Zavget™

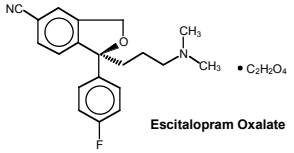
(Escitalopram)

زیوگیٹ

Tablets 10mg

DESCRIPTION

ZAVGET (Escitalopram), a potent selective serotonin reuptake inhibitor (SSRI) is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Chemically escitalopram oxalate is designated S-(+)-1-[3-(dimethyl-amino) propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile oxalate. Its molecular formula is $C_{20}H_{21}FN_2O.C_2H_2O_4$ and has the following structural formula:



Escitalopram Oxalate

QUALITATIVE AND QUANTITATIVE COMPOSITION

ZAVGET (Escitalopram) tablets 10mg is available for oral administration as:

Each film-coated tablet contains:
Escitalopram… 10mg
(as escitalopram oxalate USP)

CLINICAL PHARMACOLOGY
Mechanism of Action

The antidepressant action of escitalopram is presumed to be linked to the potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT).
Escitalopram has high affinity for the primary binding site and an allosteric modulating effect on the serotonin transporter. Allosteric modulation of the serotonin transporter enhances binding of escitalopram to the primary binding site, resulting in more complete serotonin reuptake inhibition.

Pharmacokinetics

Absorption
Absorption is almost complete and independent of food intake (mean t_{max} is 4 hours after multiple dosing). 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 26L/kg. The binding of escitalopram to human plasma proteins is approximately 56%.

Metabolism
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. Unchanged escitalopram is the predominant compound in plasma. Biotransformation of escitalopram to the demethylated metabolite is mediated primarily by CYP2C19. Some contribution by the enzymes CYP3A4 and CYP2D6 is possible.

Excretion
The elimination half-life ($t_{1/2\beta}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cloral) is about 0.6L/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.

Special Populations

Elderly Patients (>65 years)
Escitalopram appears to be eliminated more slowly in elderly patients compared to younger patients. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects and C_{max} was unchanged.

Hepatic Insufficiency
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.

Renal Insufficiency
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).

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.

THERAPEUTIC INDICATIONS

ZAVGET (Escitalopram) is indicated for the treatment of:

- Major depressive disorder.
- Panic disorder with or without agoraphobia.
- Social anxiety disorder (social phobia).
- Generalized anxiety disorder.
- Obsessive-compulsive disorder.

DOSAGE AND ADMINISTRATION

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

Major depressive disorder:

Adolescents (12 to 17 years of age)
The recommended dose of Zavget (escitalopram) is 10mg once daily. If the dose is increased to 20mg, this should occur after a minimum of three weeks.

Adults
The recommended dose of Zavget (escitalopram) is 10mg once daily. Depending on the individual patient response, the dose may be increased to a maximum of 20mg daily. If the dose is increased to 20mg, this should occur after a minimum of one week. 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 5mg is recommended for the first week before increasing the dose to 10mg daily. The dose may be further increased, up to a maximum of 20mg daily, dependent on individual patient response. Maximum effectiveness is reached after about 3 months. The treatment lasts several months.

Social anxiety disorder:

The usual dosage is 10mg once daily. Usually 2-4 weeks are necessary to obtain symptom relief. The dose may be subsequently, depending on individual patient response, be decreased to 5mg or increased to a maximum of 20mg daily. Social anxiety disorder is a disease with a chronic course and treatment for 12 weeks is recommended to consolidate response. Long term treatment for 6 months can be considered on an individual basis to prevent relapse; treatment benefits should be re-evaluated at regular intervals.

Generalised anxiety disorder:

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

Obsessive-compulsive disorder:

Initial dose is 10mg once daily. Depending on individual patient response, the dose may be increased to 20mg daily. As OCD is a chronic disease, patients should be treated for sufficient period to ensure that they are symptom free. Treatment benefits and dose should be re-evaluated at regular intervals.

Special Populations

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.

Patients with Renal Impairment
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 30mL/min.).

Patients with Hepatic Impairment
An initial dose of 5mg daily for the first two weeks of treatment is recommended in patients with mild to moderate hepatic impairment. Depending on individual patient response, the dose may be increased to 10mg 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 5mg daily during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10mg daily.

Discontinuation
When stopping treatment with ZAVGET (Escitalopram) the dose should be gradually reduced over a period of at least one or two weeks in order to reduce the risk of discontinuation symptoms.

ADVERSE EFFECTS

Following are the adverse effects reported during treatment with escitalopram:

Very Common
Nausea.

