HALOPERIDOL TABLETS BP 5 MG

Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

1.1 (Invented) name of the medicinal product

INN (GENERIC NAME)

HALOPERIDOL TABLETS BP 5 MG

1.2 Strength :- 5 MG

1.3 Pharmaceutical form:- Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HALOPERIDOL TABLETS BP 5 MG
Each uncoated tablet contains:
- Haloperidol BP (5 mg)
- Excipients: (0 QS)

Batch Size: 25,25,000 Tablets

Sr. No.	Ingredients	Specification	Quantity/ Tablet (mg)	% overages	Reason for inclusion
Active					
1.	Haloperidol	BP	5.000	0%	Active
Ingredients					
2.	Maize Starch*	BP	90.830	8%	Diluent
3.	Dicalcium Phosphate	BP	32.460	0%	Diluent
4.	Microcrystalline Cellulose	BP	19.000	0%	Diluent
5.	Maize Starch*	BP	4.400	8%	Diluent
6.	Gelatin	BP	1.000	0%	Binder
7.	Sodium Starch Glycollate	BP	5.000	0%	Disintegrant
8.	Methyl Paraben	BP	0.100	0%	Preservative
9.	Propyl Paraben	BP	0.010	0%	Preservative
10.	Alizarin Green	In-house	0.210	0%	Colour
Lubrication					
11.	Purified Talc	BP	5.000	0%	Lubricant
12.	Magnesium Stearate	BP	2.000	0%	Lubricant
13.	Sodium Starch Glycollate	BP	5.000	0%	Disintegrant

*Loss on drying of Maize starch 8%
BP = British Pharmacopoeia

3. PHARMACEUTICAL FORM. :

Pink coloured, circular, flat, uncoated tablets, having a break line on one side & embossing “5” on one side of each tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Management of manifestations of psychotic disorders. Control of tics and vocal utterances of Tourette's disorder.

4.2 Posology and method of administration:

The dosages as suggested below are only averages, one should always try to tailor the dose to the patient's response. This often implies an upward titration in the acute phase, and a gradual reduction in the maintenance phase, in order to determine the minimal effective dose. Higher doses should only be given to patients responding poorly to lower dosages.
Adults
Moderate symptomatology: 0.5-2 mg, 2 or 3 times daily.
Severe symptomatology: 3-5 mg, 2 or 3 times daily.
Geriatric or debilitated patients: 0.5-2 mg, 2 or 3 times daily.
Chronic or resistant patients: 3-5 mg, 2 or 3 times daily.
Patients who remain severely disturbed or inadequately controlled may require dosage adjustment. Daily dosages up to 100 mg may be necessary in some cases to achieve an optimal response.
Children 3-12 Years of Age (15-40 kg body weight)
The initial dosage is 0.5 mg/day. If required, dosage should be increased by an increment of 0.5 mg at 5- to 7-day intervals, until the desired therapeutic effect is achieved. The total dosage may be administered in divided doses, 2-3 times daily.
Maintenance Dosage
After a satisfactory response has been achieved, dosage should then be gradually reduced to the lowest
effective maintenance level.

4.3 Contraindications:

- Comatose states
- Central nervous system (CNS) depression due to alcohol or other depressant drug
- Parkinson's disease
- Known hypersensitivity to HALDOL
- Lesions of basal ganglia

- In common with other neuroleptics, haloperidol has the potential to cause rare prolongation of the

QT interval. Use of haloperidol is therefore contra-indicated in patients with clinically significant cardiac disorders e.g. recent acute myocardial infarction, uncompensated heart failure, arrhythmias treated with class IA and III antiarrhythmic medicinal products, QTc interval prolongation, history of ventricular arrhythmia or torsades de pointes clinically significant bradycardia, second or third degree heart block and uncorrected hypokalaemia. Haloperidol should not be used concomitantly with other QT prolonging drugs.

