GENERIC NAME:	HALOPERIDOL INJECTION 5 MG/ML

MODULE 1 - ADMINISTRATIVE INFORMATION

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of drug product

HALOPERIDOL INJECTION 5 MG/ML

1.1 (Trade) name of product

HALOPERIDOL INJECTION 5 MG/ML

1.2 Strength

Each ml contains:

Haloperidol BP.....5 mg

Excipients…..... Q.S.

1.3 Pharmaceutical Dosage Form

Small volume parenteral

GENERIC NAME:	HALOPERIDOL INJECTION 5 MG/ML

MODULE 1 - ADMINISTRATIVE INFORMATION

2. Qualitative & Quantitative Composition

2.1 Qualitative Declaration

Each ml contains:

Haloperidol BP.....5 mg

Excipients ..... Q.S.

2.2 Quantitative Declaration

Batch Formula:

Batch Size: 10,000 Ampoules

Sr. No.	Ingredients	Specification	Rationale	Label Claim	Overages	Quantity /Unit (mg)	Quantity/ Batch (Kg)
1.	Haloperidol	BP	Active	5 mg	---	5.00	0.05
2.	Lactic Acid	BP	Adjust pH	---	---	Q.S. to adjust pH	Q.S. to adjust pH
3.	Sodium Hydroxide	USP	Adjust pH	---	---	Q.S. to adjust pH	Q.S. to adjust pH
4.	Water for injection	BP	Solvent	---	---	Q.S	Q.S

GENERIC NAME:	HALOPERIDOL INJECTION 5 MG/ML

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3. Pharmaceutical Dosage Form

Solution for injection

4.1 Therapeutic Indications

HALOPERIDOL INJECTION 5 MG/ML is indicated in adult patients for:

• Rapid control of severe acute psychomotor agitation associated with psychotic disorder or manic episodes of bipolar I disorder when oral therapy is not appropriate.

• Acute treatment of delirium when non-pharmacological treatments have failed.

• 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.

• 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.

• Combination treatment of postoperative nausea and vomiting when other medicinal products are ineffective or not tolerated.

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 (see section 5.2).

The dose recommendations for HALOPERIDOL INJECTION 5 MG/ML are presented in Table 1.

Table 1: Haloperidol dose recommendations for adults aged 18 years and above

Rapid control of severe acute psychomotor agitation associated with psychotic disorder or manic episodes of bipolar I disorder when oral therapy is not appropriate
• 5 mg intramuscularly. • 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 (see section 4.4). Treatment with HALOPERIDOL INJECTION 5 MG/ML must be discontinued as soon as clinically indicated and, if

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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 or not tolerated

• 1 to 2 mg intramuscularly.

Treatment withdrawal

Gradual withdrawal of haloperidol is advisable (see section 4.4).

Special populations

Elderly

The recommended initial haloperidol dose in elderly patients is half the lowest adult dose.

Further doses may be administered and adjusted according to the patient's response. Careful and gradual dose up-titration in elderly patients is recommended.

The maximum dose is 5 mg/day.

Doses above 5 mg/day should only be considered in patients who have tolerated higher doses and after reassessment of the patient's individual benefit-risk profile.

Renal impairment

The influence of renal impairment on the pharmacokinetics of haloperidol has not been evaluated. No dose adjustment is recommended, but caution is advised when treating patients with renal impairment.

However, patients with severe renal impairment may require a lower initial dose, with further doses administered and adjusted according to the patient's response (see section 5.2).

Hepatic impairment

The influence of hepatic impairment on the pharmacokinetics of haloperidol has not been evaluated. Since haloperidol is extensively metabolised in the liver, it is recommended to halve the initial dose. Further doses may be administered and adjusted according to the patient's response (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of HALOPERIDOL INJECTION 5 MG/ML in children and adolescents below 18 years of age have not been established. No data are available.

Method of administration

HALOPERIDOL INJECTION 5 MG/ML is recommended for intramuscular administration only (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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 (see section 4.5).

4.4 Special Warnings and Precautions for Use

Increased mortality in elderly people with dementia

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Rare cases of sudden death have been reported in psychiatric patients receiving antipsychotics, including haloperidol (see section 4.8).

Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death. Analyses of seventeen placebo-controlled studies (modal duration of 10 weeks), largely in patients taking atypical antipsychotics, revealed a risk of death in 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 study, the rate of death in patients treated with antipsychotics 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 treatment of elderly patients with haloperidol is also associated with increased mortality. This association may be stronger for haloperidol than for atypical antipsychotic medicinal products, is most pronounced in the first 30 days after the start of treatment, and persists for at least 6 months. The extent to which this association is attributable to the medicinal product, as opposed to being confounded by patient characteristics, has not yet been elucidated.

HALOPERIDOL INJECTION 5 MG/ML is not indicated for the treatment of dementia-related behavioural disturbances.

