SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CIDOL-5 Injection /Haloperidol Injection BP 5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Haloperidol BP 5mg

3. PHARMACEUTICAL FORM

Solution for Injection
A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Haloperidol is a butyrophenone neuroleptic drug with a wide range of actions. It is indicated for the rapid control of the symptoms of hostility, aggression, hyperactivity, disruptive and violent behaviour, confusion, emotion withdrawal, hallucination and delusions associated with acute and chronic schizophrenia, mania and hypomania and organic brain syndrome.
Haloperidol is also indicated for the treatment of nausea and vomiting.

4.2 Posology and Method of Administration

Posology

Adults

A low initial dose is recommended and this must be adjusted according to the patient's response in order to determine the minimal effective dose.
The dose recommendations for Haloperidol solution for injection are presented in below.
Haloperidol dose recommendations for adults aged 18 years and above.

Rapid control of severe acute psychomotor agitation associated with psychotic disorder or manic episodes bipolar I disorder when oral therapy is not appropriate
May be repeated hourly until sufficient symptom control is achieved.
• In the majority of patients, doses of up to 15 mg/day are sufficient. The maximum dose is 20 mg/day.
• The continued use of haloperidol should be evaluated early in treatment. Treatment with haloperidole injection must be discontinued as soon as clinically indicated and, if further treatment is needed, oral haloperidol should be initiated at a 1:1 dose conversion rate followed by dose adjustment according to clinical response.
Acute treatment of delirium when non-pharmacological treatments have failed.
• 1 to 10 mg intramuscularly.
• Treatment should be started at the lowest possible dose, and the dose should be adjusted in increments at 2- to 4 hour intervals if agitation continues, up to a maximum of 10 mg/day.
Treatment of mild to moderate chorea in Huntington's disease, when other medicinal products are ineffective or not tolerated, and oral therapy is not appropriate
• 2 to 5 mg intramuscularly.
• May be repeated hourly until sufficient symptom control is achieved or up to a maximum of 10 mg/day.
Single or combination prophylaxis in patients at moderate to high risk of postoperative nausea and vomiting when other medicinal products are ineffective or not tolerated
• 1 to 2 mg intramuscularly, at induction or 30 minutes before the end of anaesthesia.
Combination treatment of postoperative nausea and vomiting when other medicinal products are ineffective not tolerated
• 1 to 2 mg intramuscularly.

Method of administration
Haloperidol solution for injection is recommended for intramuscular administration only.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed.
- Comatose state.
- Central nervous system (CNS) depression.
- Parkinson's disease.
- Dementia with Lewy bodies.
- Progressive supranuclear palsy.
- Known QTc interval prolongation or congenital long QT syndrome.
- Recent acute myocardial infarction.
- Uncompensated heart failure.
- History of ventricular arrhythmia or torsades de pointes.
- Uncorrected hypokalaemia.
- Concomitant treatment with medicinal products that prolong the QT interval.

4.4 Special warnings and precautions for use

Cardiovascular Effects
Cases of sudden death, QT prolongation, and torsade de pointes have been reported in patients receiving haloperidol. Higher than Recommended doses of any formulation and intravenous Administration of haloperidol appear to be associated with a higher Risk of qt-prolongation and torsade 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 qt syndrome). Haloperidol must not be administered Intravenously. If haloperidol is administered intravenously, the ecg Should be monitored for qt prolongation and arrhythmias.

Hematologic

Venous Thromboembolism
Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs, including haloperidol injection, in case reports and/or observational studies. When prescribing Haloperidol Injection USP all potential risk factors for VTE should be identified and preventative measures undertaken.

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 the syndrome 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.
Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs and for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

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.

Withdrawal Emergent Syndrome

Generally, patients receiving short-term antipsychotic therapy experience no untoward effects if treatment is abruptly discontinued. However, in some patients, abrupt withdrawal of antipsychotic medication can precipitate transient dyskinetic signs which in certain cases are indistinguishable from tardive dyskinesia except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the incidence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw their use.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestation 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 Haloperidol Injection USP (intramuscular).

Respiratory

A number of cases of bronchopneumonia, some fatal, have followed the use of antipsychotic drugs, including Haloperidol Injection USP (intramuscular). It has been postulated that lethargy and decreased sensation of thirst due to central inhibition may lead to dehydration, hemoconcentration and reduced pulmonary ventilation. Therefore, if the above signs and symptoms appear, especially in the elderly, the physician should institute remedial therapy promptly.

Driving and Hazardous Activities

Haloperidol may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be warned accordingly.

Endocrine and Metabolism

Hyperglycemia: Diabetic ketoacidosis (DKA) has occurred in patients with no reported history of hyperglycemia. Patients should have baseline and periodic monitoring of blood glucose and body weight.

