HALDOL®

haloperidol decanoate

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

HALDOL haloperidol decanoate 50 mg/mL Injection

HALDOL CONCENTRATE haloperidol decanoate 100 mg/mL Injection

2. QUANTITATIVE AND QUALITATIVE COMPOSITION

HALDOL 50 mg/ml

Haloperidol decanoate 70.52 mg, equivalent to 50 mg haloperidol base, per millilitre.

HALDOL CONCENTRATE 100 mg/ml

Haloperidol decanoate 141.04 mg, equivalent to 100 mg haloperidol base, per millilitre.

Excipient(s) of known effect: Contains sesame seed products.

For a full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Injection (depot)

HALDOL Injection (long acting) is a slightly amber, slightly viscous solution, free from visible foreign matter, filled in 1 mL amber glass ampoules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HALDOL is indicated for the maintenance therapy of psychoses in adults, particularly for patients requiring prolonged parenteral neuroleptic therapy.

4.2 Dose and method of administration

Administration

HALDOL should be administered by deep intramuscular injection into the gluteal region. It is recommended to alternate between the two gluteal muscles for subsequent injections. A 2 inch-long, 21 gauge needle is recommended. The maximum volume per injection site should not exceed 3 mL. The recommended interval between doses is 4 weeks.

DO NOT ADMINISTER INTRAVENOUSLY.

Patients must be previously stabilised on oral haloperidol before converting to HALDOL.

Treatment initiation and dose titration must be carried out under close clinical supervision. The starting dose of HALDOL should be based on the patient's clinical history, severity of symptoms, physical condition and response to the current oral haloperidol dose. Patients must always be maintained on the lowest effective dose.

Dosage - Adults

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

Transition from oral haloperidol • A haloperidol decanoate dose of 10 to 15 times the previous daily dose of oral haloperidol is recommended. • Based on this conversion, the haloperidol decanoate dose will be 25 to150 mg for most patients, • The maximum recommended initial haloperidol decanoate dose is 100 mg.
Continuation of treatment • Adjust the haloperidol decanoate dose by up to 50 mg every 4 weeks (based on individual patient response) until an optimal therapeutic effect is obtained. • The most effective dose is expected to range between 50 and 200 mg. • The maximum dosage is 300 mg every 4 weeks.
Dosing interval • Usually 4 weeks between injections. • Adjust the dosing interval as required (based on individual patient response).
Supplementation with non-decanoate haloperidol • Consider supplementation with non-decanoate haloperidol during transition to HALDOL, dose adjustment or episodes of exacerbation of psychotic symptoms (based on individual patient response). • The combined total dose of haloperidol from both formulations must not exceed the corresponding maximum oral haloperidol dosage of 20 mg/day.

Special Populations

Paediatrics

The safety and efficacy of HALDOL in children and adolescents below 18 years of age have not been established. No data are available.

Elderly

Table 2. Haloperidol decanoate dose recommendations for elderly patients

Transition from oral haloperidol • A low haloperidol decanoate dose of 12.5 to 25 mg is recommended.
Continuation of treatment • Adjust the haloperidol decanoate dose by up to 25 mg every 4 weeks (based on individual patient response) until an optimal therapeutic effect is obtained. • The maximum dosage is half that specified for adults.
Dosing interval • Usually 4 weeks between injections. • Adjust the dosing interval as required (based on individual patient response).
Supplementation with non-decanoate haloperidol • Consider supplementation with non-decanoate haloperidol during transition to HALDOL, dose adjustment or episodes of exacerbation of psychotic symptoms (based on individual patient response). • The combined total dose of haloperidol from both formulations must not exceed the corresponding maximum oral haloperidol dosage of 10 mg/day or the previously administered oral haloperidol dose in patients who have received long-term treatment with oral haloperidol.

Renal impairment

The influence of renal impairment on the pharmacokinetics of haloperidol has not been evaluated. No dosage adjustment is recommended, but caution is advised when treating patients with renal impairment (see **Pharmacokinetics – Special populations: Renal impairment**).

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, and adjust the dosage with smaller increments and at longer intervals than in patients without hepatic impairment (see **Precautions – Hepatobiliary concerns** and **Pharmacokinetics – Special populations: Hepatic impairment**).

