NEW ZEALAND DATA SHEET

LOXALATE®

1. Product Name

LOXALATE, 10 mg, 20 mg, film-coated tablets.

2. Qualitative and Quantitative Composition

Each tablet contains 10 mg or 20 mg of escitalopram.

Excipients with known effect: Microcrystalline Cellulose, Colloidal Silicon Dioxide, Opadry White.

Allergen declaration: Sulfites, Soya Bean Products and Lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Loxalate Tablets 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 Tablets 20 mg: 12.5 mm x 7 mm oblong normal convex white film coated tablet debossed "EC|20" on one side and "G" on the other.

The tablets can be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

Adults - 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

Dose

Adults

Major depression

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

Social anxiety disorder

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

Long-term treatment of patients responding to a 16-week open treatment phase has been studied for at least 24 weeks in patients receiving 10 or 20 mg 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.

Special populations

Elderly patients (> 65 years of age)

A longer half-life and a decreased clearance have been demonstrated in the elderly. 10 mg is the recommended maximum maintenance dose in the elderly (see section 4.4 and 5.2.)

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).

Reduced hepatic function

An initial dose of 5 mg 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).

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 < 20 mL/min) (see section 4.4).

Poor metabolisers of CYP2C19

For patients who are known to be poor metabolisers with respect to CYP2C19, an initial dose of 5mg daily during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg (see sections 5.2 and 4.5).

Discontinuation

Significant numbers of discontinuation symptoms may occur with abrupt discontinuation of escitalopram. To minimise 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.

Method of administration

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

4.3 Contraindications

Hypersensitivity to citalopram, escitalopram or to any of the excipients listed in section 6.1.

Monoamine oxidase inhibitors

Cases of serious reactions 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). Some cases presented with features resembling serotonin syndrome (see section 4.8).

Escitalopram should not be used in combination with a MAOI. Escitalopram may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 14 days should elapse after discontinuing escitalopram treatment before starting a MAOI or RIMA.

Concomitant use in patients taking pimozide is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

Warnings

Children and adolescents (under 18 years of age)

In clinical trials, adverse events related to suicidality (suicidal thoughts and suicidal behaviours) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in children and adolescents treated with SSRIs (and venlafaxine) compared to those treated with placebo.

Clinical worsening and suicide risk

Patients of any age with major depressive disorder may experience worsening of their depression and/or emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Patients should be closely monitored, especially at the beginning of therapy or when the dose is changed, until such improvement occurs.

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.

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients. The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any antidepressant. Therefore, 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. Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly.

Pooled analyses of short-term studies of antidepressant medications have 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.

The following symptoms have been reported in adult and paediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania. 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, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Mania and bipolar disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood 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. It should be noted that escitalopram is not approved for use in treating bipolar disorder.

QTc-prolongation and Torsade de Pointes

Escitalopram is associated with a dose-dependent increase in the QTc interval (see section 4.8). In addition, there have been cases of QTc interval prolongation and torsade de pointes reported during the post-marketing period, predominantly in patients with risk factors for QTc prolongation.

Escitalopram should be used with caution in patients with risk factors for QTc prolongation/TdP. Risk factors include congenital long QT syndrome, age > 65 years, female sex, structural heart disease/LV dysfunction, hypokalaemia and severe hypomagnesaemia, high plasma levels of escitalopram (e.g. higher doses, medical conditions such as hepatic or renal disease, or use of medicines that inhibit the metabolism of escitalopram), and the concomitant use of other QTc prolonging medicines (see section 4.5)

In high risk patients (i.e. congenital long QT syndrome, pre-existing QT prolongation or multiple risk factors), an ECG should be performed prior to starting treatment, at steady state, after dose increases or after starting any potentially interacting medicine. Electrolytes should be monitored periodically and any abnormalities should be corrected prior to starting escitalopram. An ECG should also be performed in all patients experiencing symptoms that could be indicative of an arrhythmia (e.g. dizziness, palpitations, syncope or new onset seizures).

Consideration should be given to stopping escitalopram treatment or reducing the dose if the QTc interval is > 500 ms or increases by > 60 ms.

Sexual dysfunction

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

Precautions

Information for patients and families

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

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 and section 4.8). 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.

Reversible cerebral vasoconstriction syndrome

Reversible cerebral vasoconstriction syndrome (thunderclap headache) has been associated with serotonergic agents such as SSRIs or triptans.

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), 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).

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.

Mydriasis

Mydriasis has been reported in association with SSRIs such as escitalopram. Therefore, caution should be used when prescribing escitalopram in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

ECT (electroconvulsive therapy)

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

Serotonin syndrome

Caution is advisable if escitalopram is used concomitantly with medicinal products with serotonergic effects as this may increase the risk of serotonin syndrome. This includes monoamine oxidase inhibitors (see section 4.3), sumatriptan or other triptans, tryptophan, and opioids for example pethidine, dextromethorphan, tramadol (see section 4.5). In rare cases serotonin syndrome has been reported in patients using SSRIs concomitantly with serotonergic medicinal products.