Hyperprolactinemia: Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

Genitourinary

Rare cases of priapism have been reported with antipsychotic use, such as haloperidol. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

General
Although not reported with haloperidol injection (intramuscular), decreased serum cholesterol and/or cutaneous and ocular changes have been reported in patients receiving chemically-related drugs.
The use of alcohol with this drug should be avoided due to possible additive effects and hypotension.

PRECAUTIONS
Haloperidol injection should be administered cautiously to patients:
- with severe cardiovascular disorders, because of the possibility of transient hypotension and/or precipitation of anginal pain. Should hypotension occur and a vasopressor be required, epinephrine should not be used since haloperidol may block its vasopressor activity and paradoxical further lowering of the blood pressure may occur. Instead, phenylephrine or norepinephrine should be used.
- receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because haloperidol may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained.
- with known allergies, or with a history of allergic reactions to drugs, including other neuroleptics.
- receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione).

Central Nervous System Effects
Haloperidol may lower the convulsive threshold and has been reported to trigger seizures in previously controlled known epileptics. When instituting haloperidol therapy in these patients, adequate anticonvulsant medication should be maintained.
Severe neurotoxicity (rigidity, inability to walk or talk) may occur in patients with thyrotoxicosis who are also receiving antipsychotic medication, including haloperidol.
Although haloperidol is a relatively non-sedating neuroleptic, sedation may occur in some patients. Therefore, physicians should be aware of this possibility and caution patients about the danger of participating in activities requiring complete mental alertness, judgment and physical coordination, such as driving and operating machinery.
Caution is also advised in patients with pheochromocytoma and conditions predisposing to epilepsy such as alcohol withdrawal and brain damage.

Psychiatric Effects
When haloperidol is used to control mania in cyclic disorders, there may be a rapid mood swing to depression.

Cardiovascular Effects
Administration to patients with severe cardiac disease should be guarded, despite the fact that haloperidol is well tolerated by patients with cardiac insufficiency. In very rare instances, it has been felt that haloperidol contributed to the precipitation of attacks in angina-prone patients.
Moderate hypotension may occur with intramuscular administration or excessive oral doses of haloperidol; however, vertigo and syncope occur rarely. Haloperidol may antagonize the action of adrenaline and other sympathomimetic agents and reverse the blood pressure-lowering effects of
adrenergic-blocking agents such as guanethidine.

General
Haloperidol has lowered the level of cholesterol in the serum and liver of monkeys. In man, mild transient decreases in serum cholesterol were reported in preliminary studies. However, in a study involving a group of schizophrenic patients on extended medication, significant lowering of serum cholesterol was not observed with haloperidol.
Skin and eye changes (ichthyosis and cataracts) have occurred with other butyrophenone derivatives but have not been observed in patients receiving haloperidol. However, it is advisable that all patients receiving haloperidol for a prolonged period of time be carefully observed for any changes in the skin and eyes. If such changes are seen, the drug should be discontinued promptly.
The antiemetic action of haloperidol may obscure signs of toxicity due to overdosage of other drugs or mask the symptoms of some organic diseases such as brain tumour or intestinal obstructions.

4.5 Interaction with other medicinal products and other forms of interaction

Antiparkinson medicinal products of the anticholinergic type may be prescribed as required to manage extrapyramidal symptoms, but it is recommended that they are not prescribed routinely as a preventive measure. If concomitant treatment with an antiparkinson medicinal product is required, it may have to be continued after stopping haloperidol if its excretion is faster than that of haloperidol in order to avoid the development or aggravation of extrapyramidal symptoms. The possible increase in intraocular pressure must be considered when anticholinergic medicinal products, including antiparkinson medicinal products, are administered concomitantly with haloperidol.

Seizures/Convulsions

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

Hepatobiliary concerns

As haloperidol is metabolised by the liver, half the initial dose and caution is advised in patients with hepatic impairment (see sections 4.2 and 5.2). Isolated cases of liver function.

Endocrine system concerns

Thyroxin may facilitate Haloperidol toxicity. Antipsychotic therapy in patients with hyperthyroidism must be used only with caution and must always be accompanied by therapy to achieve a euthyroid state.

Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligo or amenorrhoea (see section 4.8). Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics and human breast tumours has been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Haloperidol must be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours. Hypoglycaemia and syndrome of inappropriate antidiuretic hormone secretion have been reported with haloperidol.

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 identi{ed before and during treatment with Haloperidol and preventive measures undertaken.

Treatment response and withdrawal

In schizophrenia, the response to antipsychotic treatment may be delayed.

If antipsychotics are withdrawn, recurrence of symptoms related to the underlying condition may not become apparent for several weeks or months.

There have been very rare reports of acute withdrawal symptoms (including nausea, vomiting and insomnia) after abrupt withdrawal of high doses of antipsychotics. Gradual withdrawal is advisable as a precautionary measure.