Clinical experience with HALDOL at doses greater than 300 mg (6 mL) per month has been limited.

4.3 Contraindications

HALDOL is contraindicated:

- in individuals who are hypersensitive to haloperidol or any of the excipients.
- in comatose states from any cause.
- in the presence of CNS depression due to alcohol or other depressant drugs.
- in patients with significant depressive states.
- In patients with previous spastic diseases.
- in Parkinson's disease.
- in senile patients with pre-existing Parkinson-like symptoms.
- In patients with dementia with Lewy bodies.
- In patients with progressive supranuclear palsy.

4.4 Special warnings and precautions for use

Mortality

Rare cases of sudden death have been reported in psychiatric patients receiving antipsychotic agents, including HALDOL (see **section 4.8**).

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 has not yet been elucidated.

Cardiovascular Effects

Very rare reports of QTc interval prolongation and/or ventricular arrhythmias, in addition to rare reports of sudden death, have been reported with haloperidol (see **section 4.8**). They may occur more frequently with high doses, in predisposed patients or with a QTc interval that exceeds 500 ms.

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, hypokalaemia, hypomagnesaemia, subarachnoid haemorrhage, starvation or alcohol abuse, should be monitored carefully (ECGs and potassium levels), particularly during the initial phase of treatment, to obtain steady plasma levels. Caution is advised in these patients.

The risk of QT prolongation and/or ventricular arrhythmias may be increased with higher doses (see **sections 4.5, 4.8** and **4.9**) or with parenteral use, particularly intravenous administration.

HALDOL 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.

HALDOL (haloperidol decanoate) MUST NOT BE ADMINISTERED INTRAVENOUSLY.

Tachycardia and hypotension (including orthostatic hypotension) have also been reported in occasional patients (see **section 4.8**).

Cerebrovascular Events

In randomised, placebo-controlled clinical trials 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 reported 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. HALDOL must be used with caution in patients with risk factors for stroke.

Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible involuntary, dyskinetic movements, is known to occur in patients treated with neuroleptics with antipsychotic properties and other drugs with substantial neuroleptic activity. The syndrome is characterised by rhythmical involuntary movements of the tongue, face, mouth or jaw. Although the dyskinetic syndrome may remit partially or completely if the medication is withdrawn, it is irreversible in some patients. The prevalence of the syndrome appears to be highest among the elderly, especially elderly women. At the present time there is uncertainty as to whether neuroleptic drugs differ in their potential to cause tardive dyskinesia.

Since there is a significant prevalence of this syndrome associated with the use of neuroleptic drugs, and since there is no known effective treatment, chronic use of these drugs should generally be restricted to patients for whom there is no alternative therapy available with better risk acceptability. If manifestations of tardive dyskinesia are detected during the use of a neuroleptic, the drug should be discontinued.

The risk of a patient developing tardive dyskinesia and of the syndrome becoming irreversible appear to increase with the duration of treatment and the total amount of drugs administered, although, in some instances, tardive dyskinesia may develop after relatively short periods of treatment at low doses. The risk of developing tardive dyskinesia may, therefore, be minimised by reducing the dose of the neuroleptic drug used and its duration of administration, consistent with the effective management of the patient's condition. Continued use of neuroleptics should be periodically reassessed.

Neuroleptic Malignant Syndrome

As with other neuroleptic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperthermia, hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated serum creatine

phosphokinase levels, myoglobinuria (rhabdomyolysis), and acute renal failure. Hyperthermia is often an early sign of this syndrome. NMS is potentially fatal, requires intensive symptomatic treatment and immediate discontinuation of neuroleptic treatment and careful monitoring instituted. Dantrolene and bromocriptine have been used for the treatment of NMS.

Extrapyramidal Symptoms

In common with all antipsychotics, extrapyramidal symptoms may occur, e.g. tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia.

Anti-parkinson drugs of the anticholinergic type may be prescribed as required, but should not be prescribed routinely as a preventive measure. If concomitant anti-parkinson medication is required, it may have to be continued after stopping HALDOL if its excretion is faster than that of HALDOL to avoid the development or aggravation of extrapyramidal symptoms. The possible increase in intraocular pressure must be considered when anticholinergic drugs, including anti-parkinson agents, are administered concomitantly with HALDOL.

