Entapro®

Escitalopram oxalate

WARNINGS : SUICIDALITY AND ANTIDEPRESSANT DRUGS
Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Entapro or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Entapro is not approved for use in pediatric patients.

QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each Entapro tablet contains escitalopram oxalate equivalent to 5 mg, 10mg, or 20 mg escitalopram.
CLINICAL PARTICULARS:
Therapeutic Indications:
Entapro is indicated for:
- The treatment of Major Depressive Disorder (MDD).
- The treatment of Generalized Anxiety Disorder (GAD).

POSOLOGY AND METHOD OF ADMINISTRATION:
Adults
Depression
- The normally recommended dose of Entapro is 10 mg taken as one daily dose. The dose may be increased by doctor's instructions to a maximum of 20 mg per day. If the dose is increased to 20 mg, this should occur after a minimum of one week.

Generalized Anxiety Disorder
- The starting dose of Entapro is 10 mg as one daily dose. The dose may be further increased as per doctor's instructions to a maximum of 20 mg per day. If the dose is increased to 20 mg, this should occur after a minimum of one week.

Special Populations
Elderly patients, Hepatic impairment:
- 10 mg as one daily dose is the recommended dose for most elderly patients and patients with hepatic impairment.

Renal Impairment:
- No dosage adjustment is necessary for patients with mild or moderate renal impairment. Entapro should be used with caution in patients with severe renal impairment.

Children and adolescents (<18 years):
- Entapro should not be used in the treatment of children and adolescents under the age of 18 years.

Remember that:
- Entapro can be administered with or without food.
- As with other medicines for the treatment of depression and panic disorder it may take a few weeks before the patient feels any improvement. Therefore patients should continue to take Entapro even if it takes some time before feeling any improvement in their condition.
- Patient must not change the dose of his medicine without talking to the doctor first.
- The duration of the treatment may vary for each individual.
- Patients should continue to take the tablet for as long as the doctor recommends, even if they begin to feel better. The underlying illness may persist for longtime and if the patient stops his treatment too soon, symptoms may return.
- If the patient forgets to take a dose, he should take the next dose at the usual time and do not take a double dose.
- Abrupt cessation of this kind of medication may cause mild and transient discontinuation symptoms such as dizziness, nausea and headache. When the patient has completed his course of treatment it is therefore advised that the dose of Entapro is gradually reduced over a couple of weeks.

PHARMACOLOGICAL PROPERTIES:
Pharmacodynamic Properties:
Entapro is a Selective Serotonin reuptake Inhibitor and belongs to a group of medicines known as antidepressants. Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. These medicines help to normalize the levels of serotonin in the brain. Disturbances in the serotonin system of the brain are key factors in the development of depression and related disorders.
Pharmacokinetic Properties:
The single and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 27-32 hours. With once-daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of escitalopram in plasma in young healthy subjects was 2.2-2.5 times the plasma concentrations observed after a single dose.
Absorption and Distribution:
Following a single oral dose (20 mg tablet) of escitalopram, peak blood levels occur at about 5 hours. Absorption of escitalopram is not affected by food. The binding of escitalopram to human plasma proteins is approximately 56%.
Metabolism and Elimination:
Following oral administrations of escitalopram, the fraction of drug recovered in the urine as escitalopram and S-demethylcitalopram (S-DCT) is about 8% and 10%, respectively.
Escitalopram is metabolized to S-DCT and S-didemethylcitalopram (S-DDCT). In humans, unchanged escitalopram is the predominant compound in plasma. At steady state, the concentration of the escitalopram metabolite S-DCT in plasma is approximately one-third that of escitalopram. The level of S-DDCT was not detectable in most subjects. In vitro studies show that escitalopram is at least 7 and 27 times more potent than S-DCT and S-DDCT, respectively, in the inhibition of serotonin reuptake, suggesting that the metabolites of escitalopram do not contribute significantly to the antidepressant actions of escitalopram.
In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of escitalopram.
CONTRAINDICATIONS:
- Allergy (hypersensitivity) to escitalopram or any of the other ingredients of Entapro.
- Concomitant use in patient taking non-selective monoamine oxidase inhibitors (MAOIs), such as phenelzine, iproniazid isocarboxazid, nialamide, and tranylcypromine which are also used for the treatment of depression is contraindicated. If the patient has taken any of these medicines he/she will need to wait 14 days before starting taking Entapro tablets. After stopping Entapro, patient must allow 14 days before taking any of these medicines.
- Concomitant use with pimozide is contraindicated.