4.4 Special warnings and precautions for use:

Increased Mortality in Elderly Patients with Dementia Related Psychosis

Rare cases of sudden death have been reported in psychiatric patients receiving antipsychotic drugs, including Haldol.
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.
Cardiovascular effects
Very rare reports of QT prolongation and/or ventricular arrhythmias, in addition to rare reports of sudden death, have been reported with haloperidol. They may occur more frequently with high doses and in predisposed patients.
The risk-benefit of haloperidol treatment should be fully assessed before treatment is commenced and patients with risk factors for ventricular arrhythmias such as cardiac disease, family history of sudden death and/or QT prolongation; uncorrected electrolyte disturbances, subarachnoid hemorrhage, starvation or alcohol abuse, should be monitored carefully (ECGs and potassium levels), particularly during the initial phase of treatment, to obtain steady plasma levels.
The risk of QT prolongation and/or ventricular arrhythmias may be increased with higher doses or with parenteral use, particularly intravenous administration. ECG monitoring should be performed for QT interval prolongation and for serious cardiac dysrhythmias if Haldol is administered intravenously.
Tachycardia and hypotension have also been reported in occasional patients.

Haloperidol should be used with caution in patients known to be slow metabolisers of CYP2D6, and during use of cytochrome P450 inhibitors. Concomitant use of antipsychotics should be avoided.

Baseline ECG is recommended prior to treatment in all patients, especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination. During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual basis. Whilst on therapy, the dose should be reduced if QT is prolonged, and haloperidol should be discontinued if the QTc exceeds 500 ms. Periodic electrolyte monitoring is recommended, especially for patients taking diuretics, or during intercurrent illness.

An approximately 3-fold increase risk of cerebrovascular adverse events have been seen in randomized placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Haloperidol should be used with caution in patients with risk factors for stroke.

Neuroleptic malignant syndrome

In common with other antipsychotic drugs, Haldol has been associated with neuroleptic malignant syndrome: a rare idiosyncratic response characterized by hyperthermia, generalised muscle rigidity, autonomic instability,and altered consciousness. Hyperthermia is often an early sign of this syndrome. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Tardive dyskinesia

As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or after drug discontinuation. The syndrome is mainly characterized by rhythmic involuntary movements of the tongue, face, mouth or jaw. The manifestations may be permanent in some patients. The syndrome may be masked when treatment is reinstituted, when the dosage is increased or when a switch is made to a different antipsychotic drug. Treatment should be discontinued as soon as possible.

Extrapyramidal symptoms

In common with all antipsychotics, extra pyramidal symptoms may occur, e.g. tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia. Antiparkinson drugs of the anticholinergic type may be prescribed as required, but should not be prescribed routinely as a preventive measure. If concomitant antiparkinson medication is required, it may have to be continued after stopping Haldol if its excretion is faster than that of Haldol in order to avoid the development or aggravation of extrapyramidal symptoms. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including antiparkinson agents, are administered concomitantly with Haldol.

Seizures/convulsions

It has been reported that seizures can be triggered by Haldol. Caution is advised in patients suffering from epilepsy and in conditions predisposing to convulsions (e.g., alcohol withdrawal and brain damage).

Hepatobiliary concerns

As Haldol is metabolized by the liver, caution is advised in patients with liver disease. Isolated cases of liver function abnormalities or hepatitis, most often cholestatic, have been reported.

Endocrine system concerns
Thyroxin may facilitate Haldol toxicity. Antipsychotic therapy in patients with hyperthyroidism should be used only with great caution and must always be accompanied by therapy to achieve a euthyroid state. Hormonal effects of neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligo- or amenorrhoea. Very rare cases of hypoglycaemia and of Syndrome of Inappropriate ADH Secretion have been reported.
Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Haldol and preventive measures undertaken.
Additional considerations
In schizophrenia, the response to antipsychotic drug treatment may be delayed. Also, if drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months. Acute withdrawal symptoms including nausea, vomiting and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Relapse may also occur and gradual withdrawal is advisable. As with all antipsychotic agents, Haldol should not be used alone where depression is predominant. It may be combined with antidepressants to treat those conditions in which depression and psychosis coexist.

