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

LEVAZEO SR 75

(Levosulpiride Extended Release Tablets)

DOSAGE FORM

Levosulpiride Extended Release Tablet

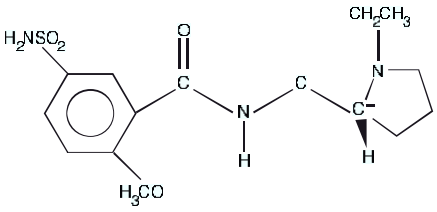
COMPOSITION

Each uncoated extended release tablet contains :

Levosulpiride 75 mg

DESCRIPTION

Levosulpiride is the levorotatory enantiomer of sulpiride. The chemical name of levosulpiride is S-(-)-N-[l-ethyl-2-pirrolidinyl)methyl]-5-sulfamoyl-2-methoxybenzamide. It has a molecular formula is $C_{15}H_{23}N_3O_4S$, molecular weight is 341.42 and chemical structure is :



CLINICAL PHARMACOLOGY

Mechanism of action

Levosulpiride is selective blocks D_2 receptors at the submucosal and myenteric plexus peripheral level. Significant amounts of dopamine are present in the gastrointestinal tract, where it causes a marked inhibitory effect on motility. Dopamine acting at inhibitory dopamine D_2 receptors located on excitatory neuronal structures and smooth muscle was found to cause reduction in lower oesophageal sphincter tone, gastric tone and intragastric pressure, as well as inhibition of gastro duodenal co-ordination. Blockade of peripheral D_2 receptors is considered the main mechanism by which antidopaminergic prokinetic drugs, such as levosulpiride, exert their gastrointestinal stimulatory effect.

Antidopaminergic properties of levosulpiride at D_2 receptors of the chemoreceptor trigger zone in the area postrema of the fourth ventricle floor is responsible for anti emetic property.

Pharmacokinetics

The bioavailability of levosulpiride, when given orally is low (about 27% to 34%) with incomplete absorption as opposed to presystemic metabolism. Food reduces absorption by 30%. Bioequivalence between the IR (2□100mg) and ER 200 mg tablet has been demonstrated (AUC_{0-t} mean ratio 98.5%, 90% confidence interval 85.01-114.12; AUC0-∞ mean ratio 97.6%, 90% confidence interval 85.56-111.21). The time to peak concentration is 3 to 9 hours with median t_{max} 5.5 hours. The oral AUC values for levosulpiride extended release tablet for a dose of 200 mg is 6050 ng.hr/ml. Levosulpiride displays a protein binding of about 14% and a volume of distribution of 1 to 2.7 L/kg which is similar in elderly and younger subjects.

Metabolism does not occur and the drug is excreted unchanged into the urine. The renal clearance is 15 to 30%. The drug is substantially excreted in the feces due to poor absorption. The lack of hepatic metabolism makes metabolic interactions with cytochrome P-450 related substrates very unlikely. The elimination half life ranges from 4.7 to 14.6 hours for oral 200mg dose of levosulpiride ER tablet. The elimination half life is prolonged in patients with renal impairment. The peak concentrations, time to peak levels and the elimination half life is similar in younger and elderly patients.

INDICATIONS

For the treatment of different gastrointestinal problems like functional dyspepsia, nausea, vomiting and diabetic gastroparesis.

DOSAGE AND ADMINISTRATION

In adults, the recommended dosage is 1 tablet of 75 mg once daily before meals.

USE IN SPECIAL POPULATIONS

Pregnancy and Lactation

Not to be used during presumed or confirmed pregnancy and during the lactation period.

CONTRAINDICATIONS

- Hypersensitivity to the drug or any other excipients of the formulation
- Pheochromocytoma as it can cause hypertensive attack probably due to release of catecholamine from tumor; such attacks can be controlled with phentolamine.
- Epilepsy.
- Concomitant prolactin dependent tumors like pituitary gland prolactinomas and breast cancer.
- Pregnancy and lactation.
- Association with levodopa
- In manic conditions and in the manic stages of manic depressive psychoses.

WARNINGS AND PRECAUTIONS

Extrapyramidal reactions, mainly akathisia, and for that dosage reduction warranted. Increased motor agitation at higher dosages Neuroleptic malignant syndrome, a potentially fatal complication, which is characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported. In such an event, or in the event of hyperthermia of undiagnosed origin, all antipsychotic drugs, including Levosulpiride, should be discontinued. Elderly patients are more susceptible to postural hypotension, sedation and extrapyramidal effects. Patients with a convulsion Prolongations of QTc interval or factors that may predispose QTc interval prolongation (Bradycardia, hypokalemia, congenital QTc prolongation, decreased intracardiac conduction) Patients with a history cerebrovascular events (stroke, Venous thromboembolism). Treatment with other neuroleptics.

Special Population

Children

Clinical experience in children under 14 years of age is insufficient to permit specific recommendations.

Elderly
The dose should be reduced if there is evidence of renal impairment.

ADVERSE EFFECTS
Adverse drug reaction:
Cardiovascular disorders
- Postural hypotension
- QT interval prolongation and ventricular arrhythmias such as torsade de pointes and ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death.

Endocrine disorders
- Hyperprolactinaemia, reversible effects of levosulpiride on functioning of hypothalamic pituitary gonadal axis.

General disorders and administration site conditions
- Neuroleptic malignant syndrome
- Weight gain

Hepatobiliary disorders
- Increase in hepatic enzymes

Nervous system disorders
- Sedation or drowsiness. Insomnia has been reported.

Extrapyramidal symptoms and related disorders
- Parkinsonism and related symptoms: tremor, hypertonia, hypokinesia, hypersalivation
- Acute dyskinesia and dystonia (spasm torticollis, oculogyric crisis, trismus), Akathisia
  These symptoms are generally reversible upon administration of antiparkinsonian medication.
- Tardive dyskinesia (characterised by rhythmic, involuntary movements primarily of the tongue and/or the face) have been reported, as with all neuroleptics, after a neuroleptic administration of more than 3 months. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms.
- Convulsions have been reported, in particular in patients with epilepsy.

Reproductive system and breast disorders
- Disorders related to hyperprolactinaemia
- Galactorrhoea
- Amenorrhoea
- Gynaecomastia
- Breast enlargement and breast pain
- Orgasmic dysfunction, erectile dysfunction, change in libido

Skin and subcutaneous tissue disorders
- Maculo-papular rash

Vascular disorders
- Venous thromboembolism, pulmonary embolism and deep vein thrombosis have been reported with antipsychotic drugs-frequency unknown

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
No data regarding carcinogenesis, mutagenesis, impairment of fertility is available

DRUG INTERACTIONS
Levodopa: reciprocal antagonism of effects between levopoda and neuroleptics.
Alcohol: alcohol enhances the sedative effects of neuroleptics.
Bradycardia inducing medications: Beta blockers, calcium channel blockers (verapamil, diltiazem), clonidine, and digitalis
Medications which induce electrolyte imbalance (particularly hypokalemia) hypokalaemic diuretics, stimulant laxatives, IV amp hoterecin B, glucocorticoids, and tetracosectides
Class Ia antiarrhythmic agents such as quinidine, disopyramide
Class III antiarrhythmic agents such as amiodarone, sotalol
Other medications such as pimozide, haloperidol; methadone, imipramine antidepressants; lithium, cisapride, thioridazine, IV erythromycin, halofantrine, pentamidine
Antihypertensive agents: antihypertensive effect and possibility of enhanced postural hypotension
CNS depressants including narcotics, analgesics, sedative H_1 antihistamines, barbiturates, benzodiazepines and other anxiolytics, clonidine and derivatives
Antacids or sucralfate: The absorption of sulpiride is decreased after co-administration; hence, sulpiride should be administered two hours before these drugs
Lithium increases the risk of extrapyramidal side effects
Sulpiride may reduce the effectiveness of ropinorole

OVERDOSAGE
In the normal therapeutic dose range the possibility of the side effects are less. But extra-pyramidal disturbances and sleep disorders may occur with higher doses and in patients who are sensitive to dopamine antagonists.
In such cases therapy should be stopped or the dose should be reduced as dictated by the clinical condition of the patient.

EXPIRY DATE
Do not use later than expiry date.

STORAGE
Store at a temperature not exceeding $30^{O}C$, protected from light and moisture.
Keep out of reach of children

PRESENTATION
Levazeo SR 75 is available in strips of 10 tablets.

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Manufactured by :
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