APPROVED
The Order of Ministry of
Health of Ukraine
23.02.2022 No. 360
Registration certificate
No. UA/19243/01/01
No. UA/19243/01/02

INSTRUCTION
for medical use

CIKLOX®

Composition:
active substance: escitalopram oxalate;
1 tablet contains escitalopram oxalate equivalent to escitalopram 10 mg or 20 mg;
excipients: microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, purified talc, magnesium stearate, Opadry white 03F58750 (hypromellose, titanium dioxide (E 171), macrogol, talc).

Pharmaceutical form. Film coated tablets.
Basic physico-chemical properties: white to off white color, oval shape, biconvex, film coated tablet, with break line on one side and plain other side.

Pharmacotherapeutic group. Antidepressants. Selective serotonin reuptake inhibitors (SSRIs).
ATC-code: N06A B10.

Pharmacological properties.
Pharmacodynamics.
Mechanism of action
Escitalopram is a selective inhibitor of serotonin (SSRIs) (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, dopamine 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 serotonin re-uptake is the only likely mechanism of action explaining the pharmacological and clinical effects of escitalopram.
Pharmacodynamic effects
In a double-blind, placebo-controlled ECG study in healthy subjects, the change from baseline in QTc (Fridericia-correction) was 4.3 ms (90% confidence interval (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 "Contraindications" and "Interactions with other medicinal products and other forms of interaction", "Special warnings and precautions for use", "Overdose", "Adverse reactions" sections).
Clinical efficacy
Depression
Escitalopram has been found to be effective in the acute treatment of depression in three out of four double-blind, placebo controlled short-term (8-week) studies. In a long-term relapse

prevention study, 274 patients who had responded during an initial 8-week open label treatment phase with escitalopram 10 or 20 mg/day, were 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-month 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.

Obsessive-compulsive disorder

In a randomised, double-blind, clinical study, 20 mg/day escitalopram separated from placebo on the Yale-Brown Obsessive Compulsive Scale (YBOCS) total score after 12 weeks. After 24 weeks, both 10 and 20 mg/day escitalopram were superior as compared to placebo.

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

Pharmacokinetics.

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 bioavailability 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) 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 "Administration and dosage" section).

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 "Administration and dosage" section).

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 "Administration and dosage" section).

Polymorphism

Insufficient activity of the CYP2C19 isoenzyme showed double plasma concentrations of the drug compared to the normal metabolism of escitalopram. No significant changes in AUC were observed in CYP2D6 isoenzyme deficiency (see "Administration and dosage" section).

Clinical characteristics.

Indications.

- Major depressive episodes;
- panic disorder with or without agoraphobia;
- social anxiety disorder (social phobia);
- obsessive-compulsive disorder;
- generalised anxiety disorder.

Contraindications.

- Hypersensitivity to escitalopram or to any of the excipients;
- concomitant treatment with non-selective irreversible monoamine oxidase inhibitors (MAO-inhibitors) due to the risk of serotonin syndrome with agitation, tremor, hyperthermia etc. (see "Interactions with other medicinal products and other forms of interaction" section);
- combination of escitalopram with reversible MAO-A inhibitors (e.g. moclobemide) or the reversible non-selective MAO-inhibitor linezolid due to the risk of onset of a serotonin syndrome (see "Interactions with other medicinal products and other forms of interaction" section);
- long QT syndrome (congenital or acquired);
- co-administration with medicinal products known to prolong the QT interval (see "Interactions with other medicinal products and other forms of interaction" section).

Interactions with other medicinal products and other forms of interaction.

Contraindicated 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 "Contraindications" section). In some cases, the patient developed serotonin syndrome (see "Adverse reactions" section).

Escitalopram is contraindicated in combination with non-selective, irreversible MAOIs. Escitalopram may be started 14 days after discontinuing treatment with an irreversible MAOI. At least 7 days should elapse after discontinuing escitalopram treatment, before starting a non-selective, irreversible MAOI.

Reversible, selective MAO-A inhibitor (moclobemide)

Due to the risk of serotonin syndrome, the combination of escitalopram with a MAO-A inhibitor such as moclobemide is contraindicated (see "Contraindications" section). If the combination proves necessary, it should be started at the minimum recommended dosage and clinical monitoring should be reinforced (see "Contraindications" section).

Reversible, non-selective MAO-inhibitor (linezolid)

Concomitant use of escitalopram with the antibiotic linezolid is contraindicated in patients treated with escitalopram. If the combination proves necessary, it should be given with minimum dosages and under close clinical monitoring (see "Contraindications" section).

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 (e.g. astemizole, mizolastine), is contraindicated.