Seizures/ Convulsions

Seizures can be triggered by haloperidol. If indicated, adequate anticonvulsant therapy should be concomitantly maintained. Caution is advised in patients suffering from epilepsy and in conditions predisposing to convulsions (e.g. alcohol withdrawal and brain damage).

Hepatobiliary concerns

Since haloperidol is extensively metabolised in the liver, dosage adjustment and caution is advised in patients with hepatic impairment. (see **section 4.2 – Special populations: Hepatic impairment** and **section 5.2 – Special populations: Hepatic impairment**) Isolated cases of liver function abnormalities or hepatitis, most often cholestatic, have been reported (see **section 4.8**).

Endocrine System Concerns

Thyroxin may facilitate haloperidol toxicity. Antipsychotic therapy in patients with hyperthyroidism should 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 oligomenorrhoea or amenorrhoea. Very rare cases of hypoglycaemia and of syndrome of inappropriate antidiuretic hormone secretion have been reported (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 HALDOL and preventive measures undertaken.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high-risk patients should accompany therapy.

Treatment initiation

Patients being considered for HALDOL therapy must be initially treated with oral haloperidol to exclude the possibility of an unexpected adverse sensitivity to haloperidol.

When HALDOL is used to control mania in bipolar disorders, there may be a rapid mood swing to depression.

Antiemetic action may obscure the diagnosis of an underlying condition characterised by nausea and vomiting.

It is advisable to carefully observe the patients who receive haloperidol decanoate for a long period in order to identify any changes in the skin or eyes. Oculocutaneous changes have been observed following use of butyrophenones structurally related to haloperidol.

Patients with depression

As with all antipsychotic medicines, 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 (see **section 4.5**).

HALDOL should be administered with caution to:

Patients with severe cardiovascular disorders, because of the possibility of transient hypotension and/or precipitation of anginal pain. When antihypertensives and haloperidol are used concomitantly the use of vasopressors such as noradrenaline may be indicated if the resulting hypotension is prolonged and severe. Adrenaline must not be used since haloperidol may reverse its action and cause profound hypotension.

Patients receiving anticonvulsant medications with a history of seizures, or with EEG abnormalities, because haloperidol may lower the convulsive threshold.

Patients who are elderly or debilitated. These patients should be observed for evidence of over-sedation, which, unless alleviated, could result in complications such as terminal stasis pneumonia.

Patients with thyrotoxicosis. Antipsychotic medication, including HALDOL may result in severe neurotoxicity (rigidity, inability to walk or talk). Antipsychotic treatment in these patients should always be accompanied by appropriate monitoring and therapy.

Patients with known allergies or with a history of allergic reactions to drugs.

Patients receiving anticoagulants (see **section 4.5**).

Use in Children

Safety and efficacy in children have not been established; therefore, HALDOL is not recommended for use in the paediatric age group.

Information for Patients

HALDOL may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. Patients should be advised not to drive or operate machinery during treatment, until their susceptibility is known.

The use of alcohol with this drug should be avoided due to possible additive effects and hypotension.

4.5 Interactions with other medicines and other forms of interaction

Cardiovascular effects

As with other antipsychotic medicines, caution is advised when prescribing haloperidol HALDOL is used in combination with medications known to prolong the QTc interval (see **section 4.4 – Cardiovascular effects**). Examples include:

- Class IA antiarrhythmics (e.g. disopyramide, quinidine,procainamide).
- Class III antiarrhythmics (e.g. amiodarone, dofetilide, dronedarone, ibutilide, sotalol).
- Certain antidepressants (e.g. citalopram, escitalopram).
- Certain antibiotics (e.g. erythromycin, levofloxacin, moxifloxacin).
- Certain antifungals (e.g. pentamidine).

- Certain antimalarials (e.g. halofantrine).
- Certain gastrointestinal drugs (e.g. dolasetron).
- Certain drugs used in cancer (e.g. toremifene, vandetanib).
- Certain other drugs (e.g. bepridil, methadone).

