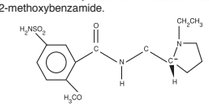
For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only. 8037204-805

# LEVAZEO 25
(Levosulpiride Tablets)

**COMPOSITION**
Each uncoated tablet contains:
Levosulpiride 25 mg
Excipients q.s.

**DESCRIPTION**
Levosulpiride is the levorotatory enantiomer of sulpiride. The chemical structure of levosulpiride is S-(-)-N-[1-ethyl -2-pirrolidinyl) methyl]-5-sulfamoyl-2-methoxybenzamide.



**CLINICAL PHARMACOLOGY**
**Mechanism of action**
Levosulpiride has antidopaminergic action both at central level and 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 is found to cause reduction in lower oesophageal sphincter tone, gastric tone and intragastric pressure, as well as inhibition of gastroduodenal 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 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%. The time to peak concentration is 3 to 4 hours and the peak concentrations achieved are 0.043 mcg/ml for a dose of 25 mg, 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 25 mg is 732 ng/ml/hour; 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 25 is indicated for the treatment of gastro-intestinal problems like functional dyspepsia, nausea, vomiting and diabetic gastroparesis.
**DOSAGE AND ADMINISTRATION**
In adults, the recommended dosage is 1 tablet of 25 mg 3 times daily before meals.
Elderly: Caution is advised when used in elderly patients and the dose should be carefully stabilized.
**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 trelease 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.

**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 amphoterecin 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 H1 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 normal therapeutic dose range the possibility of side effects are less. But 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 the date of expiry.
**STORAGE**
Store at a temperature not exceeding 30$^{O}$C, protected from light and moisture.
Keep all medicines out of reach of children.
**PRESENTATION**
LEVAZEO 25 is available in blister of 10 tablets.

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Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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