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).

If serotonin syndrome is suspected, a dose reduction or discontinuation of at least one of the serotonergic medicines being taken should be considered depending on the severity of the symptoms and symptomatic treatment initiated.

St. John's Wort

Concomitant use of SSRIs and herbal remedies containing St. John's Wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions (see section 4.5).

Bone fractures

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.

Alcohol

No pharmacodynamic or pharmacokinetic interactions are expected between escitalopram and alcohol. However, as with other psychotropic drugs patients should be advised to avoid alcohol use while taking escitalopram (see section 4.5).

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).

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.

Elderly patients (> 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 section 4.2).

Impaired hepatic function

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 4.2).

Impaired renal function

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 section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic Interactions

Contraindicated combinations

MAO inhibitors

Co-administration with MAO inhibitors may cause serotonin syndrome (see section 4.3).

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 noted at a low dose of pimozide, concomitant administration of escitalopram and pimozide is contraindicated (see section 4.3).

Combinations requiring precautions for use

Medicines that prolong the QT interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. Torsades de pointes) is increased with concomitant use of other medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QTc interval. ECG monitoring is recommended in patients on concomitant medicines that prolong the QTc interval (see section 4.4).

Serotonergic medicinal products, St John’s Wort

Co-administration with serotonergic drugs (e.g. opioids for example pethidine, dextromethorphan, tramadol or sumatriptan) may lead to an enhancement of serotonergic effects (see section 4.4). Similarly, *Hypericum perforatum* (St John’s Wort) should be avoided as adverse interactions have been reported with a range of drugs including antidepressants.

Lithium, 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.

Medicinal products lowering the seizure threshold

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

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).

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.

Pharmacokinetic Interactions

Effects of other medicinal products on the pharmacokinetics of escitalopram

The metabolism of escitalopram is mainly mediated by CYP2C19. CYP3A4 and CYP2D6 may also contribute to the metabolism although to a smaller extent. The metabolism of the major metabolite SDCT (demethylated escitalopram) seems to be partly catalysed by CYP2D6.

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 (single dose) 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 Poor metabolisers of CYP2C19 under section 4.2).

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 Poor metabolisers of CYP2C19 under section 4.2).

Effects of escitalopram on the pharmacokinetics of other medicinal products

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 nortryptyline 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.

In vitro studies have demonstrated that escitalopram may also cause weak inhibition of CYP2C19. Caution is recommended with concomitant use of medicinal products that are metabolised by CYP2C19.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C.

Animal studies have shown reproductive toxicity (see Section 5.3).

Escitalopram should be used during pregnancy only if clearly needed and only after careful consideration of the risk/benefit, taking into account the risks of untreated depression.

For escitalopram, only limited clinical data are available regarding exposed pregnancies.

In an embryo-foetal development toxicity study in rats, reduced body weight and minor delays in foetal ossification were noted at maternotoxic doses at which the systemic exposure in terms of AUC was ~ 11-fold greater than would be obtained in humans in a clinical setting. These effects were not seen when the AUC was ~ 6-fold greater, and no teratogenicity was evident when the AUC was ~ 15-fold greater. However, epidemiological studies have suggested that the use of some SSRIs and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) during pregnancy is associated with an increased risk of congenital abnormalities. The relevance for escitalopram remains unknown.

There were no peri- or postnatal effects following the dosing of pregnant rats (conception through to weaning) where the systemic exposure levels (based on AUC) were approximately twice that of those expected clinically. However, the number of still births was increased and the size, weight and postnatal survival of offspring were decreased when the systemic exposure level (AUC) was ~ 5-fold greater than the expected clinical level.

Neonates should be observed if maternal use of escitalopram continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

Neonates exposed to escitalopram, other SSRIs, or SNRIs 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 data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

Epideomiological data also have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the new born (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

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 and section 4.8).

