Escitalopram (oxalate)

Rx

Lexapro® 5 mg, 10 mg and 20 mg film-coated tablets

Antidepressant

1. NAME OF THE MEDICINAL PRODUCT

Lexapro (Escitalopram (as oxalate) 5 mg, 10 mg and 20 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 mg film coated tablet:
Each film-coated tablet contains 5 mg
Escitalopram (as 6.39mg escitalopram (as oxalate), PH.Eur and USP
10 mg film coated tablet:
Each film-coated tablet contains 10 mg
Escitalopram (as 19.16mg escitalopram (as oxalate), PH.Eur and USP
20 mg film coated tablet:
Each film-coated tablet contains 20 mg
Escitalopram (as 25.54mg escitlaopram (asoxalate), PH.Eur and USP

3. PHARMACEUTICAL FORM

Film-coated tablets

Escitalopram (as oxalate) (Lexapro) 5 mg:
Round, white, film-coated tablet marked with "EK" on one side.
Escitalopram (as oxalate) (Lexapro) 10 mg:
Oval, white, scored, film-coated tablet marked with "E" and "L" on each side of the score on one side of the tablet.
Escitalopram (as oxalate) (Lexapro) 20 mg:
Oval, white, scored, film-coated tablet marked with "E" and "N" on each side of the score on one side of the tablet.

The 10 and 20 mg tablets can be divided into equal doses

4. CLINICAL PARTICULARS

4.1 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

4.2 Posology and method of administration
Safety of daily doses above 20 mg has not been demonstrated.

Escitalopram 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. 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 symptom relief. Treatment for 3 months is recommended to consolidate response. Long-term treatment of responders for 6 months has been shown to prevent relapse and can be considered on an individual basis; treatment benefits should be re-evaluated at regular intervals.

Generalized anxiety disorder
Usual dosage is 10 mg once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily.

Treatment for 3 months is recommended to consolidate response. Long-term treatment of responders for 6 months has been shown to prevent relapse and can be considered on an individual basis; treatment benefits should be re-evaluated at regular intervals.

Obsessive-compulsive disorder (OCD)
Usual dosage is 10 mg once daily. Depending on individual patient response, the dose may be increased to 20 mg daily.

Long-term treatment of patients responding to a 16-week open treatment phase has been studied for at least 24 weeks in patients receiving 10 or 20 mg/day. As OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom free. This period may be several months or even longer.

Elderly patients (> 65 years of age)
Initial treatment with half the usually recommended dose and a lower maximum dose should be considered (see "Pharmacokinetic properties")

Children and adolescents (<18 years)
Escitalopram should not be used in the treatment of children and adolescents under the age of 18 years, see Special warnings and special 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 "Pharmacokinetic properties")

Reduced hepatic function
An initial dose of 5 mg daily for the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg daily (see "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 "Pharmacokinetic properties")

Discontinuation symptoms
When stopping treatment with escitalopram, the dose should be gradually reduced over a period of at least one to two weeks in order to avoid possible discontinuation symptoms (see "Special warnings and precautions for use" and "Undesirable effects")

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant treatment with non-selective, irreversible monoamine oxidase inhibitors (MAO-inhibitors) (see section 4.5).

Concomitant treatment with pimozide.

4.4 Special warnings and precautions for use
Antidepressants should not be used in the treatment of children and adolescents under age of 18 years. Suicide related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour 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.

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

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 the first two weeks of treatment. A low starting dose is advised to reduce the likelihood of an anxiogenic effect (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 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. 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.

A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour 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 behaviour or thoughts and unusual changes in behaviour 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, 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. SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8). Caution is advised in patients taking SSRIs, particularly with concomitant use of oral anticoagulants; medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole); 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.

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 section 4.5).

Serotonin syndrome
Caution is advisable if escitalopram is used concomitantly with medicinal products with serotonergic effects such as triptans (including sumatriptan), opioids (including tramadol), and tryptophan.
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 4.5).

Discontinuation symptoms seen when stopping treatment
Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt (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 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 "Discontinuation symptoms seen when stopping treatment", section 4.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction
Pharmacodynamic interactions
Contraindicated combinations:
Non-selective, irreversible 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 MAOI treatment (see section 4. 3). In some cases, the patient developed serotonin syndrome (see section 4.8).

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.

Pimozide
Co-administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and Cmax of pimozide, although not consistently throughout the study. The co-administration of pimozide and citalopram resulted in a mean increase in the QTc interval of approximately 10 msec. Due to the interaction noted at a low dose of pimozide, concomitant administration of escitalopram and pimozide is contraindicated.

