For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only.

PRESCRIBING INFORMATION

DEPRILEPT TABLETS (10/20 mg)

(Escitalopram Oxalate Tablets 10mg/20mg)

COMPOSITION

DEPRILEPT TABLETS 10 mg
Each film coated tablet contains
Escitalopram oxalate 12.78 mg
equivalent to Escitalopram ..... 10 mg
Inactive components:

DEPRILEPT TABLETS 20 mg
Each film coated tablet contains
Escitalopram oxalate 25.55 mg
equivalent to Escitalopram ..... 20 mg

Inactive components:
Microcrystalline Cellulose (PH101, Lactose Monohydrate, Copovidone (Plasdone-S-630), Maize Starch (Purity 21), Purified water, Silicified MCC (Prosolv SMCC 90), Croscarmellose Sodium (AC-DI-SOL), Purified Talc, Colloidal anhydrous silica, Magnesium stearate, Opadry White OY-S-58910

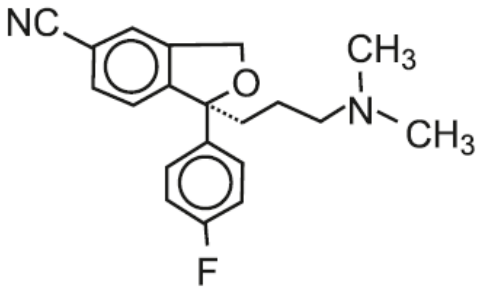
PRODUCT DESCRIPTION

DEPRILEPT TABLETS 10 mg
White to off white oval biconvex film coated tablets debossed with 'E' and '8' on either side of the eye breakline on one side and plain on the other side.

DEPRILEPT TABLETS 20 mg
White to off white oval biconvex film coated tablets debossed with 'E' and '9' on either side of the eye breakline on one side and plain on the other side.

DESCRIPTION

DEPRILEPT contain escitalopram oxalate, which is an orally administered selective serotonin reuptake inhibitor (SSRI). Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Escitalopram oxalate is designated S-(+)-1[3-(dimethyl-amino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile oxalate with the following structural formula.



$\bullet C_2H_2O_4$

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacotherapeutic group: antidepressants, selective serotonin reuptake inhibitors ATC-code: N 06 AB 10

Pharmacodynamics

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000-fold lower affinity.

Escitalopram has no or low affinity for a number of receptors including 5-HT_{1A}, 5-HT_2, DA D_1 and D_2 receptors, α_1, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors.

The inhibition of 5-HT re-uptake is the only likely mechanism of action explaining the pharmacological and clinical effects of escitalopram.

Pharmacokinetics

Absorption is almost complete and independent of food intake. Mean time to maximum concentration (mean T_{max}) is 4 hours after multiple dosing. As with racemic citalopram, the absolute bio-availability of escitalopram is expected to be about 80%.

The apparent volume of distribution ($V_{d,\beta}/F$) after oral administration is about 12 to 26 L/kg. The plasma protein binding is below 80% for escitalopram and its main metabolites.

Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Both of these are pharmacologically active. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent substance and metabolites are partly excreted as glucuronides. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28-31% and <5%, respectively, of the escitalopram concentration. Biotransformation of escitalopram to the demethylated metabolite is mediated primarily by CYP2C19. Some contribution by the enzymes CYP3A4 and CYP2D6 is possible.

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. The major metabolites have a significantly longer half-life. Escitalopram and

major metabolites are assumed to be eliminated by both the hepatic (metabolic) and the renal routes, with the major part of the dose excreted as metabolites in the urine.

There is linear pharmacokinetics. 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.

Elderly patients (> 65 years)
Escitalopram appears to be eliminated more slowly in elderly patients compared to younger patients. Systemic exposure (AUC) is about 50 % higher in elderly compared to young healthy volunteers (see DOSE AND METHOD OF ADMINISTRATION).

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 DOSE AND METHOD OF ADMINISTRATION).

Reduced renal function
With racemic citalopram, a longer half-life and a minor increase in exposure have been observed in patients with reduced kidney function (CLcr 10-53 ml/min). Plasma concentrations of the metabolites have not been studied, but they may be elevated (see DOSE AND METHOD OF ADMINISTRATION).
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 DOSE AND METHOD OF ADMINISTRATION).

INDICATIONS

- Treatment of major depressive episodes.
- Treatment of panic disorder with or without agoraphobia.
- Treatment of social anxiety disorder (social phobia).

