SUMMARY OF PRODUCT CHARACTERISTICS

1. Name Of The Medicinal Product

Escitalopram 5 mg film-coated tablets
Escitalopram 10 mg film-coated tablets
Escitalopram 20 mg film-coated tablets

2. Qualitative And Quantitative Composition

Each film-coated tablet contains 5 mg escitalopram (as oxalate).
Each film-coated tablet contains 10 mg escitalopram (as oxalate).
Each film-coated tablet contains 20 mg escitalopram (as oxalate).

3. Pharmaceutical Form

Film-coated tablet.

4. Clinical Particulars

4.1 Therapeutic indications

- Treatment of major depressive episodes.
- Treatment of generalized anxiety disorder.

4.2 Posology and method of administration

Posology

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.

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.

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/day. Treatment benefits and dose should be re-evaluated at regular intervals.

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.

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

Paediatric population Escitalopram should not be used in the treatment of children and adolescents under the age of 18 years.

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} less than 30 ml/min).

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.

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.

Discontinuation symptoms seen when stopping treatment

Abrupt discontinuation should be avoided. When stopping treatment with escitalopram the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of discontinuation symptoms. 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.

Method of administration

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

4.3 Contraindications

- Hypersensitivity to the active substance 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.
- 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.
- 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.

4.4 Special warnings and precautions for use

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

Paediatric population

Escitalopram should not be used in the treatment of pediatric population.

Suicide related behaviors (suicide attempt and suicidal thoughts), and hostility (predominately aggression, oppositional behavior and anger) were more frequently observed in clinical trials among pediatric population 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 the pediatric population 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.

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 (hypoglycaemia 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 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, 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.

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.

Haemorrhage

There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, with medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole) and in patients with known bleeding tendencies.

ECT (electroconvulsive therapy)

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

Serotonin syndrome

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 4.5).

Discontinuation symptoms seen when stopping treatment

Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt. 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, 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”.

Coronary heart disease

Due to limited clinical experience, caution is advised in patients with coronary heart disease.

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 Torsa de Pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases.

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

Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant arrhythmias and should be corrected before treatment with escitalopram is started.

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

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

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

Contra-indicated combinations:

Irreversible non-selective MAOIs

Cases of serious reactions have been reported in patients receiving an SSRI in combination with a non-selective, irreversible monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued SSRI treatment and have been started on such MAOI treatment.

In some cases, the patient developed serotonin syndrome.

Escitalopram is contra-indicated 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. 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.

Irreversible, selective MAO-B inhibitor (selegiline)

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

QT interval prolongation

Pharmacokinetic and pharmacodynamic 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), mefloquin, bupropion and tramadol).

Lithium, tryptophan

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

St. John's Wort

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

Haemorrhage

Altered anti-coagulant effects may occur when escitalopram is combined with oral anticoagulants. Patients receiving oral anticoagulant therapy should receive careful coagulation monitoring when escitalopram is started or stopped.
Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase bleeding-tendency.
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.
Medicinal products inducing hypokalaemia/hypomagnesaemia
Caution is warranted for concomitant use of hypokalaemia/hypomagnesaemia inducing medicinal products as these conditions increase the risk of malignant arrhythmias.
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 co-administered with medicinal products that are mainly metabolised by this enzyme, and that have a narrow therapeutic index, e.g. flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting medicinal products that are mainly metabolised by CYP2D6, e.g. antidepressants such as desipramine, clomipramine and nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.
Co-administration with desipramine or metoprolol resulted in both cases in a 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 Fertility, pregnancy and lactation
Fertility
Animal data have shown that citalopram 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.
Pregnancy
For escitalopram only limited clinical data are available regarding exposed pregnancies. Animal studies have shown reproductive toxicity. Escitalopram should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

Neonates should be observed if maternal use of Escitalopram continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.
The following symptoms may occur in the neonate after maternal SSRI/SNRI use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either serotonergic effects or discontinuation symptoms. In a majority of instances the complications begin immediately or soon (<24 hours) after delivery.
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.
Breastfeeding
It is expected that escitalopram will be excreted into human milk.
Consequently, breast-feeding is not recommended during treatment.

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.
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).

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	Very common	Headache
	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 Ventricular arrhythmia including torsade de pointes

Vascular disorders	Not known	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Sinusitis, yawning
	Uncommon	Epistaxis
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea, constipation, vomiting, dry mouth
	Uncommon	Gastrointestinal haemorrhages (including rectal haemorrhage)
Hepatobiliary disorders	Not known	Hepatitis, liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Sweating increased
	Uncommon	Urticaria, alopecia, rash, pruritus
	Not known	Ecchymosis, angioedemas
Musculoskeletal and connective tissue disorders	Common	Arthralgia, myalgia
Renal and urinary disorders	Not known	Urinary retention
Reproductive system and breast disorders	Common	Male: ejaculation disorder, impotence
	Uncommon	Female: metrorrhagia, menorrhagia
	Not known	Galactorrhoea Male: priapism
General disorders and administration site conditions	Common	Fatigue, pyrexia
	Uncommon	Oedema

[1] 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.

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.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the email productsafety@martindow.com.

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

Management

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

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

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidepressants, selective serotonin reuptake inhibitors

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-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.

Pharmacodynamic effects

In a double-blind, placebo-controlled ECG study in healthy subjects, the change from baseline in QTc (Frederica-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 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 known double-blind, placebo controlled short-term (8-weeks) 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.

Generalized anxiety disorder

Escitalopram in doses of 10 and 20 mg/day was effective in known 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, randomized, maintenance of efficacy study in 373 patients who had responded during the initial 12-week open-label treatment.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

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 ($t_{½\,\beta}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0.6 L/min. The major metabolites have a significantly longer half-life. Escitalopram and major metabolites are assumed to be eliminated by both the hepatic (metabolic) and the renal routes, with the major part of the dose excreted as metabolites in the urine.

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) may be 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.

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.

Reduced renal function

With racemic citalopram, a longer half-life and a minor increase in exposure are known 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 elevated.

Polymorphism

It is known 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.

5.3 Preclinical safety data

- No complete conventional battery of preclinical studies is known 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 known 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 known to be 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.
- Data from known 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 known 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 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

For 5mg:

- Sodium Croscarmellose Type A
- Microcrystalline Cellulose PH-102
- Colloidal Anhydrous Silica V200

- Magnesium Stearate
- Talc
- Corn Starch White
- Opadry White II
- Green Lake Color

For 10mg

- Sodium Croscarmellose
- Type A
- Microcrystalline Cellulose PH 102**
- Colloidal Anhydrous silica V200
- Magnesium Stearate
- Talc
- Corn Starch White
- Opadry White II
- Ponceau 4 Red Lake Color

For 20mg

- Escitalopram Oxalate*
- Sodium Croscarmellose Type A
- Microcrystalline Cellulose PH 102
- Colloidal Anhydrous silica V200
- Corn Starch White
- Magnesium Stearate
- Talc
- Opadry White II
- 85G68918
- Sunset Lake Yellow Color

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

For 5 mg:

CFF Alu Alu 140mm (140 micron) & Al.foil Safepram 5mg. (Pack Size: 14's & 28's)

For 10 mg:

CFF Alu Alu 140mm (140 micron) & Al.foil Safepram 10mg (Pack Size: 10's & 14's)

For 20 mg:

CFF Alu Alu 140mm (140 micron) & Al.foil Safepram 20mg. (Pack Size: 14's)

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder

MARTIN DOW LIMITED
Plot No. 37, Sector 19,
Korangi industrial area,
Karachi-74900,
Pakistan.

8. Marketing Authorisation Number(S)
Safepram Tablet 5mg: 049234
Safepram Tablet 10mg: 041010
Safepram Tablet 20mg: 041046

9. Date Of First Authorisation/Renewal Of The Authorisation
Safepram Tablet 5mg: 07-07-2008
Safepram Tablet 10mg: 02-08-2005
Safepram Tablet 20mg: 02-08-2005