4.5 Interaction with other medicinal products and other forms of interaction:

Concomitant use of haloperidol with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including torsade de pointes. Therefore concomitant use of these products is not recommended. Examples include certain antiarrhythmics, such as those of Class 1A (such as quinidine, disopyramide and procainamide) and class III (such as amiodarone, sotalol and dofetilide), certain antimicrobials (sparfloxacin, moxifloxacin, erythromycin IV), tricyclic antidepressants (such as amitriptyline), certain tetracyclic antidepressants (such as maprotiline), other neuroleptics (e.g. phenothiazines, pimozide and sertindole), certain antihistamines (such as terfenadine), cisapride, bretylium and certain antimalarials such as quinine and mefloquine. This list is not comprehensive. Concurrent use of drugs causing electrolyte imbalance may increase the risk of ventricular arrhythmias and is not recommended. Diuretics, in particular those causing hypokalaemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred. Haloperidol is metabolized by several routes, including glucuronidation and the cytochrome P450 enzyme system (particularly CYP 3A4 or CYP 2D6). Inhibition of these routes of metabolism by another drug or a decrease in CYP 2D6 enzyme activity may result in increased haloperidol concentrations and an increased risk of adverse events, including QT-prolongation. In pharmacokinetic studies, mild to moderately increased haloperidol concentrations have been reported when haloperidol was given concomitantly with drugs characterized as substrates or inhibitors of CYP 3A4 or CYP 2D6 isozymes, such as, itraconazole, nefazodone, buspirone, venlafaxine, alprazolam, fluvoxamine, quinidine, fluoxetine, sertraline, chlorpromazine, and promethazine. A decrease in CYP2D6 enzyme activity may result in increased haloperidol concentrations. Increases in QTc have been observed when haloperidol was given with a combination of the metabolic inhibitors ketoconazole (400 mg/day) and paroxetine (20 mg/day). It may be necessary to reduce the haloperidol dosage.
Caution is advised when used in combination with drugs known to cause electrolyte imbalance.

Effect of Other Drugs on Haloperidol
When prolonged treatment with enzyme-inducing drugs such as carbamazepine, phenobarbital, rifampicine is added to Haldol therapy, this results in a significant reduction of haloperidol plasma levels. Therefore, during combination treatment, the Haldol dose should be adjusted, when necessary. After stopping such drugs, it may be necessary to reduce the dosage of Haldol. Sodium valproate, a drug known to inhibit glucuronidation, does not affect haloperidol plasma concentrations.
Effect of Haloperidol on Other Drugs
In common with all antipsychotics, Haldol can increase the central nervous system depression produced by other CNS-depressant drugs, including alcohol, hypnotics, sedatives or strong analgesics. An enhanced CNS effect, when combined with methyldopa, has also been reported. Haldol may antagonise the action of adrenaline and other sympathomimetic agents and reverse the bloodpressure-lowering effects of adrenergic-blocking agents such as guanethidine. Haldol may impair the antiparkinson effects of levodopa. Haloperidol is an inhibitor of CYP 2D6. Haldol inhibits the metabolization of tricyclic antidepressants, thereby increasing plasma levels of these drugs.
Other Forms of Interaction
In rare cases the following symptoms were reported during the concomitant use of lithium and haloperidol: encephalopathy, extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, brain stem disorder, acute brain syndrome and coma. Most of these symptoms were reversible. It remains unclear whether this represents a distinct clinical entity. Nonetheless, it is advised that in patients, who are treated concomitantly with lithium and Haldol, therapy should be stopped immediately if such symptoms occur. Antagonism of the effect of the anticoagulant phenindione has been reported.
The dosage of anticonvulsants may need to be increased to take account of the lowered seizure threshold.

4.6 Pregnancy and lactation:

Not known.

4.7 Effects on ability to drive and use machines:

Not known.

4.8 UNDESIRABLE EFFECTS:

The safety of haloperidol was evaluated in 284 haloperidol-treated patients who participated in 3 placebo-controlled clinical studies and in 1295 haloperidol-treated patients who participated in 16 double-blind active comparator-controlled clinical studies.

Based on pooled safety data from these clinical studies, the most commonly reported adverse reactions were: extrapyramidal disorder (34%), insomnia (19%), agitation (15%), hyperkinesia (13%), headache (12%), psychotic disorder (9%), depression (8%), weight increased (8%), tremor (8%), hypertonia (7%), orthostatic hypotension (7%), dystonia (6%) and somnolence (5%).