Patients with depression

It is recommended that haloperidol is not used alone in patients in whom depression is predominant. It may be combined with antidepressants to treat those conditions in which depression and psychosis coexist.

Switch from mania to depression

There is a risk in the treatment of manic episodes of bipolar disorder for patients to switch from mania to depression. Monitoring of patients for the switch to a depressive episode with the accompanying risks such as suicidal behaviour is important in order to intervene when such switches occur.

Poor metabolisers of CYP2D6
Haloperidol should be used with caution in patients who are known poor metabolisers of cytochrome P450 (CYP) 2D6 and who are coadministered a CYP3A4 inhibitor.

Cardiovascular effects
Haloperidol is contraindicated in combination with medicinal products known to prolong the QTc interval (see section 4.3). Examples include:
• Class IA antiarrhythmics (e.g. disopyramide, quinidine).
• Class III antiarrhythmics (e.g. amiodarone, dofetilide, dronedarone, ibutilide, sotalol).
• Certain antidepressants (e.g. citalopram, escitalopram).
• Certain antibiotics (e.g. azithromycin, clarithromycin, erythromycin, levo|oxacin, moxi|oxacin, telithromycin).
• Other antipsychotics (e.g. phenothiazine derivatives, sertindole, pimozide, ziprasidone)
• Certain antifungals (e.g. pentamidine).
• Certain antimalarials (e.g. halofantrine).
• Certain gastrointestinal medicinal products (e.g. dolasetron).
• Certain medicinal products used in cancer (e.g. toremifene, vandetanib).
• Certain other medicinal products (e.g. bepridil, methadone).
This list is not exhaustive.
Caution is advised when haloperidol is used in combination with medicinal products known to cause electrolyte imbalance (see section 4.4).

Medicinal products that may increase haloperidol plasma concentrations Haloperidol is metabolised by several routes.The major pathways are glucuronidation and ketone reduction. The cytochrome P450 enzyme system is also involved, particularly CYP3A4 and, to a lesser extent, CYP2D6. Inhibition of these routes of metabolism by another medicinal product or a decrease in CYP2D6 enzyme activity may result in increased haloperidol concentrations. The effect of CYP3A4 inhibition and of decreased CYP2D6 enzyme activity may be additive. Based on limited and sometimes con|icting information, the potential increase in haloperidol plasma concentrations when a CYP3A4 and/or CYP2D6 inhibitor is coadministered may range between 20 to 40%, although in some cases, increases of up to 100% have been reported.

Examples of medicinal products that may increase haloperidol plasma concentrations (based on clinical experience or drug interaction mechanism) include:
• CYP3A4 inhibitors – alprazolam, |uvoxamine, indinavir, itraconazole, ketoconazole, nefazodone, posaconazole, saquinavir, verapamil, voriconazole.
• CYP2D6 inhibitors – bupropion, chlorpromazine, duloxetine, paroxetine, promethazine, sertraline, venlafaxine.
• Combined CYP3A4 and CYP2D6 inhibitors: |uoxetine, ritonavir.
• Uncertain mechanism – buspirone
Increased haloperidol plasma concentrations may result in an increased risk of adverse events, including QTc-prolongation . 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 is recommended that patients who take haloperidol concomitantly with such medicinal products be monitored for signs or symptoms of increased or prolonged pharmacologic effects of haloperidol, and the haloperidol dose be decreased as deemed necessary.
Medicinal products that may decrease haloperidol plasma concentrations
Coadministration of haloperidol with potent enzyme inducers of CYP3A4 may gradually decrease the plasma concentrations of haloperidol to such an extent that ef{cacy may be reduced.
Examples include:
• Carbamazepine, phenobarbital, phenytoin, rifampicin, St John's Wort (Hypericum, perforatum).
This list is not exhaustive.
Enzyme induction may be observed after a few days of treatment. Maximal enzyme induction is generally seen in about 2 weeks and may then be sustained for the same period of time after the

cessation of therapy with the medicinal product. During combination treatment with inducers of CYP3A4, it is recommended that patients be monitored and the haloperidol dose increased as deemed necessary. After withdrawal of the CYP3A4 inducer, the concentration of haloperidol may gradually increase and therefore it may be necessary to reduce the haloperidol dose. Sodium valproate is known to inhibit glucuronidation, but does not affect haloperidol plasma concentrations.

Effect of haloperidol on other medicinal products

Haloperidol can increase the CNS depression produced by alcohol or CNS-depressant medicinal products, including hypnotics, sedatives or strong analgesics. An enhanced CNS effect, when combined with methyldopa, has also been reported.
Haloperidol may antagonise the action of adrenaline and other sympathomimetic medicinal products (e.g. stimulants like amphetamines) and reverse the blood pressure-lowering effects of adrenergic-blocking medicinal products such as guanethidine.
Haloperidol may antagonise the effect of levodopa and other dopamine agonists.
Haloperidol is an inhibitor of CYP2D6. Haloperidol inhibits the metabolism of tricyclic antidepressants (e.g. imipramine, desipramine), thereby increasing plasma concentrations of these medicinal products.

