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For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

ESITAL

(Escitalopram Oxalate Tablets,10mg and 20mg)

COMPOSITION

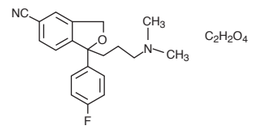
ESITAL 10 : Each film coated tablet contains Escitalopram Oxalate equivalent to Escitalopram ……10mg.

ESITAL 20 : Each film coated tablet contains Escitalopram Oxalate equivalent to Escitalopram ……20mg.

PROPERTIES

Escitalopram oxalate is an orally adminstered selective serotonin reuptake inhibitor. Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Escitalopram oxalate occurs as a fine white to slightly yellow powder.

The molecular formula is $C_{20}H_{21}FN_2O.C_2H_2O_4$ and the molecular weight is 414.40. Chemically it is S-(+)-1-(3-(dimethyl-amino) propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitril oxalate with the following structural formula:



CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of antidepressant action of Escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). Escitalopram is at least 100 fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate.

Escitalopram has no or very low affinity for serotonergic ($5\text{-}HT_{1\text{-}7}$) or other receptors including alpha-and beta-adrenergic, dopamine ($D_{1\text{-}5}$), histamine ($H_{1\text{-}3}$), muscarinic ($M_{1\text{-}5}$) and benzodiazepine receptors. Escitalopram also does not bind to or has low affinity for various ion channels including Na^+, K^+, Cl^- and Ca^{++} channels. Antagonism of muscarinic, histaminergic and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative and cardiovascular side effects of other psychotropic drugs.

PHARMACOKINETICS

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 (20mg tablet) of Escitalopram, the mean Tmax was 5±1.5 hours. Absorption of Escitalopram is not affected by food.

The absolute bioavailability of citalopram is about 80% relative to an intravenous dose, and the volume of distribution of citalopram is about 12L/kg. Data specific to Escitalopram are unavailable.

The binding of Escitalopram to human plasma proteins is approximately 56%.

Metabolism and Elimination:-

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 Escitalopram metabolite S-DCT in plasma is approximately one-third that of Escitalopram. CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of Escitalopram.

Following oral administrations of Escitalopram, the fraction of drug recovered in the urine as Escitalopram and S-demethycitalopram (S-DCT) is about 8% and 10% respectively. The oral clearance of the Escitalopram is 600 mL/min, with approximately 7% of that due to renal clearance.

Population Subgroups:-

Age – Escitalopram AUC and half-life is increased by approximately 50% in elderly subjects, and C_{max} is unchanged. 10mg is the recommended dose for elderly.

Gender –There are no differences in AUC, C_{max} and half-life between the male and female subjects so no adjustment of dosage on the basis of gender is needed.

Reduced renal function – In patients with mild to moderate renal function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No adjustment of dosage for such patients is recommended. No information is available about the pharmacokinetics of Escitalopram in patients with severely reduced renal function (creatinine clearance ≤ 20mL/min).

Reduced Hepatic function - Citalopram oral clearance was reduced by 37% and half –life was doubled in patients with reduced hepatic function compared to normal subjects. 10 mg is recommended dose of Escitalopram for most hepatically impaired patients.

INDICATIONS

ESITAL is indicated for the treatment of major depressive disorder and panic disorder with or without agoraphobia.

CONTRAINDICATIONS

Escitalopram is contraindicated in patients with a hypersensitivity to Escitalopram or citalopram or any of the inactive ingredients in Escitalopram.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOI's) is contraindicated.

WARNINGS

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. Escitalopram should not be used in combination with a MAOI's, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should be allowed after stopping Escitalopram before starting a MAOI.

PRECAUTIONS

General

Hyponatremia:-

Several cases of hyponatremia or SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with racemic citalopram. All patients with these events have recovered with discontinuation of Escitalopram or citalopram and/or medical intervention.

Activation of Mania / Hypomania:-

Activation of mania / hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. Escitalopram should be used cautiously in patients with a history of mania.

Seizures:-

Escitalopram has not been systemically evaluated in patients with a seizure disorder. Like other drugs effective in the treatment of major depressive disorder, Escitalopram should be introduced with care in patients with a history of seizure disorder.

Suicide:-

The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy.

Use in Patients with Concomitant Illness:-

Caution is advisable in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Escitalopram has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease.

In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Escitalopram in hepatically impaired patients is 10 mg / day.

Concomitant Administration with Racemic Citalopram

Since Escitalopram is the active isomer of racemic citalopram, the two agents should not be co-administered.

Use In Pregnancy, Nursing Mothers & Children

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.

Labor and Delivery

The effect of Escitalopram on labor and delivery in humans is unknown.

Nursing Mothers

There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss associated with breast feeding from a citalopram treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother and, in the second case, no follow up information was available. The decision whether to continue or discontinue either nursing or Escitalopram therapy should take into account the risks of citalopram exposure for the infant and the benefits of Escitalopram treatment for the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

CNS Drugs-Due to CNS effects of Escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Alcohol-Although racemic citalopram did not potentiate the congnitive and motor effects of alcohol, the use of alcohol by patients taking Escitalopram is not recommended.

Lithium-Lithium may enhance the serotonergic effects of Escitalopram, caution should be exercised when Escitalopram and lithium are co-administered.

Sumatriptan-There have been rare reports of weakness, hyperreflexia and in-coordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment of sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

Ketoconazole-Combined administration of racemic citalopram (40mg), and Ketoconazole (200mg) decreased the C_{max} and AUC of Ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

CYP3A4 and - 2C19 inhibitors-*In vitro* studies indicated that CYP3A4 are the primary enzymes involved in the metabolism of Escitalopram. However, co-administration of Escitalopram (20mg) and ritonavir (600mg) 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-Co-administration of Escitalopram (20mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. Caution is indicated in the coadministration of Escitalopram and drugs metabolized by CYP2D6.

Metoprolol-Administration of 20 mg/day Escitalopram for 21 days resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker Metoprolol (given in a single dose of 100 mg). Increased Metoprolol plasma levels have been associated with decreased cardio-selectivity. Co-administration of Escitalopram and Metoprolol had no clinically significant effects on blood pressure or heart rate.

Co-administration of citalopram with triazolam, carbamazepine, warfarin, theophylline, digoxin and cimetidine did not affect pharmacokinetics of either citalopram or any of the drugs.

ADVERSE EFFECTS

The most commonly observed adverse events in Escitalopram patients (incidence of approximately 5% or greater) are insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, increased sweating, fatigue and somnolence. The adverse events (incidence of approximately 1%) are palpitation, hypertension, paresthesia, tremor, migraine, light headache feeling, vomiting, heartburn, gastroenteritis, abdominal pain, allergy, fever, chest pain, increased weight, decreased weight, arthralgia, muscle cramp, increased appetite, lethargy, bronchitis, sinus congestion, sinus headache, coughing, rash, vision blurred, ear ache, tinnitus, Urinary tract infection, urinary frequency etc.

DOSAGE AND ADMINISTRATION

Initial Treatment

The recommended dose of Escitalopram is 10mg once daily. If the dose is increased to 20mg, this should occur after a minimum of one week.

Escitalopram should be administered once daily, in the morning or evening, with or without food.

Special Populations

An initial dose of 5mg daily for the first two weeks of treatment is recommended dose for most elderly patients and patients with hepatic impairment. Depending on individual patient response, the dose may be increased to 10 mg/day. No dosage adjustments are necessary for patients with mild or moderate renal impairment. Escitalopram should be used with caution in patients with severe renal impairment.

Maintenance Treatment

Systematic evaluation of continuing Escitalopram 10 or 20mg/day for periods of up to 36 weeks in patients with major depressive disorder who responded while taking Escitalopram during an 8-week acute treatment phase demonstrated a benefit of such maintenance treatment.

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 increased, up to a maximum of 20mg daily, dependent on individual patient response

Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and inhibition of Escitalopram before starting a MAOI.

OVERDOSAGE

Human Experience

There have been three reports of Escitalopram overdose involving doses of up to 600mg. All three patients recovered and no symptoms associated with the overdoses were reported.

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 Escitalopram.

In managing overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

EXPIRY DATE

Do not use later than expiry date.

STORAGE

STORE BELOW 30°C

KEEP ALL TABLETS OUT OF REACH OF CHILDREN.

PRESENTATION

ESITAL 10 : It is available as yellow coloured, round shaped, biconvex film coated tablets with breakline on one side, in blister strip of 10 tablets.

ESITAL 20 : It is available as yellow coloured, oval shaped, biconvex film coated tablets with breakline on one side, in blister strip of 10 tablets.

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Baddi 173 205, Dist. Solan (H.P.) INDIA.

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