

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SECİTA 20 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

Each dose contains Escitalopram Oxalate equivalent to 20 mg of Escitalopram.

Excipients:

Lactose monohydrate 110.06 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

Oval-shaped, white film coated tablets with scored on one side and embossed with “E20” on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutical Indications

It is indicated for:

- Major depressive episodes
- Panic disorders with or without agoraphobia
- Social anxiety disorder (social phobia)
- Generalized anxiety disorder
- Obsessive compulsive disorder (OCD)

4.2 Posology and method of administration

Posology/frequency and duration of administration

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

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.

In general, 2 - 4 weeks are necessary to obtain antidepressant response. After the symptoms improve, treatment for at least 6 months is required for consolidation of the response.

Panic disorders with or without agoraphobia

Before starting the 10 mg dose daily, initial dose of 5 mg once daily is recommended for the first week. Then, the dose may be increased to a maximum of 20 mg daily depending on individual patient response.

The maximum effect is reached after about 3 months. The treatment lasts for several months.

Social anxiety disorder (social phobia)

Usual dosage is 10 mg once daily. In order to resolve the symptoms, usually 2-4 weeks are necessary. Depending on individual patient response, the dose may be decreased to 5 mg or increased to a maximum of 20 mg daily.

Social anxiety disorder is a chronic disorder and treatment for at least 12 months is recommended for consolidation of the response. When examined long-term therapy for 6 months of patients responding to therapy, it is noticed that the response to therapy should be evaluated depending on the individuals to prevent relapse. Benefits of the therapy should be re-evaluated at regular intervals.

Social anxiety disorder is a well-defined diagnostic terminology of a specific disorder and should not be confused with extreme shyness. Drug therapy should be initiated only if this disorder significantly impacts the professional and social activities.

This therapy has not been examined in comparison with cognitive behavioral therapy. Drug therapy is a part of overall treatment strategy.

Generalized anxiety disorder

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

In patients responding to the treatment, long-term therapy (20 mg/day) has been evaluated with 6-months studies at least. Benefits of the therapy should be re-evaluated at regular intervals (see section 5.1.).

Obsessive compulsive disorder (OCD)

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

Since OCB is a chronic disorder, patients should be treated for sufficient time to ensure the resolution of symptoms.

Benefits and dose of the therapy should be re-evaluated at regular intervals (see section 5.1.).

Method of administration:

SECITA[®] is administered as a single daily dose and may be taken with or without food.

Special population:

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 section 5.2).

Reduced hepatic function

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. Careful dose titration is proposed in patients with severely reduced hepatic function (see section 5.2.).

Pediatric population (< 18 years):

SECITA[®] should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4.).

Geriatric population (> 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 section 5.2.).

Efficacy of escitalopram on elderly patients with social anxiety disorder has not been investigated.

Patients with poor metabolizers of CYP2C19:

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

Discontinuation symptoms seen when stopping treatment

Sudden discontinuation of the medicine should be avoided. In order to reduce withdrawal reactions, escitalopram treatment should be discontinued by reducing the dose gradually reduced over a period of at least one to two weeks (see section 4.4 and 4.8). If intolerable symptoms occur following the decrease of the dose or discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose more gradually.

4.3 Contraindications

It is contraindicated in patients have hypersensitivity to the escitalopram or to any of the excipients.

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 section 4.5).

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 serotonin syndrome (see section 4.5).

Escitalopram is contraindicated in patients with known QT-interval prolongation or congenital long QT syndrome.

Concomitant use of escitalopram with other medicinal products that are known to prolong the QT-interval is contraindicated.

Concomitant use with pimozide is contraindicated.

4.4 Special warnings and precautions for use

The following special warnings and precautions involve whole drugs belonging to therapeutic class of Selective Serotonin Re-Uptake Inhibitors (SSRIs).

Use in children and adolescents under 18 years of age

SECITA[®] should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviors (suicide attempt and suicidal thoughts) and hostility (predominately aggression, oppositional behavior and anger) were more frequently observed in clinical trials in children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, nevertheless a decision to treat is taken; the patient should be carefully monitored for the appearance of suicidal symptoms. Furthermore, there is no long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioral development.

Paradoxical anxiety

Some patients with panic disorder may exhibit increasing anxiety symptoms at the initial of the antidepressant treatment. This paradoxical reaction generally disappears within the first two weeks following starting to treatment. Minimum starting dose is proposed to reduce potential anxiogenic effects (see section 4.2.).

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 not be administered in patients with unstable epilepsy. Patients with controlled epilepsy should be monitored carefully.