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, acute brain syndrome and coma. Most of these symptoms were reversible. It remains unclear whether this represents a distinct clinical entity

Antagonism of the effect of the anticoagulant phenindione has been reported

4.6 Fertility, pregnancy and lactation

Safety of use of haloperidol injection in pregnancy and lactation has not been established. It should, therefore, not be administered to women of childbearing potential or nursing mothers unless, in the opinion of the physician, the expected benefits of the drug outweigh the potential hazard to the fetus or child.

4.7 Effects on ability to drive and use machines

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 Undesirable effects

On the basis of available data the undesirable effects as follows below:

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.

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 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 QTc prolongation, must be considered.

Management

There is no specific antidote. Treatment is supportive. Dialysis is not recommended in the treatment of overdose because it removes only very small amounts of haloperidol.
For comatose patients, a patent airway must be established by use of an oropharyngeal airway or endotracheal tube. Respiratory depression may necessitate arti{cial respiration. It is recommended that ECG and vital signs be monitored, and that monitoring continues until the ECG is normal. Treatment of severe arrhythmias with appropriate anti-arrhythmic measures is recommended.
Hypotension and circulatory collapse may be counteracted by use of intravenous |uids, plasma or concentrated albumin and vasopressor agents, such as dopamine or noradrenaline. Adrenaline must not be used because it might cause profound hypotension in the presence of haloperidol.

In cases of severe extrapyramidal reactions, parenteral administration of an antiparkinson medicinal product is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics; antipsychotics; butyrophenone derivatives, ATC Code: N05A D01

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 signalling 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

Absorption
Following intramuscular administration, haloperidol is completely absorbed. Peak plasma concentrations of haloperidol are attained within 20 to 40 minutes.
Distribution
Mean haloperidol plasma protein binding in adults is approximately 88 to 92%. There is a high inter-subject variability for plasma protein binding. Haloperidol is rapidly distributed to various tissues and organs, as indicated by the large volume of distribution (mean values 8 to 21 l/kg after intravenous dosing). Haloperidol crosses the blood-brain barrier easily.
It also crosses the placenta and is excreted in breast milk.

Biotransformation
Haloperidol is extensively metabolised in the liver. The main metabolic pathways of haloperidol in humans include glucuronidation, ketone reduction, oxidative N-dealkylation and formation of pyridinium metabolites. The metabolites of haloperidol are not considered to make a signi{cant contribution to its activity; however, the reduction pathway accounts approximately for 23% of the biotransformation, and back-conversion of the reduced metabolite of haloperidol to haloperidol cannot be fully ruled out. The cytochrome P450 enzymes CYP3A4 and CYP2D6 are involved in haloperidol metabolism. Inhibition or induction of CYP3A4, or inhibition of CYP2D6, may affect haloperidol metabolism. A decrease in CYP2D6 enzyme activity may result in increased haloperidol concentrations.

Elimination
The terminal elimination half-life of haloperidol is on average 21 hours (range 13 to 36 hours) after intramuscular administration. Haloperidol apparent clearance after extravascular administration ranges from 0.9 to 1.5 l/h/kg and is reduced in poor metabolisers of CYP2D6. Reduced CYP2D6 enzyme activity may result in increased concentrations of haloperidol. The inter-subject variability (coefficient of variation, %) in haloperidol clearance was estimated to

be 44% in a population pharmacokinetic analysis in patients with schizophrenia. After intravenous haloperidol administration, 21% of the dose was eliminated in the faeces and 33% in the urine. Less than 3% of the dose is excreted unchanged in the urine.

5.3 Preclinical safety data
Decrease in fertility, limited teratogenicity as well as embryo-toxic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactic acid, Water for Injection, Propyl Paraben, Methyl Paraben.

6.2 Incompatibilities
Not known

6.3 Shelf life
24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light.
Keep out of reach of children.

6.5 Nature and contents of container and special equipment for use, administration or implantation
1ml Amber Ampoule USP type-I

6.6 Special precautions for disposal and other handling

None.

7. MARKETING AUTHORISATION HOLDER

Ciron Drugs & Pharmaceuticals Pvt. Ltd.
C- 1101 /1102, Lotus Corporate Park, Graham Firth Steel Compound,
Jay Coach Junction, Western Express Highway, Goregaon (East)
Mumbai- 400 063, India.

8. MARKETING AUTHORISATION NUMBER(S)
06331/08673/NMR/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25.07.2021

10. DATE OF REVISION OF THE TEXT
14/07/2023

11. Reference

https://www.medicines.org.uk/emc/product/514/smpc#gref