Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lexapro 5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lexapro 5 mg: Each tablet contains 5 mg escitalopram (as oxalate)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablets

Product imported from the UK:
Round, white, film-coated tablet marked with “EK” on one side.

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 generalised 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.
Lexapro 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 behavioural therapy has not been assessed. Pharmacotherapy is part of an overall therapeutic strategy.

Generalised 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 (see section 5.1).

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 5.1).

Elderly patients (> 65 years of age)
Initial dosage is 5mg once daily. Depending on individual patient response the dose may be increased to 10mg daily (see section 5.2)
The efficacy of Lexapro in social anxiety disorder has not been studied in elderly patients.

Children and adolescents (<18 years)
Lexapro should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4).

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) (see section 5.2).

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 5.2).
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 section 5.2).

Discontinuation symptoms seen when stopping treatment
Abrupt discontinuation should be avoided. When stopping treatment with escitalopram the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of discontinuation symptoms (see section 4.4 and 4.8). 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.

4.3 Contraindications

Hypersensitivity to escitalopram or to any of the excipients.

Concomitant treatment with non-selective, irreversible monoamine oxidase inhibitors (MAO-inhibitors) is contraindicated due to the risk of serotonin syndrome with agitation, tremor, hyperthermia etc. (see section 4.5).

The combination of escitalopram with *reversible* MAO-A inhibitors (e.g. moclobemide) or the *reversible non-selective* MAO-inhibitor linezolid is contraindicated due to the risk of onset of a serotonin syndrome (see section 4.5).

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 4.5)

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).

Use in children and adolescents under 18 years of age
Lexapro should not be used in the treatment of children and adolescents under the age of 18 years. Suicide related behaviours (suicide attempt and suicidal thoughts), and hostility (predominately aggression, oppositional behaviour and anger) were more frequently 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 behavioural development are lacking.

Paradoxical anxiety
Some patients with panic disorder may experience increased anxiety symptoms at the beginning of treatment with antidepressants. This paradoxical reaction usually subsides within two weeks during continued treatment. A low starting dose is advised to reduce the likelihood of an anxiogenic effect (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 (hypoglycaemia or hyperglycaemia). Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

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

Other psychiatric conditions for which Lexapro 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 elderly, or patients with cirrhosis, or if used in combination with other medications which may cause hyponatraemia.

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

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

Serotonin syndrome
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 (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).

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

QT interval prolongation
Escitalopram has been found to cause a dose –dependent prolongation of the QT-interval. Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases (see sections 4.3, 4.5, 4.8, 4.9 and 5.1)

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.

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 (see section 4.3). In some cases, the patient developed serotonin syndrome (see section 4.8).

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 (see section 4.3). 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 4.3).

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.
Combinations requiring precautions for use:

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

Medicinal products lowering the seizure threshold
SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquin, bupropion and tramadol).

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

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

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 1A and 111 antiarrhythmics, antipsychotics (e.g. phenotiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, molifloxacin, erythromycin IV, pentamidine, anti-malarian treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine), is contraindicated.

Pharmacokinetic interactions
Influence of other medicinal products on the pharmacokinetics of escitalopram
The metabolism of escitalopram is mainly mediated by CYP2C19. CYP3A4 and CYP2D6 may also contribute to the metabolism although to a smaller extent. The metabolism of the major metabolite S-DCT (demethylated escitalopram) seems to be partly catalysed by CYP2D6.

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

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

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 5.3). Lexapro 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 Lexapro 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.

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 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 (≥1/1,000 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, anorexia2
Psychiatric disorders Common
Anxiety, restlessness, abnormal dreams
Female and male: libido decreased
Female: anorgasmia
Uncommon
Bruxism, agitation, nervousness, panic attack, confusional state
Rare Aggression, depersonalisation, hallucination
Not known
Mania, suicidal ideation, suicidal behaviour1
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/akathisia2
Eye disorders
Uncommon Mydriasis, visual disturbance
Ear and labyrinth disorders Uncommon Tinnitus
Cardiac disorders Uncommon
Tachycardia
Rare Bradycardia
Not known Electrocardiogram QT prolonged
Frequency unknown
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

1.
Cases of suicidal ideation and suicidal behaviours have been reported during escitalopram therapy or early after treatment discontinuation (see section 4.4).
2.
These events have been reported for the therapeutic class of SSRIs.
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 hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases (see sections 4.3, 4.4, 4.5, 4.9, and 5.1)

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.
ECG monitoring is advisable in case of overdose, in patients with congestive heart failure/bradyarrythmias, in patients using concomitant medications that prolong the QT interval, or in patients with altered metabolism e.g.liver impairment
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
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.
Escitalopram has no or low affinity for a number of receptors including 5-HT 1A, 5-HT2, DA D1 and D2 receptors, 1-, 2-, -adrenoceptors, histamine H1, 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 (Frideicia-correction) was 4.3 msec (90% C1:2.2, 6.4) at the 10mg/day dose and 10.7 msec (90% C1: 8.6, 12.8) at the supratherapeutic dose of 30mg/day (see sections 4.3, 4.4, 4.5, 4.8, and 4.9)
Clinical efficacy
Major Depressive Episodes
Escitalopram has been found to be effective in the acute treatment of major depressive episodes in three out of four double-blind, placebo controlled short-term (8-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 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.
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.
Generalised 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 randomized, 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, randomized, double blind, placebo controlled period.

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.

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 (CL_{cr} 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 systemicexposures (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 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

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Over-labelled carton containing two transparent blister strips (14 tablets per strip)
Pack size of 28 tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Primecrown 2010 Limited
4/5 Northolt Trading Estate
Belvue Road
Northolt
Middlesex UB5 5QS
United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1633/14/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th May 2011

10 DATE OF REVISION OF THE TEXT

November 2012