This list is not exhaustive.

It is recommended that concomitant use of other antipsychotic drugs be avoided.

Caution is advised when HALDOL is used in combination with drugs known to cause electrolyte imbalance (see **section 4.4 – Cardiovascular effects**).

Drugs that may increase haloperidol plasma concentrations

Haloperidol is metabolised by several routes (see **section 5.2 – Metabolism**). 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 drug or a decrease in CYP 2D6 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 – Metabolism). Based on limited and sometimes conflicting information, the average increase in haloperidol plasma concentrations when a CYP3A4 and/or CYP2D6 inhibitor was co-administered generally ranged between 20 and 40%, although in some cases, average increases of up to 100% have been reported. Examples of drugs that may increase haloperidol plasma concentrations (based on clinical experience or drug interaction mechanism) include:

- CYP3A4 inhibitors – alprazolam; itraconazole, ketoconazole, and some other azoles; nefazodone; certain antivirals.
- CYP2D6 inhibitors – chlorpromazine; promethazine; quinidine; paroxetine, sertraline, venlafaxine, and some other antidepressants.
- Combined CYP3A4 and CYP2D6 inhibitors – fluoxetine, fluvoxamine; ritonavir.
- Uncertain mechanism – buspirone.

This list is not exhaustive.

Increased haloperidol plasma concentrations may result in an increased risk of adverse events, including QTc interval prolongation (see **section 4.4 – Cardiovascular effects**). Increases in QTc have been observed when haloperidol was given with a combination of the metabolic inhibitors ketoconazole (400mg/day) and paroxetine (20mg/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 HALDOL dose be decreased as deemed necessary.

Sodium valproate, a drug known to inhibit glucuronidation, does not affect haloperidol plasma concentrations.

Medicines that may decrease haloperidol plasma concentrations

Co-administration 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 (based on clinical experience or drug interaction mechanism) 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. Therefore, during combination treatment with inducers of CYP3A4, it is recommended that patients be monitored and the HALDOL dose increased

or the dosage interval adjusted, 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 dose of HALDOL, or adjust the dosage interval.

Effect of HALDOL on Other Medicines

Although haloperidol does not provoke a respiratory depression, it can have a potentiating effect on CNS depressants such as anaesthetics, opiates, hypnotics (barbiturates) and alcohol.

An enhanced CNS effect (disorientation, memory loss, mental retardation, aggression, irritability) when combined with methyldopa has been reported.

Haloperidol may antagonise the action of adrenaline and other sympathomimetic agents and reverse the blood pressure lowering effects of adrenergic blocking agents such as guanethidine.

Haloperidol may impair the antiparkinsonian effects of levodopa.

Haloperidol is an inhibitor of CYP 2D6. It inhibits the metabolism of tricyclic antidepressants, increasing blood levels of these drugs. This may result in increased tricyclic antidepressant toxicity.

Other Forms of Interaction

An encephalopathic syndrome with reported symptoms including weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, leukocytosis, elevated serum enzymes and BUN and coma, followed by irreversible brain damage has occurred in a few patients treated with lithium plus haloperidol; a causal relationship has not been established. However, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity and treatment immediately discontinued should such signs appear.

Haloperidol has been reported to interfere with the activity of phenindione and coumarin anticoagulants. Antagonism of the anticoagulant effect of phenindione has been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy (Category C)

Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (including HALDOL) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeling disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited; in other cases, neonates have required additional medical treatment or monitoring.

HALDOL should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

Breast-feeding

Haloperidol is excreted in human breast milk. Small amounts of haloperidol have been detected in plasma and urine of breast fed newborns of mothers treated with haloperidol. Infants should not be nursed during treatment with HALDOL

4.7 Effects on ability to drive and use machines

Some degree of sedation or impairment of alertness, mental and/or physical abilities may occur, particularly with higher doses and at the start of treatment and may be potentiated by alcohol. Patients should be advised not to drive or operate machinery during treatment, until their susceptibility is known.

4.8 Undesirable Effects

Clinical Trial Data

Comparator and Open-Label Trial Data – Adverse Drug Reactions Reported at ≥1% Incidence

The safety of HALDOL (15-500 mg/month) was evaluated in 410 subjects who participated in 13 clinical trials in the treatment of schizophrenia or a schizoaffective disorder.

