Prylex®

Escitalopram

FORMS AND PRESENTATION

Prylex® 5: Film coated tablets: Box of 30.
Prylex® 10: Film coated tablets: Box of 30.
Prylex® 15: Film coated tablets: Box of 30.
Prylex® 20: Film coated tablets: Box of 30.

COMPOSITION:

Prylex® 5: Each film coated tablet contains Escitalopram Oxalate equivalent to Escitalopram 5 mg.
Prylex® 10: Each film coated tablet contains Escitalopram Oxalate equivalent to Escitalopram 10 mg.
Prylex® 15: Each film coated tablet contains Escitalopram Oxalate equivalent to Escitalopram 15 mg.
Prylex® 20: Each film coated tablet contains Escitalopram Oxalate equivalent to Escitalopram 20 mg.
Excipients: microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, talc, hydroxypropyl methylcellulose, polysorbate, polyethylene glycol, titanium dioxide.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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.

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,β/F) after oral administration is about 12 to 26 L/kg. The plasma protein binding is below 80% for Escitalopram and its main metabolites.

Biotransformation

Escitalopram is metabolized in the liver to the demethylated and didemethylated metabolites. Both of these are pharmacologically active. Alternatively, the nitrogen may be oxidized to form the N-oxide metabolite. Both parent substance and metabolites are partly excreted as glucuronides. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28-31% and <5%, respectively, of the Escitalopram concentration. Biotransformation of Escitalopram to the demethylated metabolite is mediated primarily by CYP2C19. Some contribution by the enzymes CYP3A4 and CYP2D6 is possible.

Elimination

The elimination half-life ($t_{½}$ β) 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.

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 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.

INDICATIONS

Prylex® is indicated for the treatment of major depressive episodes, panic disorder with or without agoraphobia, social anxiety disorder (social phobia), generalized anxiety disorder and obsessive-compulsive disorder.

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.
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.

PRECAUTIONS

Use in children and adolescents under 18 years of age

Prylex® should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviors (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behavior and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo.

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

The medicinal product should be discontinued in any patient who develops seizures. SSRIs should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. SSRIs should be discontinued if there is an increase in seizure frequency.

Mania

SSRIs should be used with caution in patients with a history of mania/hypomania. SSRIs should be discontinued in any patient entering a manic phase.

Diabetes

In patients with diabetes, treatment with an SSRI may alter glycemic control (hypoglycemia or hyperglycemia). Insulin and/or oral hypoglycemic dosage may need to be adjusted.

Suicide/suicidal thoughts or clinical worsening

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

Akathisia/psychomotor restlessness

The use of SSRIs/SNRIs has been associated with the development of akathisia, characterized by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

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, cirrhotic patients or patients concomitantly treated with medications known to cause hyponatraemia.

Hemorrhage

There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, with medicinal products known to affect platelet function and in patients with known bleeding tendencies.

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.

Discontinuation symptoms seen when stopping treatment

Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt.
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, diarrhea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally these symptoms are mild to moderate; however, in some patients they may be severe in intensity.
They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose.
Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that Escitalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs.

PREGNANCY AND LACTATION

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

DRUG INTERACTIONS

Pharmacodynamic interactions

Contra-indicated combinations:

Irreversible non-selective MAOIs
Escitalopram is contra-indicated in combination with non-selective, irreversible monoamine oxidase inhibitors (MAOIs). In some cases, the patient developed serotonin syndrome.
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), Reversible, non-selective MAO-inhibitor (linezolid) and Irreversible, selective MAO-B inhibitor (selegiline)
Due to the risk of serotonin syndrome, the combination of Escitalopram with the above mentioned products is contraindicated. If the combination proves necessary, it should be started at the minimum recommended dosage and clinical monitoring should be reinforced.
Combinations requiring precautions for use:
Serotonergic medicinal products
Co-administration with serotonergic medicinal products (e.g. tramadol, sumatriptan and other triptans) may lead to serotonin syndrome.
Medicinal products lowering the seizure threshold
SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion and tramadol).
Lithium, tryptophan
There have been reports of enhanced effects when SSRIs have been given together with lithium or tryptophan, therefore concomitant use of SSRIs with these medicinal products should be undertaken with caution.
St. John's Wort
Concomitant use of SSRIs and herbal remedies containing St. John´s Wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions.
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.
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 metabolized by this enzyme, and that have a narrow therapeutic index. Dosage adjustment may be warranted.
In vitro studies have demonstrated that Escitalopram may also cause weak inhibition of CYP2C19. Caution is recommended with concomitant use of medicinal products that are metabolized by CYP2C19.
ADVERSE EFFECTS
Adverse effects are most frequent during the first or second week of treatment and usually decrease in intensity and frequency with continued treatment.
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).
Investigations: Common: weight increased. Uncommon: weight decreased. Not known: liver function test abnormal.
Cardiac disorders: Uncommon: tachycardia. Rare: bradycardia.
Blood and lymphatic disorders: Not known: thrombocytopenia.
Nervous system disorders: Common: insomnia, somnolence, dizziness, paraesthesia, tremor. Uncommon: taste disturbance, sleep disorder, syncope. Rare: serotonin syndrome. Not known: dyskinesia, movement disorder, convulsion.
Eye disorders: Uncommon: mydriasis, visual disturbance.
Ear and labyrinth disorders: Uncommon: tinnitus.
Respiratory, thoracic and mediastinal disorders: Common: sinusitis, yawning. Uncommon: epistaxis.
Gastrointestinal disorders: Very common: nausea. Common: diarrhea, constipation, vomiting, dry mouth. Uncommon: gastrointestinal hemorrhages (including rectal hemorrhage).
Renal and urinary disorders: Not known: urinary retention.
Skin and subcutaneous tissue disorders: Common: sweating increased. Uncommon: urticaria, alopecia, rash, pruritus. Not known: ecchymosis, angioedemas.
Musculoskeletal, connective tissue and bone disorders: Common: arthralgia, myalgia.
Endocrine disorders: Not known: inappropriate ADH secretion.
Metabolism and nutrition disorders: Common: decreased appetite, increased appetite. Not known: hyponatraemia.
Vascular disorders: Not known: orthostatic hypotension.
General disorders and administration site conditions: Common: fatigue, pyrexia. Uncommon: oedema.
Immune system disorders: Rare: anaphylactic reaction.
Hepatobiliary disorders: Not known: hepatitis.
Reproductive system and breast disorders: Common: male: ejaculation disorder, impotence. Uncommon: female: metrorrhagia, menorrhagia. Not known: galactorrhoea, male: priapism.
Psychiatric disorders: Common: anxiety, restlessness, abnormal dreams, female and male: libido decreased, female: anorgasmia. Uncommon: bruxism, agitation, nervousness, panic attack, confusional state. Rare: aggression, depersonalization, hallucination. Not known: mania, suicidal ideation, suicidal behaviour.
The following adverse drug reactions have been reported for the therapeutic class of SSRIs: psychomotor restlessness/akathisia and anorexia.
Discontinuation symptoms are seen when stopping treatment: see "Precautions".
DOSAGE AND ADMINISTRATION
Safety of daily doses above 20 mg has not been demonstrated.
Prylex® 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.
Generalized anxiety disorder
Initial dosage is 10 mg once daily. Depending on the individual patient response, the dose may be increased to a maximum of 20 mg daily. Long-term treatment of responders has been studied for at least 6 months in patients receiving 20 mg daily. Treatment benefits and dose should be re-evaluated at regular intervals.
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.
Elderly patients (> 65 years of age)
Initial treatment with half the usually recommended dose and a lower maximum dose should be considered. The efficacy of Prylex® in social anxiety disorder has not been studied in elderly patients.
Children and adolescents (<18 years)
Prylex® 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.
OVERDOSAGE
Toxicity
Clinical data on Escitalopram overdose are limited and many cases involve concomitant overdoses of other drugs. In the majority of cases mild or no symptoms have been reported. Fatal cases of Escitalopram overdose have rarely been reported with Escitalopram alone; the majority of cases have involved overdose with concomitant medications. Doses between 400 and 800mg of Escitalopram alone have been taken without any severe symptoms.
Symptoms
Symptoms seen in reported overdose of Escitalopram include symptoms mainly related to the central nervous system (ranging from dizziness, tremor, and agitation to rare cases of serotonin syndrome, convulsion, and coma), the gastrointestinal system (nausea/vomiting), and the cardiovascular system (hypotension, tachycardia, QT prolongation, and arrhythmia) and electrolyte/fluid balance conditions (hypokalaemia, hyponatraemia).
Treatment
There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. Gastric lavage and the use of activated charcoal should be considered. Gastric lavage should be carried out as soon as possible after oral ingestion. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.
STORAGE CONDITIONS
Store below 30°C.
Keep in original pack in intact conditions.

Date of revision: December 2015.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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