Mania

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

Diabetes

In patients with diabetes, SSRI treatment may alter glycemic control (hypoglycemia or hyperglycemia). Dosage of insulin and/or oral hypoglycemic medication may need to be adjusted.

Suicide/suicidal thoughts or clinical worsening

Antidepressant drugs may increase the potential of suicidal thoughts or suicidal behavior in patients less than 24 years old. Therefore, patients should be closely monitored by caregivers of patients during dosage increase/decrease or withdrawal period, especially at the initial of therapy and first months, due to the unexpected behavior changes such as restlessness, hyperactivity or suicide potential in patients.

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk continues until significant improvement occurs. Patients should be closely monitored until such improvement occurs since improvement may not occur during the first few weeks or more of therapy. The risk of suicide may increase in the early stages of improvement according to general clinical experience.

The risk of suicide-related events may be increased in the other psychiatric situations which escitalopram is prescribed. Moreover, major depressive disorder may be accompanied by these situations. Therefore, same precautions, which are applied when treating patients with major depressive disorder, should also be applied to patients with other psychiatric disorder.

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

Akathisia/psychomotor restlessness

The use of SSRIs/SNRIs has been associated with the development of akathisia (characterized 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 harmful.

Hyponatremia

Hyponatremia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported rarely with the use of SSRIs. This is generally reversible following discontinuation of therapy. SSRIs should be used with caution in patients at risk, such as the elderly or patients with cirrhosis, or if used in combination with other medications which may cause hyponatremia.

Hemorrhage

Cutaneous bleeding abnormalities such as ecchymoses and purpura have been reported in the treatment with SSRIs. Caution should be advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants and certain medicinal products that are known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs), ticlopidine and dipyridamole) and in patients with known bleeding tendencies.

Electroconvulsive therapy (ECT)

Since there is limited clinical experience of concomitant use of SSRIs and ECT, caution is proposed.

Serotonin syndrome

In concomitant use of escitalopram with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan; caution should be advised. In patients using SSRIs concomitantly with serotonergic medicinal products, serotonin syndrome has been rarely reported. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs; treatment with SSRI and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment should be initiated.

St. Johns Wort

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

Discontinuation symptoms seen when stopping treatment

Symptoms following discontinuation of the treatment are common particularly if the treatment is discontinued suddenly (see section 4.8). In clinical trials, adverse events seen on treatment discontinuation occurred in approximately 25 % of patients treated with escitalopram and 15 % of patients taking placebo.

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 paresthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhea, palpitations, emotional instability, irritability and visual disturbances are the most commonly reported reactions. These symptoms are generally mild to moderate; however, they may be more severe in some patients. 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 accidentally missed a dose.

Generally these symptoms are self-limiting and although they usually resolve within 2 weeks, in some individuals they may be prolonged (2-3 months or more). Therefore, it is advised that escitalopram should be gradually reduced when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see section 4.2. "Discontinuation symptoms seen when stopping treatment").

Coronary heart disease

Due to limited clinical experience, caution should be advised in patients with coronary heart disease (see section 5.3.).

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 Torsades de Pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalemia or with pre-existing QT-interval prolongation or other cardiac diseases (see sections 4.3., 4.5., 4.8., 4.9. and 5.1.).

Caution is advised in patients at high risk of developing Torsades de Pointes, such as patients with congestive heart failure, recent myocardial infarction, bradiarrhythmia or tendency to hypokalemia or hypomagnesaemia due to the concurrent illness or use of medications.

Caution is advised in patients with significant bradycardia or in patients with recent acute myocardial infarction or uncompensated heart failure.

Electrolyte disturbances such as hypokalemia and hypomagnesaemia increase the risk for malignant arrhythmias. These conditions should be corrected prior to treatment with escitalopram.

If patients with stable cardiac disease are treated, an electrocardiography (ECG) assessment should be considered before starting the treatment.

If cardiac arrhythmia occurs during the treatment with escitalopram; the treatment should be discontinued and an ECG should be performed.

The risk of persistent pulmonary hypertension in the new-born

Epidemiological data suggests that using SSRIs in pregnancy, especially in the last period of the pregnancy increase the risk of persistent pulmonary hypertension in the new-born (see section 4.6.).

