**QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 5 mg escitalopram (as escitalopram oxalate)

Each film-coated tablet contains 10 mg escitalopram (as escitalopram oxalate)

Each film-coated tablet contains 20 mg escitalopram (as escitalopram oxalate)

Excipient with known effect: sucrose

Mentumir® 5 mg: Each film-coated tablet contains 0.04 mg sucrose. Mentumir® 10 mg: Each film-coated tablet contains 0.08 mg sucrose. Mentumir® 20 mg: Each film-coated tablet contains 0.16 mg sucrose.

For the full list of excipients, see section *List of excipients*.

**PHARMACEUTICAL FORM**

Film-coated tablet

Mentumir® 5 mg: White colored, round shaped, biconvex, film coated tablets plain on both the sides and 5.5 mm in diameter.

Mentumir® 10 mg: White colored, oval shaped, biconvex, film coated tablets, debossed ‘1’ on one side of the breakline and plain on other side. They are of 8.0 mm x 5.5 mm in diameter. The tablet can be divided into equal doses.

Mentumir® 20 mg: White colored, oval shaped, biconvex, film-coated tablets, debossed ‘2’ on one side of the breakline and plain on other side. They are of 11.5 mm x 7.0 mm in diameter. The tablet can be divided into equal doses.

**CLINICAL PARTICULARS**

**Therapeutic indications**

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

**Posology and method of administration**

Safety of daily doses above 20 mg has not been demonstrated. Escitalopram oxalate (Mentumir®) is 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 behavioral therapy has not been assessed. Pharmacotherapy is part of an overall therapeutic strategy.

**Generalized anxiety disorder** - Initial dosage is 10 mg once daily. Depending on the individual patient response, the dose may be increased to a maximum of 20 mg daily. Long-term treatment of responders has been studied for at least 6 months in patients receiving 20 mg daily. Treatment benefits and dose should be re-evaluated at regular intervals (see section Pharmacodynamic properties).

**Obsessive-compulsive disorder** - Initial dosage is 10 mg once daily. Depending on the individual patient response, the dose may be increased to a maximum of 20 mg daily. As OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom free. Treatment benefits and dose should be re-evaluated at regular intervals (see section Pharmacodynamic properties).

**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 section Pharmacokinetic properties). The efficacy of Escitalopram oxalate (Mentumir®) in social anxiety disorder has not been studied in elderly patients.

**Children and adolescents (<18 years)** - Escitalopram oxalate (Mentumir®) should not be used in the treatment of children and adolescents under the age of 18 years (see section Special warnings and precautions for use).

**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 (CLcr less than 30 mL/min) (see section 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 section Pharmacokinetic properties).

**Poor metabolizers of CYP2C19** - For patients who are known to be poor metabolizers 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 section Pharmacokinetic properties).

**Discontinuation symptoms seen when stopping treatment**

A 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 section Special warnings and precautions for use and 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 listed in section List of 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 Interaction with other medicinal products and other forms of interaction).

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 section Interaction with other medicinal products and other forms of interaction).

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 section Interaction with other medicinal products and other forms of interaction).

**Special warnings and precautions for use**

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 oxalate (Mentumir®) 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 among children and adolescents treated with antidepressants compared to those treated with placebo. 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 data in children and adolescents concerning growth, maturation and cognitive and behavioral 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 (see section *Posology and method of administration*).

**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 glycemic control (hypoglycemia or hyperglycemia). Insulin and/or oral hypoglycemic 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 oxalate (Mentumir®) 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. A meta-analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behavior with antidepressants compared to placebo in patients less than 25 years old. 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 behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present.

**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 detrimental.

**Hyponatremia**

Hyponatremia, 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 hyponatremia.

**Hemorrhage**

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**

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.

**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 *Interaction with other medicinal products and other forms of interaction*).
**Discontinuation symptoms seen when stopping treatment**

Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt (see section *Undesirable effects*). 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. 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 "Discontinuation symptoms seen when stopping treatment", section *Posology and method of administration*).

**Coronary heart disease**

Due to limited clinical experience, caution is advised in patients with coronary heart disease (see section *Preclinical safety data*).

**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 hypokalemia, or with pre-existing QT interval prolongation or other cardiac diseases (see sections *Contraindications, Interaction with other medicinal products and other forms of interaction, Undesirable effects, Overdose and Pharmacodynamic properties*).

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 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.
**Angle-Closure Glaucoma**

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

**Excipients**

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

**Interaction with other medicinal products and other forms of interaction**

**Pharmacodynamic interactions**

**Contra-indicated combinations**

- **Irreversible non-selective MAOIs**

Cases of serious reactions have been reported in patients receiving an SSRI in combination with a nonselective, irreversible monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued SSRI treatment and have been started on such MAOI treatment (see section **Contraindications**). In some cases, the patient developed serotonin syndrome (see section **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 section **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 section **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** Pharmacokinetick and pharmacodynamic studies of escitalopram combined with other medicinal products that prolong the QT interval have not been
performed. 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 (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), mefloquine, 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 section *Special warnings and precautions for use*).

**Hemorrhage**

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 (see section *Special warnings and precautions for use*). Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase bleeding-tendency (see section *Special warnings and precautions for use*).

**Alcohol**

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

**Medicinal products inducing hypokalemia/ hypomagnesemia**
Caution is warranted for concomitant use of hypokalaemia/hypomagnesaemia inducing medicinal products as these conditions increase the risk of malignant arrhythmias (see section Special warnings and precautions for use).

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 catalyzed 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 coadministered 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 twofold increase in the plasma levels of these two CYP2D6 substrates.

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 metabolized by CYP2C19.

Fertility, pregnancy and lactation

Pregnancy

For escitalopram only limited clinical data are available regarding exposed pregnancies. In reproductive toxicity studies performed in rats with escitalopram, embryo-fetotoxic effects, but no increased incidence of malformations, were observed (see section Preclinical safety data). Escitalopram oxalate (Mentumir®) 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 oxalate (Mentumir®) 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, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, 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.

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 (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.

**Lactation**

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

**Fertility**

Animal data have shown that citalopram may affect sperm quality (see section Preclinical safety data). 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.

**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.

**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 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 (≥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).

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Frequency</th>
<th>Undesirable Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Not known</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>Anaphylactic reaction</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Not known</td>
<td>Inappropriate ADH secretion</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Decreased appetite, increased appetite, weight increased</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Weight decreased</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Hyponatremia, anorexia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Anxiety, restlessness, abnormal dreams Female and male: libido decreased Female: anorgasmia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Bruxism, agitation, nervousness, panic attack, confusional state</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Aggression, depersonalization, hallucination</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Mania, suicidal ideation, suicidal behaviour</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Insomnia, somnolence, dizziness, paresthesia, tremor</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Taste disturbance, sleep disorder, syncope</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Serotonin syndrome</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Dyskinesia, movement disorder, convulsion, psychomotor restlessness/akathisia</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>Mydriasis, visual disturbance</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Uncommon</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Tachycardia</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Electrocardiogram QT prolonged Ventricular arrhythmia including torsade de pointes</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Not known</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Common</td>
<td>Sinusitis, yawning</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Diarrhea, constipation, vomiting, dry mouth</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Gastrointestinal hemorrhages (including rectal hemorrhage)</td>
</tr>
</tbody>
</table>
Cases of suicidal ideation and suicidal behaviors have been reported during escitalopram therapy or early after treatment discontinuation (see section Special warnings and precautions for use). These events have been reported for the therapeutic class of 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

Discontinuation of SSRIs/SNRIs (particularly when abrupt) commonly leads to discontinuation symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when escitalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section Posology and method of administration and Special warnings and precautions for use).

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 Contraindications, Special warnings and precautions for use, Interaction with other medicinal products and other forms of interaction, Overdose and Pharmacodynamic properties).
**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 800mg 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 (hypokalemia, hyponatremia).

**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 advisable 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.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic properties**

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

**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\textsubscript{1A}, 5-HT\textsubscript{2}, DA D\textsubscript{1} and D\textsubscript{2} receptors, α\textsubscript{1}-, α\textsubscript{2}-, β-adrenoceptors, histamine H\textsubscript{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.
**Pharmacodynamic effects**

In a double-blind, placebo-controlled ECG study in healthy subjects, 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 section Contraindications, Special warnings and precautions for use, Interaction with other medicinal products and other forms of interaction, Undesirable effects and Overdose).

**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 responded during an initial 8-week open label treatment phase with escitalopram 10 or 20 mg/day were randomized to continuation with escitalopram at the same dose, or to placebo, for up to 36 weeks. In this study, patients receiving continued 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-week) studies and in responders in a 6 months relapse prevention study in social anxiety disorder. In a 24-week dose-finding study, efficacy of 5, 10 and 20 mg escitalopram has been demonstrated.