Cardiovascular effects

QTc prolongation and/or ventricular arrhythmias, in addition to sudden death, have been reported with haloperidol (see sections 4.3 and 4.8). The risk of these events appears to increase with high doses, high plasma concentrations, in predisposed patients or with parenteral use, particularly intravenous administration.

HALOPERIDOL INJECTION 5 MG/ML is recommended for intramuscular administration only. However, if administered intravenously, continuous ECG monitoring must be performed for QTc interval prolongation and for ventricular arrhythmias.

Caution is advised in patients with bradycardia, cardiac disease, family history of QTc prolongation or history of heavy alcohol exposure. Caution is also required in patients with potentially high plasma concentrations (see section 4.4, Poor metabolisers of CYP2D6).

A baseline ECG is recommended before intramuscular dosing. During therapy, the need for ECG monitoring for QTc interval prolongation and for ventricular arrhythmias must be assessed in all patients, but continuous ECG monitoring is recommended for repeated intramuscular doses. ECG

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monitoring is recommended up to 6 hours after administration of HALOPERIDOL INJECTION 5 MG/ML to patients for prophylaxis or treatment of postoperative nausea and vomiting.

Whilst on therapy, it is recommended to reduce the dose if QTc is prolonged, but haloperidol must be discontinued if the QTc exceeds 500 ms.

Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for ventricular arrhythmias and must be corrected before treatment with haloperidol is started. Therefore, baseline and periodic electrolyte monitoring is recommended.

Tachycardia and hypotension (including orthostatic hypotension) have also been reported (see section 4.8). Caution is recommended when haloperidol is administered to patients manifesting hypotension or orthostatic hypotension.

Cerebrovascular events

In randomised, placebo-controlled clinical studies in the dementia population, there was an approximately 3-fold increased risk of cerebrovascular adverse events with some atypical antipsychotics. Observational studies comparing the stroke rate in elderly patients exposed to any antipsychotic to the stroke rate in those not exposed to such medicinal products found an increased stroke rate among exposed patients. This increase may be higher with all butyrophenones, including haloperidol. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other patient populations. Haloperidol must be used with caution in patients with risk factors for stroke.

Neuroleptic malignant syndrome

Haloperidol has been associated with neuroleptic malignant syndrome: a rare idiosyncratic response characterized by hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness and increased serum creatine phosphokinase levels. Hyperthermia is often an early sign of this syndrome.

Antipsychotic treatment must be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Tardive dyskinesia

Tardive dyskinesia may appear in some patients on long-term therapy or after discontinuation of the medicinal product. 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 dose is increased or when a switch is made to a different antipsychotic. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics, including haloperidol, must be considered.

Extrapyramidal symptoms

Extrapyramidal symptoms may occur (e.g. tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia). The use of haloperidol has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Acute dystonia may occur during the first few days of treatment with haloperidol, but later onset as well as onset after dose increases has been reported. Dystonic symptoms can include, but are not limited to, torticollis, facial grimacing, trismus, tongue protrusion, and abnormal eye movements, including oculogyric crisis. Males and younger age groups are at higher risk of experiencing such reactions. Acute dystonia may necessitate stopping the medicinal product.

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 abnormalities or hepatitis, most often cholestatic, have been reported (see section 4.8).

Endocrine system concerns

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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 (see section 5.3).

Hypoglycaemia and syndrome of inappropriate antidiuretic hormone secretion have been reported with haloperidol (see section 4.8).

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 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 (see section 4.5).

Switch from mania to depression

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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.

4.5 Interaction with Other Drugs, Other Forms of Interactions

Interaction studies have only been performed in adults.

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, levofloxacin, moxifloxacin, 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 (see section 5.2). 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 (see section 5.2). Based on limited and sometimes conflicting 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, fluvoxamine, indinavir, itraconazole, ketoconazole, nefazodone, posaconazole, saquinavir, verapamil, voriconazole.

• CYP2D6 inhibitors – bupropion, chlorpromazine, duloxetine, paroxetine, promethazine, sertraline, venlafaxine.

• Combined CYP3A4 and CYP2D6 inhibitors: fluoxetine, ritonavir.

• Uncertain mechanism – buspirone.

This list is not exhaustive.

Increased haloperidol plasma concentrations may result in an increased risk of adverse events, including QTc-prolongation (see section 4.4). 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 efficacy 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

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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.

Nonetheless, it is advised that in patients who are treated concomitantly with lithium and haloperidol, therapy must be stopped immediately if such symptoms occur.

Antagonism of the effect of the anticoagulant phenindione has been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (more than 400 pregnancy outcomes) indicate no malformative or foeto/ neonatal toxicity of haloperidol. However, there have been isolated case reports of birth defects following foetal exposure to haloperidol, mostly in combination with other medicinal

products. Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of haloperidol during pregnancy.

Newborn infants exposed to antipsychotics (including haloperidol) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, it is recommended that newborn infants be monitored carefully.