This drug contains lactose monohydrate; patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Contraindicated combinations:

Irreversible non-selective MAOIs

Cases of serious reactions have been reported in patients taking an SSRI in combination with a non-selective, irreversible MAOI and in patients who have recently discontinued SSRI treatment and have been started on such MAOI treatment (see section 4.3.). In some patients, serotonin syndrome has been developed (see section 4.8.). Concomitant use of escitalopram with non-selective, irreversible MAOIs is contraindicated. 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 concomitant use of escitalopram with a MAO-A inhibitor such as moclobemide is contraindicated (see section 4.3.). If this combination is necessary, the treatment should be started at the minimum recommended dosage and clinical monitoring should be advised.

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 this combination is necessary, it should be given with minimum dosages and under close clinical monitoring (see section 4.3.).

Irreversible, selective MAO-B inhibitor (selegiline)

Due to the risk of developing serotonin syndrome, caution is required in combination with selegiline (irreversible MAO-B inhibitor). Racemic citalopram have been safely co-administered with selegiline doses up to 10 mg/day.

Concurrent use of pimozide and escitalopram is contraindicated.

QT interval prolongation

Pharmacokinetic and pharmacodynamic studies of escitalopram combined with other medicinal products that prolong the QT interval have not been conducted. An additive effect of escitalopram and these medicinal products cannot be excluded. Therefore, concurrent use 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 caution should be advised in concomitant use of SSRIs with these medicinal products.

St. John's wort

Concomitant use of SSRIs and herbal preparations containing St. John's wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions (see section 4.4.).

Hemorrhage

Altered anti-coagulant effects may occur when escitalopram is combined with oral anticoagulants. Careful coagulation monitoring should be performed when escitalopram is started or stopped in patients receiving oral anticoagulant therapy (see section 4.4.). Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase bleeding-tendency (see section 4.4.).

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.

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 main metabolite demethylated escitalopram (S-DCT) 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 required. Thus, caution should be advised 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 should be advised 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 central nervous system acting medicinal products that are mainly metabolised by CYP2D6 (e.g. antidepressants such as desipramine, clomipramine and nortriptyline or antipsychotics such as risperidone, thioridazine and haloperidol). Dosage adjustment may be required.

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

In vitro studies have demonstrated that escitalopram causes weak inhibition of CYP2C19. Caution should be advised with concomitant use of medicinal products that are metabolised by CYP2C19.

4.6 Pregnancy and lactation

General recommendation

Pregnancy category: C

Women of childbearing potential/Contraception

Limited clinical data are available for using escitalopram in pregnancy.

Pregnancy

SECITA[®] 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 SECITA[®] 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 neonates after SSRI/SNRI use in later stages of pregnancy: respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypertonia, hypotonia, hyperreflexia, tremor, restlessness, irritability, lethargy, constant crying, somnolence and insomnia. These symptoms could be due to serotonergic effects or discontinuation symptoms. In a majority of cases, the complications begin immediately or soon (< 24 hours) after delivery.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn. The observed risk was approximately 5 cases per 1000 pregnancies.

In the general population, this value is 1 to 2 cases per 1000.

Lactation

Escitalopram is expected to excrete into human milk.
Breast-feeding is not recommended during treatment.

Reproduction/Fertility

In reproductive toxicity studies with escitalopram on rats, embryo-fetotoxic effects have been shown; however there has been no increase in the incidence of malformation (see section 5.3.).

4.7 Effects on ability to drive and use machines

Escitalopram does not affect intellectual function or psychomotor performance. However, impairment of judgement or skills of patients receiving psychoactive medicinal product is possible. Therefore, patients should be cautioned about the potential risk of an influence on their ability to drive a car and operate machinery.

4.8 Undesirable effects

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

Adverse reactions known for SSRIs and also reported for escitalopram in either placebo-controlled clinical studies or as spontaneous post-marketing events are listed below by system organ class and frequency.

Frequencies are taken from clinical studies; they are not placebo-corrected. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), or not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Not known: Trombocytopenia

Immune system disorder

Rare: Anaphylactic reaction

Endocrin disorders

Not known: Inappropriate ADH (antidiuretic hormone) secretion

Metabolism and nutrition disorders

Common: Decreased appetite, increased appetite, weight increased

Uncommon: Weight decreased

Not known: Hyponatremia, anorexia²

Psychiatric disorders

Common: Anxiety, restlessness, abnormal dreams; libido decreased in male and female: anorgasmia in female.