DOSE AND METHOD OF ADMINISTRATION

Safety of daily doses above 20 mg has not been demonstrated.

DEPRILEPT TABLETS are administered as a single daily dose and may be taken with or without food.

Major depressive episodes
Usual dosage 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 to obtain antidepressant response. After the symptoms resolve, treatment for at least 6 months is required for consolidation of the response.

Panic disorder with or without agoraphobia

An initial dose of 5 mg is recommended for the first week before increasing the dose to 10 mg daily. The dose may be further increased, up to a maximum of 20 mg daily, dependent on individual patient response.

Maximum effectiveness is reached after about 3 months. The treatment lasts several months.

Social anxiety disorder
Usual dosage is 10 mg once daily. Usually 2-4 weeks are necessary to obtain symptom relief. The dose may subsequently, depending on individual patient response, be decreased to 5 mg or increased to a maximum of 20 mg daily.

Social anxiety disorder is a disease with a chronic course, and treatment for 12 weeks is recommended to consolidate response. Long-term treatment of responders has been studied for 6 months and can be considered on an individual basis to prevent relapse; treatment benefits should be re-evaluated at regular intervals.
Social anxiety disorder is a well-defined diagnostic terminology of a specific disorder, which should not be confounded with excessive shyness. Pharmacotherapy is only indicated if the disorder interferes significantly with professional and social activities.

The place of this treatment compared to cognitive behavioural therapy has not been assessed.

Pharmacotherapy is part of an overall therapeutic strategy.

Elderly patients (> 65 years of age)
Initial dosage is 5 mg once daily. Depending on individual patient response the dose may be increased to 10 mg daily (see PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES).

The efficacy of escitalopram in social anxiety disorder has not been studied in elderly patients.

Children and adolescents (<18 years)
Escitalopram should not be used in the treatment of children and adolescents under the age of 18 years (see WARNINGS AND PRECAUTIONS).

Reduced renal function
Dosage adjustment is not necessary in patients with mild or moderate renal impairment. Caution is advised in patients with severely reduced renal function (CL_{CR} < 30 ml/min) [see PHARMACODYNAMIC AND C R PHARMACOKINETIC PROPERTIES].

Reduced hepatic function
An initial dose of 5 mg daily for the first two weeks of treatment is recommended in patients with mild or moderate hepatic impairment. Depending on individual patient response, the dose may be increased to 10 mg daily. Caution and extra careful dose titration is advised in patients with severely reduced hepatic function (see PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES).

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

Discontinuation symptoms seen when stopping treatment
Abrupt discontinuation should be avoided. When stopping treatment with escitalopram the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of discontinuation symptoms (see WARNINGS AND PRECAUTIONS and SIDE EFFECTS/UNDESIRABLE EFFECTS). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate

CONTRAINDICATIONS

- Hypersensitivity to escitalopram or to any of the excipients present in the formulation.
- Concomitant treatment with non-selective, irreversible monoamine oxidase inhibitors (MAO-inhibitors) is contraindicated due to the risk of serotonin syndrome with agitation, tremor, hyperthermia etc (see DRUG INTERACTIONS).
- The combination of escitalopram with reversible MAO-A inhibitors (e.g. moclobemide) or the reversible non-selective MAO inhibitor linezolid is contraindicated due to the risk of onset of a serotonin syndrome (see DRUG INTERACTIONS).
- Escitalopram is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome.
- Escitalopram is contraindicated together with medicinal products that are known to prolong the QT interval (see DRUG INTERACTIONS).
- Concomitant use in patients taking pimozide is contraindicated.

WARNINGS AND PRECAUTIONS

The following special warnings and precautions apply to the therapeutic class of SSRIs (Selective Serotonin Re-uptake Inhibitors).

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

Paradoxical anxiety
Some patients with panic disorder may experience increased anxiety symptoms at the beginning of treatment with antidepressants. This paradoxical reaction usually subsides within two weeks during continued treatment. A low starting dose is advised to reduce the likelihood of an anxiogenic effect.

Seizures
Escitalopram should be discontinued if a patient develops seizures for the first time, or if there is an increase in seizure frequency (in patients with a previous diagnosis of epilepsy). SSRIs should be avoided in patients with unstable epilepsy, and patients with controlled epilepsy should be closely monitored.

Mania

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.

Diabetes
In patients with diabetes, treatment with an SSRI may alter glycaemic control (hypoglycaemia or hyperglycaemia). Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

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

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. An increased risk of suicidal behaviour with antidepressants has been reported in young adults. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes.

Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Screening patients for bipolar disorder
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 may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms 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. It should be noted that escitalopram is not approved for use in treating bipolar depression.

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.

Hyponatraemia
Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported rarely with the use of SSRIs and generally resolves on discontinuation of therapy. 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.

Haemorrhage
There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, with 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) and in patients with known bleeding tendencies.

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

Serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions
Caution is advisable if escitalopram is used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan.

In rare cases, serotonin syndrome has been reported in patients using SSRIs concomitantly with serotonergic medicinal products. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs treatment with the SSRI and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment initiated.

Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

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 DRUG INTERACTIONS).

Discontinuation symptoms seen when stopping treatment
Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt (see SIDE EFFECTS/UNDESIRABLE EFFECTS).

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 DOSE AND METHOD OF ADMINISTRATION).

Coronary heart disease
Due to limited clinical experience, caution is advised in patients with coronary heart disease (see CONTRAINDICATIONS).

QT interval prolongation
Escitalopram has been found to cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases (see DRUG INTERACTIONS, SIDE EFFECTS/UNDESIRABLE EFFECTS and OVERDOSE).

Caution is advised in patients with significant bradycardia; or in patients with recent acute myocardial infarction or uncompensated heart failure. Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant arrhythmias and should be corrected before treatment with escitalopram is started.

If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.

If signs of cardiac arrhythmia occur during treatment with escitalopram, the treatment should be withdrawn and an ECG should be performed.

Reversible selective MAO-A inhibitors
The combination of escitalopram with MAO-A inhibitors is generally not recommended due to the risk of onset of a serotonin syndrome (see DRUG INTERACTIONS).

Use in patients with concomitant illness
Clinical experience with escitalopram in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using escitalopram in patients with diseases or conditions that produce altered metabolism or haemodynamic responses.

Escitalopram has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease.

Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. It should be used with caution in the patients with severe renal impairment (see DOSE AND METHOD OF ADMINISTRATION).

Potential for interaction with monoamine oxidase inhibitors
In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.

Furthermore, there is limited information on the effects of combined use of SSRIs and MAOIs in animal suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioural excitation. Therefore, it is recommended that escitalopram should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping escitalopram before starting an MAOI.

Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible nonselective MAOI.

Effects on ability to drive and use machines
Although escitalopram has been shown not to affect intellectual function or psychomotor performance, any psychoactive medicinal product may impair judgement or skills. Patients should be cautioned about the potential risk of an influence on their ability to drive a car and operate machinery.

Suicidality in Children and Adolescents

- Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in
- children and adolescents with major depressive disorder (MDD) and other
- psychiatric disorders
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- The indication(s) approved in paediatric for the particular drug should be clearly stated / included

DRUG INTERACTIONS

Pharmacodynamic interactions

Contraindicated combinations:

Irreversible non-selective MAOIs
Cases of serious reactions have been reported in patients receiving an SSRI in combination with a non-selective, irreversible monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued SSRI treatment and have been started on such MAOI treatment (see CONTRAINDICATIONS). In some cases, the patient developed serotonin syndrome (see SIDE EFFECTS/UNDESIRABLE EFFECTS).

Escitalopram is contraindicated in combination with non-selective, irreversible MAOIs. Escitalopram may be started 14 days after discontinuing treatment with an irreversible MAOI. At least 7 days should elapse after discontinuing escitalopram treatment, before starting a non-selective, irreversible MAOI.

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

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

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

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

Combinations requiring precautions for use:

Serotonergic medicinal products
Co-administration with serotonergic medicinal products (e.g. tramadol, sumatriptan and other triptans) may lead to serotonin syndrome.

Medicinal products 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 and butyrophenones), mefloquin, bupropion and tramadol).

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

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 WARNINGS AND PRECAUTIONS).

Haemorrhage
Altered anti-coagulant effects may occur when escitalopram is combined with oral anticoagulants. Patients receiving oral anticoagulant therapy should receive careful coagulation monitoring when escitalopram is started or stopped. Concomitant use of non-steriodal anti-inflammatory drugs (NSAIDs) may increase bleeding-tendency (see WARNINGS AND PRECAUTIONS).

Alcohol
No pharmacodynamic or pharmacokinetic interactions are expected between escitalopram and alcohol. However, as with other psychotropic medicinal products, the combination with alcohol is not advisable.