In addition, the safety of haloperidol decanoate was evaluated in 410 patients who participated in 3 comparator studies (1 comparing haloperidol decanoate versus fluphenazine and 2 comparing the decanoate formulation to oral haloperidol), 9 open label studies and 1 dose response study.

Table 2 lists adverse reactions as follows:

• Reported in clinical studies with haloperidol.

• Reported in clinical studies with haloperidol decanoate and relate to the active moiety.

• From postmarketing experience with haloperidol and haloperidol decanoate.

Adverse reaction frequencies are based on (or estimated from) clinical trials or epidemiology studies with haloperidol, and classified using the following convention:

Very common: ≥ 1/10
Common: ≥1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to <1/1,000
Very rare: <1/10,000
Not known: cannot be estimated form the available data

The adverse reactions are presented by System Organ Class and in order of decreasing seriousness within each frequency category.

Table 2: Adverse reactions

System Organ Class	**Adverse Reactions**				
	Frequency				
	Very Common	**Common**	**Uncommon**	**Rare**	**Not Known**
Blood and lymphatic system disorders			Leukopenia		Agranulocytosis; Neutropenia; Pancytopenia; Thrombocytopenia
Immune system disorders			Hypersensitivity		Anaphylactic reaction
Endocrine disorders				Hyperprolactinaemia	Inappropriate antidiuretic hormone secretion
Metabolic and nutritional disorders					Hypoglycaemia
Psychiatric disorders	Agitation; Insomnia	Depression; Psychotic disorder	Confusional state; Libido Decreased; Loss of libido;		

			Restlessness		
Nervous system disorders	Extrapyramidal disorder; Hyperkinesia; Headache	Tardive dyskinesia; Dystonia; Dyskinesia; Akathisia; Bradykinesia; Hypokinesia; Hypertonia; Somnolence; Tremor; Dizziness	Convulsion; Parkinsonism; Sedation; Muscle Contractions Involuntary	Motor dysfunction; Neuroleptic malignant syndrome; Nystagmus;	Akinesia; Cogwheel rigidity; Masked Facies
Eye disorders		Oculogyric Crisis; Visual disturbance	Vision blurred		
Cardiac disorders			Tachycardia		Ventricular Fibrillation; Torsade de pointes; Ventricular Tachycardia; Extrasystoles
Vascular disorders		Orthostatic Hypotension; Hypotension			
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Bronchospasm	Laryngeal Oedema; Laryngospasm
Gastrointestinal disorders		Constipation; Dry mouth; Salivary hypersecretion; Nausea; Vomiting			
Hepatobiliary disorders		Liver function test abnormal	Hepatitis; Jaundice		Acute Hepatic Failure; Cholestasis
Skin and subcutaneous tissue disorders		Rash	Photosensitivity Reaction; Urticaria; Pruritus; Hyperhidrosis		Angioedema; Leukocytoclastic Vasculitis; Dermatitis Exfoliative
Musculoskeletal and connective tissue disorders			Torticollis; Muscle rigidity; Muscle Spasms; Musculoskeletal stiffness	Trismus; Muscle Twitching	Rhabdomyolysis

Renal and urinary disorders		Urinary retention			
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal (see 4.6)
Reproductive system and breast disorders		Erectile dysfunction	Amenorrhoea; Dysmenorrhoea; Galactorrhoea; Breast Discomfort; Breast Pain;	Menorrhagia; Menstrual Disorder; Sexual Dysfunction	Priapism Gynaecomastia ,
General disorders and administration site conditions			Gait disturbance; Hyperthermia; Oedema		Sudden Death; Face Oedema; Hypothermia
Investigations		Weight increased; Weight decreased		Electrocardiogram QT prolonged	

Electrocardiogram QT prolonged, ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia), torsade de pointes and sudden death have been reported with haloperidol.

Class effects of antipsychotics

Cardiac arrest has been reported with antipsychotics.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotics. The frequency is unknown.