Uncommon: Bruxizm, agitation, nervousness, panic attack, confusional state

Rare: Aggression, depersonalization, hallucination

Not known: Mania, suicidal ideation, suicidal behaviour¹

Nervous system disorders

Common: Insomnia, somnolence, dizziness, paresthesia, tremor

Uncommon: Taste disturbance, sleep disorder, syncope

Rare: Serotonin syndrome

Not known: Dyskinesia, movement disorder, convulsion, psychomotor restlessness/akathisia²

Eye disorders

Uncommon: Mydriasis, visual disturbance

Ear and labyrinth disorders

Uncommon: Tinnitus

Cardiac disorders

Uncommon: Tachycardia

Rare: Bradycardia

Not known: Electrocardiogram QT prolongation, Ventricular arrhythmia including Torsades de Pointes

Vascular disorders

Not known: Orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Common: Sinusitis, yawning

Uncommon: Nose-bleeding

Gastrointestinal disorders

Very common: Nausea

Common: Diarrhea, constipation, vomiting, dry mouth

Uncommon: Gastrointestinal hemorrhages (including rectal hemorrhages)

Hepato-biliary disorders

Not known: Hepatitis, liver function test abnormalities

Skin and subcutaneous tissue

Common: Sweating increased

Uncommon: Urticaria, alopecia, rash, pruritus

Not known: Ecchymosis, angioedema

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: Edema

¹Cases of suicidal ideation and suicidal behaviors have been reported during escitalopram therapy or early after treatment discontinuation (see section 4.4.).

² These events have been reported for SSRIs.

Class effects

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.

Discontinuation symptoms seen when stopping treatment

Especially abrupt discontinuation of SSRIs/SNRIs commonly leads to discontinuation symptoms. Dizziness, sensory disturbances (including paresthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhea, palpitations, emotional instability, irritability and visual disturbances are the most commonly reported reactions. These events are generally mild to moderate and are self-limiting; however, in some patients they may be severe and/or prolonged. Therefore, it is advised that when escitalopram treatment is no longer required, discontinuation of therapy should be carried out gradually (see section 4.2. and 4.4.).

QT interval prolongation

Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalemia, or with pre-existing QT interval prolongation or other cardiac diseases (see sections 4.3., 4.4., 4.5., 4.9. and 5.1.).

4.9 Overdose and treatment

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 fatal 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 are 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 (hypokalemia, hyponatremia).

Treatment

There is no specific antidote. Airway should be kept open, 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 should be monitored 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).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, selective serotonin reuptake inhibitors
ATC code: N06AB10

Mechanism of action

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-HT₂, dopamine (DA) D₁ and D₂ receptors, α_1 -, α_2 -, β -adrenoreceptors, histamine H₁, muscarine cholinergic, benzodiazepine, and opioid receptors.

Pharmacodynamic effects

In a double-blind, placebo-controlled ECG study conducted in healthy volunteers, the change from baseline in QTc (Fridericia-correction) was 4.3 ms (90 % CI: 2.2, 6.4) at the 10 mg/day dose and 10.7 ms (90 % CI: 8.6, 12.8) at the supratherapeutic dose 30 mg/day (see sections 4.3., 4.4., 4.5., 4.8. and 4.9.).

Clinical efficacy

Major Depressive Episodes

Escitalopram has been found to be effective in the acute treatment of major depressive episodes in three out of four double-blind, placebo controlled short-term (8-week) studies.

In a long-term relapse prevention study, 274 patients who had been in open label treatment phase with escitalopram 10 or 20 mg/day for an initial 8-week, were randomised to continuation with escitalopram or placebo at the same dose for up to 36 weeks. In this study, patients receiving escitalopram experienced a significantly longer time to relapse over the subsequent 36 weeks compared to those receiving placebo.

Social Anxiety Disorder

Escitalopram was effective in both three short-term (12 weeks) studies and in responders in a 6-month relapse prevention study in social anxiety disorder. In a 24-week dose-adjusting study, efficacy of 5, 10 and 20 mg escitalopram has been demonstrated.

Generalised Anxiety Disorder

10 and 20 mg/day of escitalopram doses were effective in four out of four placebo-controlled studies.

In pooled data from three studies with similar design, ratio of responders in 421 patients receiving escitalopram and 419 patients receiving placebo were 47.5 % and 28.9 % and the ratio of remitters was 37.1 % and 20.8 %, respectively. Sustained effect with escitalopram was seen from week 1.

Maintenance of efficacy of escitalopram 20 mg/day was demonstrated in a 24–76 week, randomised, maintenance of efficacy study in 373 patients who had responded during the initial 12-week open-label treatment.

Obsessive-Compulsive Disorder

In a randomised, double-blind clinical study, 20 mg/day escitalopram separated from placebo on the Y-BOCS total score after 12 weeks. At the end of the 24 weeks, both 10 and 20 mg/day escitalopram were superior when compared to placebo.

