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

LEVAZEO

(Levosulpiride Tablets)

COMPOSITION

Each uncoated tablet contains :

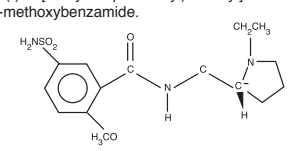
Levosulpiride	50 mg
Excipients	q.s.

Each uncoated tablet contains :

Levosulpiride	100 mg
Excipients	q.s.

DESCRIPTION

Levosulpiride is the levorotatory enantiomer of sulpiride. The chemical structure of levosulpiride is S-(-)-N-[l-ethyl-2- pirrolidinyl) methyl]-5 sulfamoyl-2-methoxybenzamide.



CLINICAL PHARMACOLOGY

Mechanism of action

The mechanism of action of levosulpiride is not fully understood. The drug is a selective though weak D_2 antagonist. It shows dose dependent regional specificity in receptor occupancy and behavioral effects. The preferential blockade of centrally located DA autoreceptors at lower doses and blockade of post synaptic DA receptors at higher doses seems to contribute to the antidepressant and antipsychotic effects of levosulpiride.

Typical antipsychotics are 10-20 times more potent at the D_2 than at the D_3 receptor, while levosulpiride is only 2-3 times more potent at D_2. This lower D_2/D_3 affinity ratio might explain some of the regional preferences of levosulpiride and greater activity on autoreceptors and lower extra- pyramidal side effects associated with D_2 blockade compared to other antipsychotics.

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%. The time to peak concentration is 3 to 4 hours and the peak concentrations achieved are 0.09 mcg/ml for a dose of 50 mg; 0.2 mcg/ml for 100 mg and 0.34 mcg/ml for a dose of 200 mg. The oral AUC values for levosulpiride for a dose of 50 mg is 1275 ng/ml/hour; 100 mg it is 1980 ng/ml/hour and for a dose of 200 mg, the reported AUC value is 3500 ng/ml/hour. The oral AUC values are similar in the younger and elderly patients.

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 6 to 10 hours depending upon the dosage form and route of administration. 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

Levazeo is indicated for the treatment of schizophrenia and depression in adults.

DOSAGE AND ADMINISTRATION

Dosage should be individualized.

Schizophrenia: The recommended dose for adults is 2-3 tablets of Levosulpiride 100mg daily in divided doses.

Maintenance therapy: The recommended maintenance dose of Levosulpiride is 3 tablets of 50 mg in divided doses. The dose can be reduced gradually on individual patient's response and recommendations by the doctor.

Depression: For adults the usually recommended dosage is 2-3 tablets of Levosulpiride 50mg daily in divided doses.

Elderly: Caution is advised when used in the elderly patients and the dose should be carefully stabilized. A possible reduction in dosage should be considered as per the
patient response and tolerance.

Renal impairment: Levosulpiride is primarily excreted renally, and dose adjustments have been suggested in renal insufficiency.

The following modifications are recommended during long-term levosulpiride therapy: creatinine clearance 30 to 60 milliliters / minute: 70% of normal dose; creatinine clearance 10 to 30 milliliters/minute: 50% of normal dose; creatinine clearance less than 16 milliliters/minute: 34% of normal dose; alternatively, the dosage interval can be prolonged by a factor of 1.5, 2 and 3 respectively.

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

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS), a potentially fatal symptom complex, has been reported in association with other antipsychotic drugs. NMS is associated with hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. In such an event, or with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs must be discontinued. The treatment of NMS involves immediate discontinuation of administration of antipsychotic drugs and establishment of intensive symptomatic therapy (particular care should be taken to reduce hyperthermia and correct the dehydration). If resumption of treatment with antipsychotic drugs becomes essential, the patient should be carefully monitored.

Extrapyramidal reactions

Extrapyramidal reactions, mainly akathisia, have been reported with other antipsychotic drugs and for that dosage reduction is warranted.

Gastrointestinal diseases

Levosulpiride should not be used when gastrointestinal stimulation of motility can be harmful, e.g., in presence of gastrointestinal hemorrhage, mechanical obstructions or perforations.

Effects on ability to drive and use machines

Levosulpiride may cause drowsiness in some patients especially at higher doses, thus patients should be advised to exercise caution when driving or operating machinery.

Others

Caution should be exercised in the following patients :

- Patients with convulsion,
- Patients with manic states such as in the manic phase of manic depressive psychosis
- Patients with cardiac insufficiency.
- Patients with cerebrovascular events including risk factors for stroke
- 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)
- Consuming 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. Elderly patients are more susceptible to postural hypotension, sedation and extrapyramidal effects.

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.

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 amphoterecin B, gluco-corticoids, 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, benzo-diazepines 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.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

No data regarding carcinogenesis, mutagenesis, impairment of fertility is available

DRUG INTERACTIONS

Caution is advised when levosulpiride is taken concomitantly with other centrally acting drugs. It can potentiate the cognitive and motor effects of alcohol. The effect of levosulpiride on gastrointestinal motility can be antagonized by anti-cholinergic drugs; narcotics and analgesic drugs.

OVERDOSAGE

Extrapyramidal 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°C, protected from light and moisture.

Keep all medicines out of reach of children.

PRESENTATION

Levazeo 50 & 100 tablets are available in blister of 10 tablets.

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Vill. Bhud & Makhnu Majra, Baddi-173 205,
Teh. Nalagarh, Dist. Solan (H.P.), INDIA.