Breast-feeding

Haloperidol is excreted in human milk. Small amounts of haloperidol have been detected in plasma and urine of breast-fed newborns of mothers treated with haloperidol. There is insufficient information on the effects of haloperidol in breast-fed infants. A decision must be made whether to discontinue breastfeeding or to discontinue haloperidol therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

Haloperidol elevates prolactin level. Hyperprolactinaemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients (see section 4.4).

4.7 Effects on ability to drive and operate 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

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

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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 Faces
Eye disorders		Oculogyric Crisis; Visual disturbance	Vision blurred		
Cardiac disorders			Tachycardia		Ventricular Fibrillation; Torsade de pointes; Ventricular Tachycardia; Extra systoles
Vascular disorders		Orthostatic Hypotension; Hypotension			
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Bronchospasm	Laryngeal Oedema; Laryngospasm
Gastrointestinal disorders		Constipation; Dry mouth; Salivary hypersecretion; Nausea; Vomiting			

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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.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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 and 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 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 (see section 5.2).

For comatose patients, a patent airway must be established by use of an oropharyngeal airway or endotracheal tube. Respiratory depression may necessitate artificial 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 fluids, 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

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5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics; antipsychotics; butyrophenone derivatives,

ATC code: N05AD01

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

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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 significant 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.

Linearity/non-linearity

A linear relationship exists between haloperidol dose and plasma concentrations in adults.

Special populations

Elderly

Haloperidol plasma concentrations in elderly patients were higher than in younger adults administered the same dose. Results from small clinical studies suggest a lower clearance and a longer elimination half-life of haloperidol in elderly patients. The results are within the observed variability in haloperidol pharmacokinetics. Dose adjustment is recommended in elderly patients (see section 4.2).

Renal impairment

The influence of renal impairment on the pharmacokinetics of haloperidol has not been evaluated. About one-third of a haloperidol dose is excreted in urine, mostly as metabolites. Less than 3% of administered haloperidol is eliminated unchanged in the urine. Haloperidol metabolites are not

considered to make a significant contribution to its activity, although for the reduced metabolite of haloperidol, back-conversion to haloperidol cannot be fully ruled out. Even though impairment of renal function is not expected to affect haloperidol elimination to a clinically relevant extent, caution is advised in patients with renal impairment, and especially those with severe impairment, due to the long half-life of haloperidol and its reduced metabolite, and the possibility of accumulation (see section 4.2).

Because of the high haloperidol distribution volume and its high protein binding, only very small amounts are removed by dialysis.

Hepatic impairment

The influence of hepatic impairment on the pharmacokinetics of haloperidol has not been evaluated. However, hepatic impairment may have significant effects on the pharmacokinetics of haloperidol because it is extensively metabolised in the liver. Therefore, half the initial dose and caution is advised in patients with hepatic impairment (see sections 4.2 and 4.4).

Pharmacokinetic/pharmacodynamics relationships

Therapeutic concentrations

Based on published data from multiple clinical studies, therapeutic response is obtained in most patients with acute or chronic schizophrenia at plasma concentrations of 1 to 10 ng/ml. A subset of patients may require higher concentrations as a consequence of a high inter-subject variability in haloperidol pharmacokinetics.

In patients with first-episode schizophrenia, therapeutic response may be obtained at concentrations as low as 0.6 to 3.2 ng/ml, as estimated based on measurements of D2 receptor occupancy and assuming that a D2 receptor occupancy level of 60 to 80% is most appropriate for obtaining therapeutic response and limiting extrapyramidal symptoms. On average, concentrations in this range would be obtained with doses of 1 to 4 mg daily.

Due to the high inter-subject variability in haloperidol pharmacokinetics and the concentration-effect relationship, it is recommended to adjust the individual haloperidol dose based on the patient's response, taking into account data suggesting a lag time of 5 days to reach half of the maximal therapeutic response. Measurement of haloperidol blood concentrations may be considered in individual cases.

Cardiovascular effects

MODULE 1 - ADMINISTRATIVE INFORMATION

The risk of QTc prolongation increases with haloperidol dose and with haloperidol plasma concentrations.

Extrapyramidal symptoms

Extrapyramidal symptoms can occur within the therapeutic range, although the frequency is usually higher with doses producing higher than therapeutic concentrations.

6. Pharmaceutical particulars

6.1 List of excipients

Lactic Acid

Sodium Hydroxide

Water for injection

6.2 Incompatibilities

Not Applicable.

6.3 Shelf-Life

36 Months

6.3 Special Precautions for Storage

Do not store above 30° C.

6.4 Nature and Contents of Container

1 ml solution filled in amber colour glass ampoules. 10 Ampoules packed in a plastic tray. Such a tray packed in monocarton along with package insert.

7. Marketing authorisation holder

GENERIC NAME:	HALOPERIDOL INJECTION 5 MG/ML

MODULE 1 - ADMINISTRATIVE INFORMATION

ZENITH BIOTECH LIMITED

HEAD OFFICE: NO. 20 Plastic Estate

Oba Anambra State, Nigeria.

8. Marketing authorisation number(s)

9. Date of first authorisation/renewal of the authorisation

10. Date of revision of the text