In a 16-week open-label study, prevention of relapse was demonstrated for 10 and 20 mg/day escitalopram in patients who responded to escitalopram and who entered a 24-week, randomised, double-blind, placebo controlled study.

5.2 Pharmacokinetic properties

General properties

Absorption

Absorption is almost complete and independent from food intake. Mean time to reach maximum concentration (mean T_{max}) is 4 hours after multiple dosing.

As with racemic citalopram, the absolute bioavailability of escitalopram is about 80 %.

Distribution

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

Biotransformation

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

Elimination:

The elimination half-life ($t_{1/2\beta}$) following 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 suggested to be eliminated by the hepatic (metabolic) and the renal routes, major part of the dose is excreted as metabolites in the urine.

It shows linear pharmacokinetics. Steady-state plasma levels are reached in about 1 week. Average steady-state concentrations of 50 nmol/L (20–125 nmol/L) are reached at a daily dose of 10 mg.

Characteristics in patients

Elderly patients (> 65 years)

Escitalopram is eliminated more slowly in elderly patients than younger patients. Systemic exposure (AUC) is about 50 % higher in elderly compared to young healthy volunteers (see section 4.2.).

Reduced hepatic function

In patients with mild or moderate hepatic impairment (Child-Pugh Criteria A and B), the half-life of escitalopram was about two-times longer and the exposure was about 60 % higher than in subjects with normal liver function (see section 4.2.).

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 (CL_{cr} 10-53 mL/min). Plasma concentrations of the metabolites have not been studied, but they may be increased (see section 4.2.).

Polymorphism

It has been observed that poor metabolisers with respect to CYP2C19 have two-times higher plasma concentration of escitalopram when compared rich metabolisers. No significant change in exposure was observed in poor metabolisers with respect to CYP2D6 (see section 4.2.).

5.3 Preclinical safety data

Since the interrelated toxicokinetic and toxicological studies conducted on rats with escitalopram and citalopram showed a similar profile; no complete conventional series of preclinical studies was performed with escitalopram. Therefore, all the citalopram information can be extrapolated to escitalopram.

In comparative toxicological studies in rats, escitalopram and citalopram caused cardiac toxicity, including congestive heart failure, after treatment for some weeks, when using dosages that caused general toxicity. The cardiotoxicity was seen to correlate with peak plasma concentrations rather than to systemic exposures (AUC). Peak plasma concentrations at no-effect-level were in excess (8-fold) of those achieved in clinical use, while AUC for escitalopram was only 3-4-fold higher than the exposure achieved in clinical use. For citalopram AUC values for the S-enantiomer were 6-7-fold higher than that of the therapeutic dosages. The findings are probably related to an exaggerated influence on biological amines. I.e., secondary to the primary pharmacological effects; resulting in hemodynamic effects (reduction in coronary flow) and ischemia. However, the cardiotoxic mechanism in rats is not well known. Clinical experience obtained with citalopram and the clinical trial experience with escitalopram does not indicate that these findings have a clinical correlate. Increased content of phospholipids has been observed in some tissues like lung, epididymides and liver following treatment for long-term therapy with escitalopram and citalopram in rats. Findings in the epididymides and liver were seen at exposures similar to that in human. The effect is reversible after discontinuation of the treatment. Accumulation of phospholipids (phospholipidosis) in animals has been observed in connection with many cationic amphiphilic medicines. It is not known if this has any significant relevance for human.

During the developmental toxicity study in the rats, embryotoxic effects (reduced fetal weight and reversible delay of ossification) were observed when exceeded the therapeutical doses (in terms of AUC). No increased frequency of malformations was recorded. A pre- and post-natal study showed reduced survival during the lactation period when exceeded the clinical doses (in terms of AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Microcrystalline Cellulose
- Lactose Monohydrate
- Colloidal Anhydrous Silica
- Croscarmellose Sodium
- Polyvinyl Pyrrolidone K30
- Magnesium Stearate
- Opadry White 04F28674
 - HPMC 15cP
 - Talc
 - Titanium Dioxide
 - Macrogol (PEG 6000)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Presented in PVC-PE-PVDC/Aluminum foil blister package with 28, 56 and 84 film coated tablets, along with patients' leaflet within cardboard box.

6.6 Special precautions for disposal and other handling

Unused products or waste materials should be disposed in accordance with the "Medical Waste Disposal Directive" and "Packaging and Packaging Waste Directive".

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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