phase) (Reduction of Y-BOCS ≥ 25%) (APTS I, LOCF)	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 11.

Table 11

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**
	PBO	157	81	51.59
ESC (10 or 20 mg) vs PBO: *p≤0.05; **p≤0.001 ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; ESC = escitalopram 10 & 20 mg; PBO = placebo				

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Data specific to escitalopram are unavailable. Absorption is expected to be almost complete and independent of food intake (mean Tmax 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 (Vd,β /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 (t½β) after multiple dosing is about 30 hours and the oral plasma clearance (Cloral) is about 0.6 L/min.

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 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 to 125 nmol/L) are achieved at a daily dose of 10 mg.

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.2 DOSE AND METHOD OF 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 < 30 mL/min).

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 Cmax 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, Cmax 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

5.3 5.3 PRECLINICAL SAFETY DATA

Preclinical Safety

High doses of escitalopram, which resulted in plasma Cmax, 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 experience with citalopram, and the clinical trial experience with escitalopram, do not indicate that these findings have a clinical correlate.

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.

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 80 mg/kg/day, respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet contains the following excipients – microcrystalline cellulose, colloidal anhydrous silica, purified talc, croscarmellose sodium, magnesium stearate. The coating on each tablet, Opadry White OY-LS-28908 (ID: 2596), contains lactose monohydrate.

6.2 INCOMPATIBILITIES

Refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 ºC. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

LOXALATE Tablets 5 mg (escitalopram oxalate equivalent to 5 mg of escitalopram)	supplied in PVC/PVDC/Al blister packs or HDPE bottles with PP child resistant closures of 28 and 30 tablets.
LOXALATE Tablets 10 mg (escitalopram oxalate equivalent to 10 mg of escitalopram)	supplied in PVC/PVDC/Al blister packs of 28 and 30 tablets. PP pails packs of 74,600 or 14,500 tablets*
LOXALATE Tablets 20 mg (escitalopram oxalate equivalent to 20 mg of escitalopram)	supplied in PVC/PVDC/Al blister packs of 28 and 30 tablets. PP pails packs of 37,300 or 7,000 tablets*

Some strengths, pack sizes and/or pack types may not be marketed.

* Bulk pack for dose administration to aid Packers

Australian Register of Therapeutic Goods (ARTG)

AUST R 119961 – LOXALATE escitalopram oxalate 5mg tablets blister packs

AUST R 119963 – LOXALATE escitalopram oxalate 5mg tablets bottles

AUST R 119964 – LOXALATE escitalopram oxalate 10mg tablets blister packs

AUST R 119966 – LOXALATE escitalopram oxalate 20mg tablets blister packs

AUST R 294580 – LOXALATE escitalopram oxalate 10mg tablets bulk pack

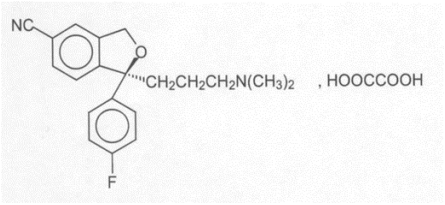
AUST R 294581 – LOXALATE escitalopram oxalate 20mg tablets bulk pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Molecular formula: C20H21 FN2O.C2H2O4
Molecular weight: 414.42

CAS Number

219861-08-2

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, sparingly soluble in ethanol and freely soluble in methanol. No polymorphic forms have been detected.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

22 May 2008 (LOXALATE 5 mg blister pack & bottle, LOXALATE 10 mg & 20 mg blister pack)

28 March 2018 (LOXALATE 10 mg & 20 mg bulk pack)

10 DATE OF REVISION

12/11/2025

Summary Table of Changes

Section Changed	Summary of New Information
2	Update to the allergen declaration
All	Minor editorial changes

LOXALATE® is a Viatris company trade mark

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