4.9 OVERDOSE:

Symptoms and signs

The manifestations of haloperidol overdose are an exaggeration of the known pharmacological effects and adverse reactions. The most prominent symptoms are: severe extrapyramidal reactions, hypotension,

sedation. An extrapyramidal reaction is manifest by muscular rigidity and a generalised or localised tremor.

Hypertension rather than hypotension is also possible.

In extreme cases, the patient would appear comatose with respiratory depression and hypotension that could be severe enough to produce a shock-like state. The risk of ventricular arrhythmias, possibly associated with QT-prolongation, should be considered.

Treatment

There is no specific antidote. Treatment is largely supportive . Activated charcoal may be administered

For comatose patients, a patent airway should be established by use of an oropharyngeal airway or endotracheal tube. Respiratory depression may necessitate artificial respiration. ECG and vital signs should be monitored and monitoring should continue until the ECG is normal. Severe arrhythmias should be treated with appropriate anti-arrhythmic measures. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin and vasopressor agents such as dopamine or noradrenaline. Adrenaline should not be used, since it might cause profound hypotension in the presence of Haldol. In cases of severe extrapyramidal reactions, antiparkinson medication (e.g. benztropine mesylate 1 to 2 mg IM or IV) should be administered parenterally.

5 Pharmacological Properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: antipsychotics, ATC code: N05AD01

Mechanism of action

Haloperidol is an antipsychotic, belonging to the group of the butyrophenones. Haloperidol is a potent central dopamine receptor antagonist and, therefore, is classified among the very incisive antipsychotics. Haloperidol has no antihistaminergic or anticholinergic activity.

Pharmacodynamic effects

As a direct consequence of the central dopamine blocking effect, haloperidol has an incisive activity on delusions and hallucinations (probably due to an interaction in the mesocortical and limbic tissues) and an 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 extrapyramidal motor side-effects (dystonia, akathisia and parkinsonism).

The more peripheral antidopaminergic effects explain the activity against nausea and vomiting (via the chemoreceptor-trigger zone), the relaxation of the gastro-intestinal sphincters and the increased prolactin release (through an inhibition of the activity of the prolactin inhibiting factor, PIF, at the level of the adenohypophysis).

5.2 Pharmacokinetic properties:

Absorption

Following oral administration, the bioavailability of the drug is 60 to 70%. Peak plasma levels of haloperidol occur within two to six hours of oral dosing and about twenty minutes after intramuscular administration.

Distribution

Plasma protein binding is 92%. The volume of distribution at steady state (VDss) is large (7.9 ± 2.5 L/kg). Haloperidol crosses the blood-brain barrier easily.

Metabolism

Haloperidol is metabolized by several routes including the cytochrome P450 enzyme system (particularly CYP3A4 or CYP 2D6) and glucuronidation.

Elimination

The mean plasma half-life (terminal elimination) is 24 hours (range 12 to 38 hours) after oral administration and 21 hours (range 13 to 36 hours) after intramuscular administration. Excretion occurs with the faeces (60%) and the urine (40%). About 1% of the ingested haloperidol is excreted unchanged with the urine.

Therapeutic Concentrations

It has been suggested that a plasma haloperidol concentration range from 4 µg/L to an upper limit of 20 to 25 µg/L is required for a therapeutic response.

5.3 Preclinical safety data:

Not known.

6 Pharmaceutical Particulars

6.1 List of Excipients.

Sr. No.	Excipients	Quality standard	Overages (%)
1.	Maize Starch	BP	8%
2.	Dicalcium Phosphate	BP	0%
3.	MicroCrystalline Cellulose	BP	0%
4.	Maize Starch	BP	8%
5.	Gelatin	BP	0%
6.	Sodium Starch Glycollate	BP	0%
7.	Brilliant Blue Supra	IHS	0%
8.	Methyl Paraben	BP	0%
9.	Propyl Paraben	BP	0%
10.	Purified Talc	BP	0%
11.	Magnesium stearate	BP	0%
12.	Sodium Starch Glycollate	BP	0%

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store below 30^0C

6.5 Nature and contents of container

Jar pack of 1000 tablets