Breastfeeding

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 breastfeed should always be made as an individual risk/benefit analysis.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

4.7 Effects 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.

4.8 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 and Preferred Term	**Placebo n (%)**	**Escitalopram n (%)**
Patients Treated	1795	2632
Patients with Treatment Emergent Adverse Event	1135 (63.2)	1891 (71.8)
GASTROINTESTINAL SYSTEM DISORDERS		
nausea	151 (8.4)	481 (18.3)*
diarrhoea	91 (5.1)	207 (7.9)*
mouth dry	74 (4.1)	152 (5.8)*
dyspepsia	30 (1.7)	33 (1.3)
constipation	42 (2.3)	71 (2.7)
abdominal pain	47 (2.6)	68 (2.6)
vomiting	29 (1.6)	54 (2.1)
flatulence	15 (0.8)	31 (1.2)
CENTRAL and PERIPHERAL NERVOUS SYSTEM DISORDERS		
headache	305 (17.0)	506 (19.2)
dizziness	64 (3.6)	147 (5.6)*
paraesthesia	13 (0.7)	35 (1.3)
migraine	17 (0.9)	23 (0.8)
tremor	15 (0.8)	33 (1.3)
PSYCHIATRIC DISORDERS		
insomnia	82 (4.6)	245 (9.3)*
somnolence	62 (3.5)	217 (8.2)*
anorexia	12 (0.7)	56 (2.1)*
libido decreased	21 (1.2)	102 (3.9)*
anxiety	44 (2.5)	77 (2.9)
appetite decreased	8 (0.5)	35 (1.3)*
agitation	6 (0.3)	33 (1.3)*

System Organ Class and Preferred Term	Placebo n (%)	Escitalopram n (%)
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, GENERAL		
hypertension	24 (1.3)	13 (0.5)
HEART RATE AND RHYTHM DISORDERS		
palpitations	15 (0.8)	30 (1.1)
SECONDARY TERMS		
inflicted 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 rate of adverse events in 10mg 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 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

Electrocardiograms from escitalopram, racemic citalopram, and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically relevant changes in pulse rate for any one treatment group.

Cases of QT prolongation have been reported during the post-marketing period, predominantly in patients with pre-existing cardiac disease. In a double-blind, placebo-controlled study in healthy subjects, the change from baseline QTc (Fridericia correction) was 4.3 msec at the 10 mg/day dose and 10.7 msec at 30 mg/day/dose.

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”.

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 Undesirable 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, oedema, peripheral oedema, rigors, malaise, syncope, chest pain, chest tightness, fever, hernia, scar, carpal tunnel syndrome, oedema of extremities, limb pain, leg pain, neck pain.

Cardiovascular disorders, general

Uncommon: hypertension aggravated, hypotension, abnormal ECG.

Central and peripheral nervous system disorders

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

Gastrointestinal system disorders

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

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

Myo-, endo-, pericardial and valve disorders

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

Neoplasm

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

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

Red blood cell disorders

Uncommon: anaemia hypochromic, anaemia.

Reproductive disorders / female

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

Reproductive disorders / male

Uncommon: ejaculation delayed, prostatic disorder.

Resistance mechanism disorders

Uncommon: infection fungal, moniliasis genital, abscess, infection, viral infection, herpes zoster, herpes simplex, infection bacterial, infection parasitic, infection (tuberculosis), moniliasis, otitis media.

Respiratory system disorders

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

Skin and appendages disorders

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

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: taste perversion, dry eyes, eye irritation, visual disturbance, ear infection NOS, taste alteration, vision blurred.

Urinary system disorders

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

Vascular (extracardiac) disorders

Uncommon: flushing, hot flush [gs], cerebrovascular disorder, 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, vision 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, 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 Undesirable effects section: stomatitis, drug interaction NOS, feeling abnormal, hypersensitivity NOS, non-accidental overdose, injury NOS.

The following cardiac disorders have been reported post-marketing: cardiac arrest, electrocardiogram QTc prolonged, ventricular arrhythmia, Torsades de Pointes, ventricular tachycardia.

Postpartum haemorrhage has been reported for the therapeutic class of SSRIs/SNRIs (see section 4.4 and section 4.6).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

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. 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 (hypokalaemia, hyponatraemia).

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 further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, selective serotonin reuptake inhibitors.

ATC code: N06AB10

Mechanism of action

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

Clinical trials

Major depression

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 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 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.

Generalised anxiety disorder (GAD)

The efficacy of escitalopram in the treatment of Generalised Anxiety Disorder (GAD) was demonstrated in four placebo-controlled studies one fixed-dose study (5, 10, and 20 mg/day) and three flexible-dose studies (10 to 20 mg/day).

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.

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. The treatment difference to placebo at week 8 in the individual studies was: -9.6, -9.2, and -11.3, respectively, in favour of escitalopram ($p \leq 0.05$).

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 ($p \leq 0.01$).

The results of the primary analysis (pooled data) was supported by secondary LOCF analyses (pooled data), where escitalopram was statistically significantly superior to placebo on the HAM-A psychic anxiety subscale score ($p \leq 0.001$), the HAM-A item 1 (anxious mood) score ($p \leq 0.001$), and the HAM-A item 2 (tension) score ($p \leq 0.01$). Escitalopram was also more effective than placebo on the CGI-S score ($p \leq 0.01$) and on the CGI-I score at week 8 ($p \leq 0.001$). 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 ($p \leq 0.05$).