Combinations requiring precautions for use:
Reversible, selective MAO A inhibitor (moclobemide)
Due to the risk of serotonin syndrome, the combination of escitalopram with a MAO A inhibitor is not recommended (see section 4.4). If the combination proves necessary, it should be started at the minimum recommended dosage and clinical monitoring is strongly recommended.

Escitalopram may be started at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide.

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

Serotonergic medicinal products
Co-administration with serotonergic medicinal products e.g. opioids (including tramadol) and triptans (including sumatriptan) 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, 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 4.4).

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 (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 major metabolite S DCT (demethylated escitalopram) seems to be partly catalysed by CYP2D6.

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

Co-administration of escitalopram with cimetidine (moderately potent general enzyme-inhibitor) resulted in moderate (approximately 70%) increase in the plasma concentrations of escitalopram.

Caution should thus be exercised at the upper end of the dose range of escitalopram when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, fluoxetine, fluvoxamine, lansoprazole, ticlopidine) and with cimetidine.

A reduction in the dose of escitalopram may be necessary based on clinical judgement.

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 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 metabolised by CYP2C19.

4.6 Pregnancy and lactation
Pregnancy
Limited clinical data are available regarding exposure to escitalopram during pregnancy.

Animal studies have shown reproductive toxicity (see section 5.3)
Escitalopram should not be used during pregnancy unless clearly needed and after careful consideration of the risk/benefit ratio.

Newborns should be observed if maternal use of escitalopram continues into the later stages of pregnancy, particularly in the third trimester. If escitalopram is used until or shortly before birth, discontinuation effects in the newborn are possible.

The following symptoms may occur in the newborn 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 discontinuation effects or excess serotonergic activity. In a majority of instances, such 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.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).

Breast-feeding
It is expected that escitalopram will be excreted into human milk and breast-feeding is not recommended during the treatment.

Fertility
Animal data have shown that some SSRIs may affect sperm quality (see section 5.3).
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.

4.7 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.

4.8 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.

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 (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (≤1/10000), or not known (can not be estimated from the available data).

System organ class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Not known	Thrombocytopenia
Immune system disorders	Rare	Anaphylactic reaction
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[1]
Psychiatric disorders	Common	Anxiety, restlessness, abnormal dreams, libido decreased Female: anorgasmia
	Uncommon	Bruxism, agitation, nervousness, panic attack, confusional state
	Rare	Aggression, depersonalisation, hallucination
	Not known	Mania, suicidal ideation, suicidal behaviour[2]
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[1]
Eye disorders	Uncommon	Mydriasis, visual disturbance
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Tachycardia
	Rare	Bradycardia
	Not known	Electrocardiogram QT prolonged
Vascular disorders	Not known	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Sinusitis, yawning
	Uncommon	Epistaxis
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea, constipation, 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 Female: postpartum haemorrhage[3] Male: priapism
General disorders and administration site conditions	Common	Fatigue, pyrexia
	Uncommon	Oedema

[1]These events have been reported for the therapeutic class of SSRIs.

[2]Cases of suicidal ideation and suicidal behaviours have been reported during escitalopram therapy or early after treatment discontinuation (see section 4.4).

[3]This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4, 4.6).

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

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 4.2 and 4.4).

4.9 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 prolongation, and arrhythmia) and electrolyte/fluid balance conditions (hypokalaemia, hyponatraemia).

Treatment
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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. Allosteric modulation of the serotonin transporter enhances binding of escitalopram to the primary binding site, resulting in more complete serotonin reuptake inhibition.

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.

Escitalopram is the S-enantiomer of the racemate (citalopram) and is the enantiomer to which the therapeutic activity is attributed. Pharmacological studies have shown that the R-enantiomer is not inert but counteracts the serotonin-enhancing and consequent pharmacological properties of the S-enantiomer.
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-weeks) studies.
The antidepressant effect was evident as early as after two weeks for both 10 and 20 mg doses of escitalopram. After 8 weeks of therapy, escitalopram 20 mg was superior to citalopram 40 mg. A dose-response relationship for escitalopram was clearly seen in the severely depressed patients indicating that they are likely to benefit from a higher dose of escitalopram (20 mg) than the usual starting dose (10 mg).

In a long-term (24-week) double-blind study of escitalopram 10 mg vs citalopram 20 mg, escitalopram was as least as effective as citalopram, and half as many escitalopram patients withdrew because of adverse effects. 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 randomised 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.