SPECIAL WARNING &SPECIAL PRECAUTION FOR USE:
PRECAUTIONS:
Discontinuation of treatment:
Symptoms including dizziness, sensory disturbance (e.g. paraesthesia), anxiety, sleep disturbances (including intense dreams), agitation, tremor, nausea, sweating and confusion have been reported following abrupt discontinuation of SSRIs including escitalopram. While these events are usually self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with escitalopram.
No particular patient group appears to be at higher risk of these symptoms; it is therefore recommended that when antidepressant treatment is not longer required, gradual discontinuation by dose-tapering be considered.
Abnormal bleeding:
SSRIs including Entapro may cause an increased incidence of s bleeding (shown as events ranged from increased tendency to develop bruises, epistaxis, petechiae to life-threatening hemorrhages). The risk is increased when patient has tendencies to develop bleedings, and If also takes a medicine known to affect the rate of clotting of the blood (like aspirin, non-steroidal anti-inflammatory drugs some antipsychotics or tricyclic antidepressants).This risk is also increased if patient takes ticlopidine, dipyridamole (both medicines are used to reduce the risk of thrombosis) or oral anticoagulants.
Hyponatremia:
As like other SSRIs, hyponatraemia may occur, predominantly in the elderly and may be associated with the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). The hyponatraemia generally reverses on discontinuation of escitalopram.
Activation of Mania/Hypomania:
As with all drugs effective in the treatment of major depressive disorder, escitalopram should be used cautiously in patients with a history of mania.
Epilepsy or a history of seizures:
Seizures are a potential risk with all antidepressant medication. Caution should be advised when administering Entapro if the patient experienced seizures or an increased frequency of seizures while being treated with Entapro.
WARNINGS:
Use in children and adolescents under 18 years of age:
Entapro 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. 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 behavioral development are lacking.
Potential for Interaction with Monoamine Oxidase Inhibitors:
In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Entapro should not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should be allowed after stopping Entapro before starting an MAOI.
INTERACTION WITH OTHER MEDICAL PRODUCTS AND OTHER FORMS OF INTERACTION:
Patients must tell the doctor or the pharmacist if they are taking or have recently taken any other medicines, including medicines obtained without prescription.
When using Entapro with the following medicines, caution should be exercised:
Lithium: Coadministration of racemic citalopram and lithium had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when Entapro and lithium are coadministered.
Metoprolol: coadminstration with escitalopram increases the Cmax and AUC of beta-adrenergic blocker metoprolol. Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Entapro and metoprolol had no clinically significant effects on blood pressure or heart rate.
Sumatriptan: There have been rare reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.
Cimetidine: may cause increased blood levels of escitalopram. The clinical significance of these findings is unknown.
St. John's Wort (hypericum perforatum) - a herbal remedy used for low spirit the risk of side effects may increase if patient takes Entapro concomitantly with herbal remedies containing St. John>s Wort.
Oral anti-coagulants (medicines like warfarin) efficacy may be altered. Therefore, doctors should probably check the coagulation time of the patient when starting and. discontinuing Entapro in order to verify that the dose of anti-coagulant is still adequate.
Pimozide: In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean C_{max} or AUC of pimozide. The mechanism of this pharmacodynamic interaction is not known.
CYP3A4 and -2C19 Inhibitors - In vitro studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram and ritonavir, a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance.
Drugs Metabolized by Cytochrome P4502D6 - In vitro studies did not reveal an inhibitory effect of escitalopram on CYP2D6. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6.
PREGNANCY AND LACTATION:
FDA Pregnancy Category C
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.
Racemic citalopram, like many other drugs, is excreted in human breast milk. The decision whether to continue or discontinue either nursing or Entapro therapy should take into account the risks of citalopram exposure for the infant and the benefits of Entapro treatment for the mother.
If you are pregnant, ask your doctor or pharmacist before taking any medicine.
EFFECT ON ABILITY TO DRIVE AND USE MACHINES:
Entapro does not cause drowsiness; however, as with any new medicine patients should take care while driving or using machinery until they know how it affects on them.
OVERDOSE:
In clinical trials of escitalopram, there were reports of escitalopram overdose, including overdoses of up to 600 mg, with no associated fatalities. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of escitalopram has been rarely reported.
Symptoms most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, included convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes.
Management of Overdose
Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for Entapro.
SIDE EFFECTS:
Like all medicines, Entapro can cause side effects, although not everybody gets them. The side effects are usually mild and usually disappear after a few days of treatment. Be aware that many of the effects may also be symptoms of your illness and therefore will improve when you start to get better.
If the side effects are troublesome or lost for more than a week, ask your doctor.
Side effects include:
Very common: nausea.
Common: sinusitis, decreased appetite, difficulties falling asleep, feeling sleepy, dizziness, yawning, diarrhea, constipation, increased sweating, sexual disturbances (delayed ejaculation, problems with erection, decreased sexual drive and women may experience difficulties achieving orgasm), fatigue and fever.
Uncommon: Disturbed sleep and taste disturbance.
Rare: Dizziness when you stand up due to low blood pressure, decreased levels of sodium in the blood (the symptoms are feeling sick and unwell with weak muscles or confused), blurring of vision, vomiting, dry mouth, abnormal liver function test (increased amounts of liver enzymes in the blood)and pains in muscles and joints.
High fever, agitation, confusion, trembling and abrupt contractions of muscles may be signs of a serotonin syndrome.
Seizures, tremors, movement disorders (involuntary movements of the muscles), hallucinations, mania, confusion, agitation, anxiety, depersonalization, panic attacks and nervousness, difficulties urinating, flow of milk in women that are not nursing, rash, increased tendency to develop bruises, itching and swelling.
If you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.
PHARMACEUTICAL PARTICULARS
List of excipients
Each tablet contains the following inactive ingredients:
Purified Talc, silicified microcrystalline cellulose, croscarmellose sodium type A, magnesium stearate, polysorbate, titanium dioxide, Polyethylene glycol and hydroxypropyl methylcellulose.
STORAGE:
Store below 30°C.
AVAILABILITY:
Entapro is available as film-coated tablets of 5mg, 10mg, and 20mg.

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 pharmacists who sold the medicament.
- The doctor and the pharmacists 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.

Keep medicaments out of the reach of children
Council of Arab Health Ministers
Union of Arab Pharmacists

Manufactured by **SPIMACO**
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