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

Social anxiety disorder (SAD)

The efficacy of escitalopram in the treatment of Social Anxiety Disorder (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) study, and relapse prevention study.

In the short term, over a 12-week period, escitalopram was statistically significantly better than placebo on the primary, and almost all the secondary measures of efficacy.

The long-term efficacy of escitalopram in the treatment of SAD is based on the results from a placebo-controlled, fixed-dose active-reference study (paroxetine) and a relapse prevention study.

In the placebo-controlled, active-reference study, escitalopram was effective both in the short- and in the long-term, with an effect size at least as high as that of the reference treatment paroxetine.

The treatment difference to placebo at 12 weeks on the primary measure of efficacy (mean change from baseline in LSAS total score, LOCF) was: -9.2 (5 mg) ($p < 0.001$), -5.1 (10 mg) ($p = 0.059$), and -10.3 (20 mg) ($p < 0.001$). A further improvement in mean LSAS total score was seen from week 12 to 24, where superior efficacy relative to placebo was seen for all three doses of escitalopram. In the LOCF analysis, the extra improvement in mean LSAS total score over the last 12 weeks of treatment was 9.3 (20 mg), 7.0 (10 mg) and 5.9 (5 mg) points for escitalopram, compared with 6.6 points for paroxetine and 4.6 points for placebo. 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.

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 ($p \leq 0.01$).

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, $p \leq 0.001$). 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 ($p \leq 0.001$).

Obsessive-compulsive disorder (OCD)

In the short-term (12 weeks), 20 mg/day escitalopram separated from placebo on the Y-BOCS total score and the Y-BOCS subscales scores of obsessions and rituals, and also on the NIMH-OCS total score. In the observed cases analysis, both 10 mg/day ($p = 0.005$) and 20 mg/day ($p < 0.001$) escitalopram were effective.

The long-term maintenance effect has been demonstrated in two studies; a 24 weeks placebo-controlled, dose-finding study and a 16 weeks placebo-controlled, relapse prevention study.

In the 24-week, placebo-controlled, dose-finding study, both 10 mg/day ($p < 0.05$) and 20 mg/day ($p < 0.01$) escitalopram were significantly more effective than placebo, as measured by the primary outcome measure, the Y-BOCS total, as well as on the secondary subscales of the Y-BOCS obsessions and rituals, and the NIMH-OCS (10 mg/day ($p < 0.01$) and 20 mg/day ($p < 0.001$) escitalopram).

Maintenance of efficacy and prevention of relapse was demonstrated for 10 and 20 mg/day escitalopram in patients who responded to escitalopram in a 16-week open treatment phase and who were entering a 24-week (double-blind placebo-controlled randomized) relapse prevention trial. In the observed relapse prevention trial, both 10 mg/day ($p = 0.014$) and 20 mg/day ($p < 0.001$) escitalopram showed significantly fewer relapses.

A significant and beneficial effect of escitalopram on quality of life was observed (as assessed by the SF-36 and SDS) in the OCD studies with escitalopram.

5.2 Pharmacokinetic properties

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%.

Biotransformation

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.

Elimination

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 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.

Linearity

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 sections 4.4 and 4.2).

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 < 20 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 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 section 4.2).

Clinical Trials

Major depression

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 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 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.

5.3 Preclinical safety data

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.

Carcinogenicity, mutagenicity and impairment of fertility

No carcinogenicity, mutagenicity or impairment of fertility studies were performed with escitalopram. However, other preclinical 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.

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

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 at exposure well in excess of human exposure. No animal data related to this aspect are available for escitalopram.

Animal data indicate some SSRIs may affect sperm quality. Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

6. Pharmaceutical Particulars

6.1 List of excipients

Loxalate tablets contain

In the tablet core:

- colloidal silicon dioxide
- croscarmellose sodium
- microcrystalline cellulose
- purified talc
- magnesium stearate

In the tablet coating

- hypromellose
- titanium dioxide
- lactose
- macgrol 4000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Blister pack PVC/PVDC/Alu blister tray. Pack-sizes of 28 and 84 film-coated tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. Medicines Schedule

Prescription Medicine.

8. Sponsor Details

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9. Date of First Approval

06 May 2010

10. Date of Revision of the Text

19 October 2023

Summary table of changes

Section	Summary of new information
2	Allergen information moved from section 6.1 to section 2.
4.1	Expansion of indication to treatment of social anxiety disorder, generalised anxiety disorder and obsessive-compulsive disorder.
4.2	Dosage added for additional indications.
4.4	Information on bone fractures moved from section 4.8 to 4.4.
4.8	Hyperprolactinemia associated with SSRIs/SNRIs.
5.1	Added section on clinical trials

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