Common
Decreased appetite, increased appetite, weight increased, anxiety, restlessness, abnormal dreams, libido decreased, anorgasmia, insomnia, somnolence, dizziness, paraesthesia, tremor, sinusitis, yawning, diarrhea, constipation, vomiting, dry mouth, sweating increased, arthralgia, myalgia, ejaculation disorder, impotence, fatigue and pyrexia.

Uncommon
Weight decreased, bruxism, agitation, nervousness, panic attack, confusional state, taste disturbance, sleep disorder, syncope, mydriasis, visual disturbance, tinnitus, tachycardia, epistaxis, gastrointestinal hemorrhages (including rectal hemorrhage), urticaria, alopecia, rash, pruritis, metrorrhagia, menorrhagia and oedema.

Rare
Anaphylactic reaction, serotonin syndrome, aggression, depersonalisation, hallucination and bradycardia.

Withdrawal 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, diarrhea, palpitations, emotional instability, irritability and visual disturbances.

CONTRAINDICATIONS

Escitalopram is contraindicated:

- In patients with hypersensitivity to escitalopram or to any of the excipients.
- To use concomitantly with non-selective, irreversible monoamine oxidase inhibitors (MAO-inhibitors).
- To use concomitantly with reversible MAO-A inhibitors (e.g. moclobemide) or the reversible non-selective MAO-inhibitor linezolid.
- In patients with known QT interval prolongation or congenital long QT syndrome.
- To use concomitantly with drugs that are known to prolong the QT interval.
- To use concomitantly with pimozide.

PRECAUTIONS

Paradoxical anxiety
Some patients with panic disorder may experience increased anxiety symptoms at the beginning of treatment with antidepressants. A low starting dose is advised to reduce the likelihood of an anxiogenic effect.

Seizures
Escitalopram should be discontinued if a patient develops seizures for the first time, or if there is an increase in seizure frequency. SSRIs should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be closely monitored.

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

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

Suicide/suicidal thoughts or clinical worsening
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.

Akathisia/psychomotor restlessness
The use of SSRIs/SNRIs has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness. In patients who develops these symptoms, increasing the dose may be detrimental.

Hyponatremia
Hyponatremia has been reported rarely with the use of SSRIs and generally resolves on discontinuation of therapy. Caution should be exercised in patients at risk.

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

Serotonin syndrome
In rare cases, serotonin syndrome has been reported in patients using SSRIs concomitantly with serotonergic medicinal products. If this occurs treatment with the SSRI and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment initiated.

Coronary heart disease
Caution is advised in patients with coronary heart disease.

QT interval prolongation
Escitalopram has been found to cause a dose-dependent prolongation of the QT interval. 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.

Pregnancy

There are no adequate and well-controlled studies in pregnant women.Therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Escitalopram is excreted in human breast milk. Therefore, breast-feeding is not recommended during treatment.

Drug Interactions

Drugs affecting platelet function
Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants and drugs known to affect platelet function e.g. atypical antipsychotics, phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs), ticlopidine, dipyridamole and in patients with known bleeding tendencies.

Serotonergic drugs
Coadministration with serotonergic drugs (e.g. Tramadol, sumatriptan and other triptans) may lead to an enhancement of serotonergic effects.

Products lowering the seizure threshold
Caution is advised when SSRIs is concomitantly administered with drugs 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 with lithium or tryptophan and therefore concomitant use of SSRIs with these drugs should be undertaken with caution.

Centrally acting drugs
Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

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

Cimetidine/CYP2C19 Inhibitors
Coadministration of escitalopram with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine resulted in an increase of plasma concentrations of escitalopram. Therefore, caution is advised and a reduction in the dose of escitalopram may be necessary based on monitoring of side-effects during concomitant treatment.

CYP2D6 Enzyme
Escitalopram is an inhibitor of CYP2D6. Caution is recommended when escitalopram is coadministered with drugs that are mainly metabolised by CYP2D6 and that have a narrow therapeutic index e.g. flecainide, propafenone and metoprolol or some CNS acting medicinal products that are mainly metabolised by CYP2D6 e.g. antidepressants such as desipramine, clomipramine and nortryptyline or anti-psychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.

Alcohol
The combination of SSRIs and alcohol is not advisable.

OVERDOSAGE

Symptoms
Overdose of escitalopram include symptoms mainly related to the central nervous system (ranging from dizziness, tremor and agitation to rare cases of serotonin syndrome, convulsion and coma), the gastrointestinal system (nausea/vomiting) and the cardiovascular system (hypotension, tachycardia, QT interval prolongation and arrhythmia) and electrolyte/fluid balance conditions (hypokalemia, hyponatremia).

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. 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.

STORAGE

Store at 25°C (Excursions permitted between 15°C - 30°C).
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

ZAVGET (Escitalopram) Tablets 10mg are available in blister pack of 14's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

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