Adverse reactions reported by ≥1% of HALDOL-treated subjects in these trials are shown in **Table 3**.

Table 3. Adverse Reactions Reported by ≥1% of HALDOL-treated Subjects in Comparator and Open-Label Clinical Trials of HALDOL

System/Organ Class Adverse Reaction	**Haloperidol decanoate (n=410)** **%**
Nervous System Disorders	
Extrapyramidal disorder	13.6
Tremor	8.0
Parkinsonism	7.3
Somnolence	4.9
Masked facies	4.1
Akathisia	3.4
Sedation	2.7
Gastrointestinal Disorders	
Dry mouth	3.4
Constipation	2.0
Salivary hypersecretion	1.2
Musculoskeletal and Connective Tissue Disorders	
Muscle rigidity	6.1
Reproductive System and Breast Disorders	
Sexual dysfunction	1.5
General Disorders and Administration Site Conditions	
Injection site reaction	1.2
Investigations	
Weight increased	2.9

Comparator and Open-Label Trial Data – Adverse Drug Reactions Reported at <1% Incidence

Additional adverse reactions that occurred in <1% of HALDOL DECANOATE-treated subjects either of the above trial data are listed below in **Table 4**.

Table 4. Adverse Drug Reactions Reported by <1 % of HALDOL DECANOATE-treated Subjects in Comparator and Open-Label Clinical Trials of HALDOL DECANOATE

Nervous System Disorders
Akinesia
Dyskinesia
Hypertonia
Dystonia
Cogwheel rigidity

Eye disorders
Vision blurred
Visual disturbance
Oculogyric Crisis

Cardiac Disorders
Tachycardia

Cardiac effects such as QT-interval prolongation, Torsade de pointes, ventricular arrhythmias including ventricular fibrillation and ventricular tachycardia, and cardiac arrest, have been reported rarely. Cases of sudden unexplained death have also been reported.

Adverse reactions identified in clinical trials with haloperidol (non-decanoate formulations)

Adverse reactions relating to the active moiety that were identified in clinical trials with haloperidol (non-decanoate formulations) are listed in **Table 5**.

Table 5. Adverse Reactions Identified in Clinical Trials with Haloperidol (Non-Decanoate Formulations)

Endocrine Disorders
Hyperprolactinemia
Psychiatric Disorders
Libido decreased, Loss of libido, Restlessness
Nervous System Disorders
Neuroleptic malignant syndrome, Tardive dyskinesia, Bradykinesia, Dizziness, Hyperkinesia, Hypokinesia, Motor dysfunction, Muscle contractions involuntary, Nystagmus
Vascular Disorders
Hypotension, Orthostatic hypotension
Musculoskeletal and Connective Tissue Disorders
Trismus, Torticollis, Muscle spasms, Musculoskeletal stiffness, Muscle twitching
Reproductive System and Breast Disorders
Amenorrhea, Galactorrhea, Menstrual disorder, Erectile dysfunction, Breast discomfort, Breast pain, Dysmenorrhea, Menorrhagia
General Disorders and Administration Site Conditions
Gait disturbance

Post-Marketing Data

Adverse events first identified as adverse reactions during post-marketing experience with haloperidol, presented by frequency category based on incidence in clinical trials, when known, are included in **Table 6**. The post-marketing review was based on review of all cases including haloperidol and haloperidol decanoate containing products. The frequencies are provided according to 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, including isolated reports

Table 6. Adverse Reactions Identified During Post-Marketing Experience with Haloperidol (oral, solution, or decanoate) by Frequency Category Estimated From Spontaneous Reporting Rates

Blood and Lymphatic System Disorders	
Very rare	Agranulocytosis, Pancytopenia, Thrombocytopenia, Leukopenia, Neutropenia
Immune System Disorders	
Very rare	Anaphylactic reaction, Hypersensitivity
Endocrine Disorders	
Very rare	Inappropriate antidiuretic hormone secretion (presenting with hyponatraemia)
Metabolic and Nutritional Disorders	
Very rare	Hypoglycaemia, