SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product:
HAPROL

Haloperidol Injection B.P.

2. Qualitative and quantitative composition :

Sr. No.	Particulars	Grade	Qty. / ml	O.A. %	Function
1.	Haloperidol	BP	5 mg	5.0%	Active

For Full list of Excipients Refer section 6.1

3. Pharmaceutical form :
A clear,colourless solution.

4. Clinical Particulars:

4.1 Therapeutic indications:
HAPROL (haloperidol) is indicated for use in the treatment of schizophrenia & for the control of tics and vocal utterances of Tourette's Disorder.

4.2 Dosage and method of administration:
There is considerable variation from patient to patient in the amount of medication required for treatment. As with all drugs used to treat schizophrenia, dosage should be individualized according to the needs and response of each patient. Dosage adjustments, either upward or downward, should be carried out as rapidly as practicable to achieve optimum therapeutic control.
To determine the initial dosage, consideration should be given to the patient's age, severity of illness, previous response to other antipsychotic drugs, and any concomitant medication or disease state. Debilitated or geriatric patients, as well as those with a history of adverse reactions to antipsychotic drugs, may require less HAPROL (haloperidol). The optimal response in such patients is usually obtained with more gradual dosage adjustments and at lower dosage levels.

Usual Dosage: Parenteral medication, administered intramuscularly in doses of 2 mg to 5 mg, is utilized for prompt control of the acutely agitated schizophrenic patient with moderately severe to very severe symptoms.
Depending on the response of the patient, subsequent doses may be given, administered as often as every hour, although 4 hour to 8 hour intervals may be satisfactory.

Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
For the emergency control of very severely disturbed patients, an initial intramuscular dose of no more than 18 mg is recommended. The intravenous route may also be used.

Haloperidol Injection is not approved for I.V. administration. If administration I.V., the electrocardiogram (ECG) should be monitored for QT prolongation and arrhythmias.

Elderly: Lower initial doses and more gradual dosage adjustments are recommended.

Debilitated: Patients: Lower initial doses and more dosage gradual adjustment are recommended.

Discontinuation of therapy: It is not known whether gradual withdrawal of antisytotic drugs will reduse the rate of occurrence of withdrawal – emergent neurological signs, but until further evidence becomes available, it would be reasonable to gradually withdraw use of haloperidol**.**

4.3 Contraindications:

HAPROL (haloperidol) is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

4.4 Precautions and Warnings:

Increased Mortality in Elderly Patients with Dementia-Related Psychosis.

Elderly patients with dementia related psychosis treated with antipsychotic drugs are at an increased risk of death. HAPROL Injection is not approved for the treatment of patients with dementia-related psychosis.

Cardiovascular Effects:

Cases of sudden death, QT-prolongation, and Torsades de Pointes have been reported in patients receiving HAPROL. Higher than recommended doses of any formulation and intravenous administration of HAPROL appear to be associated with a higher risk of QT-prolongation and Torsades de Pointes. Although cases have been reported even in the absence of predisposing factors, particular caution is advised in treating patients with other QT-prolonging conditions (including electrolyte imbalance [particularly hypokalemia and hypomagnesemia], drugs known to prolong QT, underlying cardiac abnormalities, hypothyroidism, and familial long QTsyndrome).

HAPROL INJECTION IS NOT APPROVED FOR INTRAVENOUS ADMINISTRATION. If HAPROL Injection is administered intravenously, the ECG should be monitored for QT prolongation and arrhythmias.

Tardive Dyskinesia:

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia,

although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process.

The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered.
However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTION)

Neuroleptic Malignant Syndrome (NMS):
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.
The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HAPROL.

4.5 Interaction with other drugs:

Drug-drug interactions can be pharmacodynamic (combined pharmacologic effects) or pharmacokinetic (alteration of plasma levels). The risks of using haloperidol in combination with other drugs have been evaluated as described below.
Pharmacodynamic Interactions Since QT-prolongation has been observed during HAPROL treatment, caution is advised when prescribing to a patient with QT prolongation conditions (long QT-syndrome, hypokalemia, electrolyte imbalance) or to patients receiving medications known to prolong the QT-interval or known to cause electrolyte imbalance.

If concomitant antiparkinson medication is required, it may have to be continued after HAPROL is discontinued because of the difference in excretion rates. If both are discontinued simultaneously, extrapyramidal symptoms may occur. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including antiparkinson agents, are administered concomitantly with HAPROL.
As with other antipsychotic agents, it should be noted that HAPROL may be capable of potentiating CNS depressants such as anesthetics, opiates and alcohol.
Ketoconazole is a potent inhibitor of CYP3A4. Increases in QTc have been observed when haloperidol was given in combination with the metabolic inhibitors ketoconazole (400 mg/day) and paroxetine (20 mg/day). It may be necessary to reduce the haloperidol dosage.

4.6 Pregnancy and Lactation:

Rodents given 2 to 20 times the usual maximum human dose of haloperidol by oral or parenteral routes showed an increase in incidence of resorption, reduced fertility, delayed delivery and pup mortality. No teratogenic effect has been reported in rats, rabbits or dogs at dosages within this range, but cleft palate has been observed in mice given 15 times the usual maximum human dose. Cleft palate in mice appears to be a nonspecific response to stress or nutritional imbalance as well as to a variety of drugs, and there is no evidence to relate this phenomenon to predictable human risk for most of these agents.
There are no well controlled studies with HAPROL (haloperidol) in pregnant women. There are reports, however, of cases of limb malformations observed following maternal use of HAPROL along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy. Causal relationships were not established in these cases. Since such experience does not exclude the possibility of fetal damage due to HAPROL, this drug should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the fetus. Infants should not be nursed during drug treatment. HAPROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

4.7 Effects on ability to drive and operate machine:

Haloperidol has a moderate influence on the ability to drive and use machines. Some degree of sedation or impairment of alertness may occur, particularly with higher doses and at the start of treatment and may be potentiated by alcohol. It is recommended that patients be advised not to drive or operate machines during treatment, until their susceptibility is known.

4.8 Adverse effects:

Cardiovascular Effects:

Tachycardia, hypotension, and hypertension have been reported. QT prolongation and/or ventricular arrhythmias have also been reported, in addition to ECG pattern changes compatible with the polymorphous configuration of torsade de pointes, and may occur more frequently with high doses and in predisposed patients.
Cases of sudden and unexpected death have been reported in association with the administration of HAPROL. The nature of the evidence makes it impossible to determine definitively what role, if any, HAPROL played in the outcome of the reported cases. The possibility that HAPROL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

CNS Effects:
Extrapyramidal Symptoms (EPS):

EPS during the administration of HAPROL (haloperidol) have been reported frequently, often during the first few days of treatment.
EPS can be categorized generally as Parkinson-like symptoms, akathisia, or dystonia (including opisthotonos and oculogyric crisis).
While all can occur at relatively low doses, they occur more frequently and with greater severity at higher doses. The symptoms may be controlled with dose reductions or administration of antiparkinson drugs such as benztropine mesylate USP or trihexyphenidyl hydrochloride USP. It should be noted that persistent EPS have been reported; the drug may have to be discontinued in such cases.

Dystonia:
Class Effect:
Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.
Withdrawal Emergent Neurological Signs:
Generally, patients receiving short-term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration.
It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of HAPROL.
Tardive Dyskinesia:
As with all antipsychotic agents HAPROL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur. After drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females.
The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop.

Tardive Dystonia:
Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible.

Other CNS Effects:
Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole:
Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HAPROL.

Hematologic Effects:
Reports have appeared citing the occurrence of mild and usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis. Agranulocytosis has rarely been reported to have occurred with the use of HAPROL, and then only in association with other medication.

Liver Effects:
Impaired liver function and/or jaundice have been reported.
Dermatologic Reactions: Maculopapular and acne form skin reactions and isolated cases of photosensitivity and loss of hair.

4.8 Over dosage:

Manifestations:
In general, the symptoms of overdosage would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) severe extrapyramidal reactions, 2) hypotension, or 3) sedation. The patient would appear comatose with respiratory depression and hypotension which could be severe enough to produce a shock-like state. The extrapyramidal reactions would be manifested by muscular weakness or rigidity and a generalized or localized tremor as demonstrated by the akinetic or agitans types respectively. With accidental overdosage, hypertension rather than hypotension occurred in a two-year old child. The risk of ECG changes associated with torsade de pointes should be considered. (For further information regarding torsade de pointes)
Treatment:
Since there is no specific antidote, treatment is primarily supportive. A patent airway must be established by use of an oropharyngeal airway or endotracheal tube or, in prolonged cases of coma, by tracheostomy.
Respiratory depression may be counteracted by artificial respiration and mechanical respirators. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. ECG and vital signs should be monitored especially for signs of Q-T prolongation or dysrhythmias and monitoring should continue until the ECG is normal. Severe arrhythmias should be treated with appropriate anti-arrhythmic measures.

5. Pharmacological properties :

5.1 Pharmacodynamic properties :

Pharmacodynamic

Mechanism of action

Haloperidol is an antipsychotic belonging to the butyrophenones group. It is a potent central dopamine type 2 receptor antagonist, and at recommended doses, has low alpha-1 antiadrenergic activity and no antihistaminergic or anticholinergic activity.

Pharmacodynamic effects Haloperidol suppresses delusions and hallucinations as a direct consequence of blocking dopaminergic signaling in the mesolimbic pathway. The central dopamine blocking effect has activity on the basal ganglia (nigrostriatal bundles). Haloperidol causes efficient psychomotor sedation, which explains the favourable effect on mania and other agitation syndromes.

The activity on the basal ganglia probably underlies the undesirable extrapyramidal motor effects (dystonia, akathisia and parkinsonism).

The antidopaminergic effects of haloperidol on lactotropes in the anterior pituitary explain hyperprolactinaemia due to inhibition of dopamine-mediated tonic inhibition of prolactin secretion. Additionally, the antidopaminergic effect on the chemoreceptor-trigger zone of the area postrema explains the activity against nausea and vomiting.

5.2 Pharmacokinetic properties :

Haloperidol is readily absorbed from the gastrointestinal tract. It is metabolised in the liver and is excreted in the urine and, via the bile, in the faeces; there is evidence of enterohepatic recycling. Owing to first-pass metabolism in the liver, plasma concentrations after oral doses are lower than those after intramuscular injection.

Moreover, there is wide intersubject variation in plasma concentrations of haloperidol. In practice, however, no strong correlation has been found between plasma concentrations of haloperidol and its therapeutic effect.

Paths of metabolism of haloperidol include oxidative *N*-dealkylation and reduction of the ketone group to form an alcohol known as reduced haloperidol.

Haloperidol has been reported to have a plasma elimination half-life ranging from about 12 to 38 hours after oral doses. Haloperidol is about 92% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Haloperidol is distributed into breast milk.

5.3 Pre-clinical Safety Data:

Non-clinical data reveal no special hazards for humans based on conventional studies of repeat dose toxicity and genotoxicity. In rodents, haloperidol administration showed a decrease in fertility, limited teratogenicity as well as embryo-toxic effects.

In a carcinogenicity study of haloperidol, dose-dependent increases in pituitary gland adenomas and mammary gland carcinomas were seen in female mice. These tumours may be caused by prolonged dopamine D2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.

Haloperidol has been shown to block the cardiac hERG channel in several published studies in vitro. In a number of in vivo studies, intravenous administration of haloperidol in some animal models has caused significant QTc prolongation at doses around 0.3 mg/kg, producing Cmax plasma levels at least 7 to 14 times higher than the therapeutic plasma concentrations of 1 to 10 ng/ml that were effective in the majority of patients in clinical studies. These intravenous doses, which prolonged QTc, did not cause arrhythmias. In some animal studies, higher intravenous haloperidol doses of 1 mg/kg or greater caused QTc prolongation and/or ventricular arrhythmias at Cmax

plasma levels at least 38 to 137 times higher than the therapeutic plasma concentrations that were effective in the majority of patients in clinical studies.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Lactic acid B.P.
Water for injection B.P. (Bulk)

6.2 Incompatibilities:

Haloperidol Injection should not be mixed with other products unless their compatibility is known.

6.3 Shelf – life:

24 Months

6.4 Special precautions for storage:

Store below 25°C., protected from light. Do not freeze.

6.5 Nature and contents of container:

1 mL amber ampoule with purple band snap off. Such 5 ampoules are packed in a blister pack. Two such blister packs are packed in an inner printed carton along with package insert.

6.6 Special Precautions for Handling and Disposal:

Use as directed by a physician.

7. Marketing authorization holder:

M/s. NEON LABORATORIES LIMITED
140, Damji Shamji Industrial Complex,
28, Mahal Indl. Estate, Mahakali Caves Road,
Andheri (East), Mumbai - 400 093

8. Marketing authorization number :

07805/07602/NMR/2019

9. Date of first authorization / Renewal of the authorisation:

Date of first authorization-23-09-2022

10. Date of revision of the text:

July 2023