<u>Combinations requiring precautions for use</u>

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), antipsychotics (phenothiazines, thioxanthenes, and butyrophenones), mefloquine, bupropion and tramadol).

Lithium, tryptophan

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

St. John's wort

Concomitant use of SSRIs and herbal remedies containing St. John's wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions (see "Special warnings and precautions for use" section).

Anticoagulants

Altered anti-coagulant effects may occur when escitalopram is combined with anticoagulants. Patients receiving oral anticoagulant therapy should receive careful coagulation monitoring when escitalopram is started or stopped.

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

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

<u>Influence of other medicinal products on the pharmacokinetics of escitalopram</u>

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 enzyme 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.

Special warnings and precautions for use.

The following special warnings and precautions apply to the therapeutic class of SSRIs.

Paediatric population

Ciklox® should not be used in the treatment of paediatric population (aged under 18). Suicide related behaviours (suicide attempt and suicidal thoughts), and hostility (predominately aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among the paediatric 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 paediatric population 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 “Administration and dosage” section).

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 escitalopram is prescribed can also be associated with an increased risk of suicide-related events. It is necessary to carefully monitor the condition of patients in the treatment of other psychiatric disorders due to the possibility of simultaneous development of depression.

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.

Bleeding abnormalities and haemorrhage

There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with SSRIs. Therefore, caution should be exercised when treating patients with known bleeding tendencies, 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).

SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see “Pregnancy and breast-feeding” and “Adverse reactions” sections).

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 "Interactions with other medicinal products and other forms of interaction" section).

Discontinuation symptoms seen when stopping treatment

Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt (see "Adverse reactions" section). 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.

Sexual dysfunction

SSRIs/SNRIs may cause symptoms of sexual dysfunction (see "Adverse reactions" section). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

Coronary heart disease (CHD)

Due to limited clinical experience, caution is advised in patients with CHD.

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, 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.

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

Angle-closure glaucoma

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

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per sodium dose, that is to say essentially "sodium-free".

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. Ciklox® 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 Ciklox® 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.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see "Special warnings and precautions for use" and "Adverse reactions" sections).

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. Human case reports with some SSRIs have shown that an effect on sperm quality is reversible.

No other effect on fertility was observed so far.

Effects on ability to drive and use machines.

Although escitalopram has been shown not to affect intellectual function or psychomotor performance, any psychoactive medicinal product may impair judgement or skills. Patients should be cautioned about the potential risk of an influence on their ability to drive a car and operate machinery.

Administration and dosage.

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

Ciklox® 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 and depends on the severity of the disease.

Social anxiety disorder (social phobia)

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.
It is recommended to continue treatment for 3 months to strengthen the effect. Long-term treatment for 6 months has been proven to prevent relapse and can be considered on an individual basis; treatment benefits should be re-evaluated at regular intervals.
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 obsessive-compulsive disorder 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.
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.
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 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.
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 “Special warnings and precautions for use” and “Adverse reactions” sections). 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.
Paediatric population
The drug should not be used in the treatment of children and adolescents under the age of 18 years (see “Special warnings and precautions for use” section).

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 800 mg of escitalopram alone have been taken without any severe symptoms.

Symptoms

Symptoms seen in reported overdose of escitalopram include symptoms mainly related to the CNS (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.

Adverse reactions.

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 and in medical use 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 (cannot be estimated from the available data).

Blood and lymphatic system disorders: not known – thrombocytopenia.

Immune system disorders: rare – anaphylactic reaction.

Endocrine disorders: not known – inappropriate antidiuretic hormone 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 in men and women, anorgasmia in women; uncommon – bruxism (teeth-grinding), agitation (exaltation), 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 (fainting); rare – serotonin syndrome; not known – dyskinesia, movement disorder, convulsion, psychomotor restlessness/akathisia[1].

Eye disorders: uncommon – mydriasis (dilation) of the pupil), 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 (bruise), 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; postpartum hemorrhage[3].
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.
[3] This event has been reported for the therapeutic class of SSRIs/SNRIs (see "Special warnings and precaution for use" and "Pregnancy and lactation" sections).

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.
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 tricyclic antidepressants. 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, 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 to the State Enterprise "State Expert Center of the Ministry of Health of Ukraine", and to the applicant via the website feedback form: https://kusum.ua/pharmacovigilance/.

Shelf-life.
2 years.

Storage conditions.
Store at the temperature below 25ºC.
Keep out of reach of children.

Package.
14 tablets in a blister; 2 or 4 blisters are in a carton package.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of its business activity.
Plot No. M-3, Indore Special Economic Zone, Phase-II, Pithampur, Distt. Dhar, Madhya Pradesh, Pin 454774, India.

Date of last revision.