Panic disorder
The efficacy of escitalopram in the treatment of panic disorder was demonstrated in a 10-week flexible dose study that compared 5-20 mg/day escitalopram to placebo and racemic citalopram 10-40 mg/day.

Escitalopram was statistically significantly superior to placebo as demonstrated by measurement of panic attack frequency, severity, duration, and accompanying symptoms. Citalopram was also efficacious compared to placebo in the majority of efficacy measures.

For the majority of treatment emergent adverse events reported for at least 5% of patients, reporting frequencies were higher in the citalopram group than in the escitalopram group.

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 placebo-controlled long-term study (24 weeks) efficacy of 5, 10 and 20 mg escitalopram has been demonstrated.

Escitalopram 20 mg/day was statistically significantly superior to paroxetine 20 mg/day as well as to the 5 mg/day and 10 mg/day doses of escitalopram in the treatment of social anxiety. Transient discontinuation symptoms were seen (lasting for less than 2 weeks in all active treatment groups), with significantly higher levels in paroxetine patients than in escitalopram patients (P≤ 0.05).
In pooled data comprising 670 escitalopram-treated patients and 341 placebo-treated patients, there were 58.1% vs 40.2 % responders (CGI-I score of 1 or 2) and 24.8% vs 12.9% remitters (CGI-S score of 1 or 2) (P≤0.001).

Generalised anxiety disorder
Escitalopram in doses of 10 and 20 mg/day was effective in four out of four placebo-controlled studies. 5 mg/day was not effective.

In pooled data from three studies with similar 8-week design and comprising 421 escitalopram-treated patients and 419 placebo-treated patients, there were 47.5% vs 28.9% responders and 37.1% vs 20.8% remitters (P≤0.001). Sustained effect was seen from week 1.

In the fourth study (12 weeks), which included paroxetine, escitalopram 10mg/day was significantly superior to paroxetine 20 mg/day. Transient discontinuation symptoms were seen, with significantly higher levels for paroxetine than for escitalopram 5, 10 and 20 mg/day (P≤0.01).

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

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

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

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

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

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

5.2 Pharmacokinetic properties
Absorption
Absorption is almost complete and independent of food intake. Mean time to maximum concentration (mean Tmax) 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 (Vd,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 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.

Elimination
The elimination half-life (t½ β) after multiple dosing is about 30 hours and the oral plasma clearance (Cloral) 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.

Linearity
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 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 twice as long 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 (CLcr 10-53 ml/min). Plasma concentrations of the metabolites have not been studied, but they may be elevated (see section 4.2).

Polymorphism
It has been observed that poor metabolisers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolisers. No significant change in exposure was observed in poor metabolisers with respect to CYP2D6 (see section 4.2).

5.3 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 haemodynamic effects (reduction in coronary flow) and ischaemia. 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 some SSRIs induces a reduction of fertility index and pregnancy index, reduction in number in implantation and abnormal sperm at exposure well in excess of human exposure.
No animal data related to this aspect are available for escitalopram.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
Microcrystalline cellulose
Colloidal anhydrous silica
Talc
Croscarmellose sodium
Magnesium stearate

Coating:
Hypromellose
Macrogol 400
Titanium dioxide (E 171)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Storage Condition
Store at temperatures not exceeding 30°C.

6.5 Nature and contents of container
Availability :
5mg film-coated tablet – Blister of 14's, Box of 28's
10mg film-coated tablet – Blister of 14's, Box of 14's; Blister of 14's, Box of 28's; & Blister of 7's, Box of 7's (sample)
20mg film-coated tablet – Blister of 14's, Box of 28's

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

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

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Patient to seek medical attention immediately at the first sign of any adverse drug reaction that shall appear.

7. MARKETING AUTHORISATION HOLDER

Manufactured by
H. Lundbeck A/S
Ottiliavej 9,
Valby, 2500, Denmark

Imported and distributed by:
METRO DRUG,INC.
Sta. Rosa Estate, Barangay Macabling,
Santa Rosa, Laguna, Philippines

8. MARKETING AUTHORISATION NUMBER(S)

FDA Registration number:
5mg film-coated tablet – DRP - 7874
10mg film-coated tablet – DRP - 7875
20mg film-coated tablet – DRP - 7873

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
5mg film-coated tablet – 12 September 2008
10mg film-coated tablet – 15 July 2008
20mg film-coated tablet – 23 March 2011

Date of latest renewal:
5 mg film coated tablet - 12 September 2028
10 mg film coated tablet - 15 July 2028
20 mg film coated tablet- 21 July 2028

10. DATE OF REVISION OF THE TEXT

7th of June 2023