Drugs that interfere with haemostasis (NSAIDs, Aspirin, Warfarin, etc.)

Serotonin release by platelets plays an important role in haemostasis. An association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when escitalopram is initiated or discontinued.

Electroconvulsive Therapy (ECT)
There are no clinical studies of the combined use of ECT and escitalopram.

Pharmacokinetic interactions

Influence 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 S-DCT (demethylated escitalopram) seems to be partly catalysed by CYP2D6.

Co-administration of escitalopram with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in moderate (approximately 50%) increase in the plasma concentrations of escitalopram.

Co-administration of escitalopram with cimetidine 400 mg twice daily (moderately potent general enzyme-inhibitor) resulted in a moderate (approximately 70%) increase in the plasma concentrations of escitalopram. Caution is advised when administering escitalopram in combination with cimetidine. Dose adjustment may be warranted.

Thus, caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction in the dose of escitalopram may be necessary based on monitoring of side-effects during concomitant treatment.

Effect 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 nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.

Co-administration with desipramine or metoprolol resulted in both cases in a two fold increase in the plasma levels of these two CYP2D6 substrates.

It has been reported that escitalopram may also cause weak inhibition of CYP2C19 (*in vitro*). Caution is recommended with concomitant use of medicinal products that are metabolised by CYP2C19.

Digoxin
In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

Theophylline

Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.

Warfarin

Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.

Carbamazepine

Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered.

Triazolam

Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam

Ketoconazole

Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C and AUC of max ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

Ritonavir

Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram.

SIDE EFFECTS/UNDESIRABLE EFFECTS

Adverse reactions are most frequent during the first or second week of treatment and usually decrease in intensity and frequency with continued treatment.

Tabulated list of adverse reactions

Adverse reactions known for SSRIs and also reported for escitalopram are listed below by system organ class and frequency.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to<1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), or not known (cannot be estimated from the available data).

System organ class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Not known	Thrombocytopenia
Immune system	Rare	Anaphylactic reaction

System organ class	Frequency	Undesirable Effect
disorders		
Endocrine disorders	Not known	Inappropriate ADH secretion
Metabolism and nutrition disorders	Common	Decreased appetite, increased appetite, weight increased
	Uncommon	Weight decreased
	Not known	Hyponatraemia, anorexia[2]
Psychiatric disorders	Common	Anxiety, restlessness, abnormal dreams Female and male: libido decreased Female: anorgasmia
	Uncommon	Bruxism, agitation, nervousness, panic attack, confusional state
	Rare	Aggression, depersonalisation, hallucination
	Not known	Mania, suicidal ideation, suicidal behaviour[1]
Nervous system disorders	Common	Insomnia, somnolence, dizziness, paraesthesia, tremor
	Uncommon	Taste disturbance, sleep disorder, syncope
	Rare	Serotonin syndrome
	Not known	Dyskinesia, movement disorder, convulsion, psychomotor restlessness/ akathisia[2]
Eye disorders	Uncommon	Mydriasis, visual disturbance
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Tachycardia
	Rare	Bradycardia
	Not known	Electrocardiogram QT prolonged Ventricular arrhythmia including torsade de pointes
Vascular disorders	Not known	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Sinusitis, yawning
	Uncommon	Epistaxis
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea, constipation,

System organ class	Frequency	Undesirable Effect
		vomiting, dry mouth
	Uncommon	Gastrointestinal haemorrhages (including rectal haemorrhage)
Hepatobiliary disorders	Not known	Hepatitis, liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Sweating increased
	Uncommon	Urticaria, alopecia, rash, pruritus
	Not known	Ecchymosis, angioedemas
Musculoskeletal and connective tissue disorders	Common	Arthralgia, myalgia
Renal and urinary disorders	Not known	Urinary retention
Reproductive system and breast disorders	Common	Male: ejaculation disorder, impotence
	Uncommon	Female: metrorrhagia, menorrhagia
	Not known	Galactorrhoea Male: priapism
General disorders and administration site conditions	Common	Fatigue, pyrexia
	Uncommon	Oedema

[1]Cases of suicidal ideation and suicidal behaviours have been reported during escitalopram therapy or early after treatment discontinuation (see WARNINGS AND PRECAUTIONS).
[2]These events have been reported for the therapeutic class of SSRIs.

Class effects
An increased risk of bone fractures in patients receiving SSRIs and TCAs has been reported in epidemiological literature, mainly in patients 50 years of age and older. The mechanism leading to this risk is unknown.

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 DOSE AND METHOD OF ADMINISTRATION and WARNINGS AND PRECAUTIONS).

QT interval prolongation
Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported during the postmarketing period, predominantly in patients of female gender, with

hypokalaemia, or with preexisting QT interval prolongation or other cardiac diseases (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS and OVERDOSE).

In addition to the adverse events presented above, following adverse events have been reported with escitalopram.

Gastrointestinal disorders – indigestion, abdominal pain, abdominal cramp, flatulence, toothache, heartburn, gastroenteritis, dysphagia, gastroesophageal reflux, pancreatitis.

Reproductive disorders/female - menstrual cramps, menstrual disorder.

Respiratory, thoracic and mediastinal disorders - bronchitis, coughing, nasal congestion, sinus congestion, sinus headache, dyspnea, pulmonary embolism, pulmonary hypertension of the newborn.

Blood and lymphatic system disorders: anaemia, agranulocytis, aplastic anaemia, haemolytic anaemia, idiopathic thrombocytopenia purpura, leukopenia.

Cardiac disorders: atrial fibrillation, cardiac failure, myocardial infarction.

Ear and labyrinth disorders: vertigo

Endocrine disorders: diabetes mellitus, hyperprolactinaemia.

Eye disorders: diplopia, glaucoma.

General disorders and administration site conditions: abnormal gait, asthenia, fall, feeling abnormal, malaise, allergy, chest pain, fever, hot flushes, pain in limb, influenza-like symptoms.

Hepatobiliary disorders: fulminant hepatitis, hepatic failure, hepatic necrosis.

Immune system disorders: allergic reaction.

Metabolism and nutrition disorders: hyperglycaemia, hypoglycaemia.

Musculoskeletal and connective tissue disorders: muscle cramp, muscle stiffness, muscle weakness, rhabdomyolysis, jaw stiffness, neck/shoulder pain.

Nervous system disorders: amnesia, ataxia, choreoathetosis, cerebrovascular accident, dysarthria, dystonia, extrapyramidal disorders, hypoaesthesia, myoclonus, nystagmus, parkinsonism, restless legs, lightheaded feeling, migraine.

Pregnancy, puerperium and perinatal conditions: spontaneous abortion.

Psychiatric disorders: anger, apathy, completed suicide, depression aggravated, delirium, delusion, disorientation, feeling unreal, mood swings, nervousness, nightmare, paranoia, self-harm or thoughts of self-harm, suicide attempt, concentration impaired, lethargy.

Renal and urinary disorders: acute renal failure, dysuria, urinary frequency, urinary tract infection.

Skin and subcutaneous tissue disorders: dermatitis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis.

Vascular disorders: deep vein thrombosis, flushing, hypertensive crisis, orthostatic hypotension, phlebitis, thrombosis.

Investigations: bilirubin increased, hypercholesterolemia, INR increased, prothrombin decreased.

USE IN SPECIAL POPULATIONS

Pregnancy and Lactation

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

In reproductive toxicity in rats with escitalopram, embryo-fetotoxic effects, but no increased incidence of malformations, were reported. Escitalopram should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit. 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.

The following symptoms may occur in the neonate after maternal SSRI/SNRI use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either serotonergic effects or discontinuation symptoms. In a majority of instances the complications begin immediately or soon (<24 hours) after delivery.

It has been reported that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (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.

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

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth.

OVERDOSE

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), and the cardiovascular system (hypotension, tachycardia, QT interval prolongation, and arrhythmia) and electrolyte/fluid balance conditions (hypokalaemia, hyponatraemia).

Management
There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. Gastric lavage and the use of activated charcoal should be considered. Gastric lavage should be carried out as soon as possible after oral ingestion. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

ECG monitoring is advised in case of overdose in patients with congestive heart failure/bradyarrhythmias, in patients using concomitant medications that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment.

STORAGE
Store below 30°C, protected from moisture.

Keep all medicines out of the reach of children

SUPPLY
Blister Pack of 7's, Box of 14's
Blister strips (cold form) pack of 7's; Box of 14's.

MADE IN INDIA
SUN PHARMACEUTICAL IND. LTD.
Paonta Sahib, Dist Sirmour
Himachal Pradesh-173025

Product Registration Holder:
RANBAXY (MALAYSIA) SDN. BHD.
(A Sun Pharma Company)
Lot 23, Bakar Arang Industrial Estate,
08000 Sungai Petani, kedah
Malaysia

Revision date:
September 2022