**Generalized anxiety disorder**

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

In pooled data from three studies with similar design comprising 421 escitalopram-treated patients and 419 placebo-treated patients there were 47.5% and 28.9% responders respectively and 37.1% and 20.8% remitters. Sustained effect was seen from week 1.

Maintenance of efficacy of escitalopram 20mg/day was demonstrated in a 24 to 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. After 24 weeks, both 10 and 20 mg/day escitalopram were superior as compared to placebo.

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

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

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

Biotransformation
Escitalopram is metabolized in the liver to the demethylated and didemethylated metabolites. Both of these are pharmacologically active. Alternatively, the nitrogen may be oxidized 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.

Elimination
The elimination half-life (t\textsubscript{1/2β}) after multiple dosing is about 30 hours and the oral plasma clearance (Cl\textsubscript{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 section Posology 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 section Posology 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 (CL\textsubscript{cr} 10-53 ml/min). Plasma concentrations
of the metabolites have not been studied, but they may be elevated (see section *Posology and method of administration*).

**Polymorphism**

It has been observed that poor metabolizers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolizers. No significant change in exposure was observed in poor metabolizers with respect to CYP2D6 (see section *Posology and method of administration*).

**Preclinical safety data**

No complete conventional battery of preclinical studies was performed with escitalopram since the bridging toxicokinetic and toxicological studies conducted in rats with escitalopram and citalopram showed a similar profile. 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 seemed 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-to 4-fold higher than the exposure achieved in clinical use. For citalopram AUC values for the S-enantiomer were 6-to 7-fold higher than exposure achieved in clinical use. The findings are probably related to an exaggerated influence on biogenic amines i.e. secondary to the primary pharmacological effects, resulting in hemodynamic effects (reduction in coronary flow) and ischemia. However, the exact mechanism of cardiotoxicity in rats is not clear. Clinical experience with citalopram, and the clinical trial experience with escitalopram do not indicate that these findings have a clinical correlate.

Increased content of phospholipids has been observed in some tissues e.g. lung, epididymides and liver after treatment for longer periods with escitalopram and citalopram in rats. Findings in the epididymides and liver were seen at exposures similar to that in man. The effect is reversible after treatment cessation. Accumulation of phospholipids (phospholipidosis) in animals has been observed in connection with many cationic amphiphilic medicines. It is not known if this phenomenon has any significant relevance for man.

In the developmental toxicity study in the rat embryotoxic effects (reduced foetal weight and reversible delay of ossification) were observed at exposures in terms of AUC in excess of the exposure achieved during clinical use. No increased frequency of malformations was noted. A pre-and postnatal study showed reduced survival during the lactation period at exposures in terms of AUC in excess of the exposure achieved during clinical use.

Animal data have shown that citalopram induces a reduction of fertility index and pregnancy index, reduction in implantation number and abnormal sperm at exposure well in excess of human exposure. No animal data related to this aspect are available for escitalopram.
PHARMACEUTICAL PARTICULARS

List of excipients

Tablet core: Microcrystalline cellulose, Croscarmellose sodium, Colloidal anhydrous silica, Talc, Magnesium stearate, Sucrose stearic acid esters

Film-coating: Instacoat Universal ICG-U-6502 White (hypromellose 5 cPs, macrogol 400, titanium dioxide (E171)

Incompatibilities

Not applicable

Shelf life

24 months

Special precautions for storage

Store at temperatures not exceeding 30°C.

Nature and contents of container

Mentumir® 5 mg Film-Coated Tablet – Alu/Alu Blister Pack x 14’s (Box of 14’s)
Mentumir® 10 mg Film-Coated Tablet – Alu/Alu Blister Pack x 14’s (Box of 28’s)
Mentumir® 20 mg Film-Coated Tablet – Alu/Alu Blister Pack x 10’s (Box of 30’s)

Caution

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by

Cadila Healthcare Limited
Sarkhej – Bavla N.H.
No. 8A Moraiya, Tal. Sanand District
Ahmedabad 382 210, India

Imported and Distributed by

Abbott Laboratories
Venice Corporate Center, 8 Turin St.
Mckinley Town Center, Fort Bonifacio
Taguig City, Philippines

SOLID 1000299071 ver. 2.0 10Jun2013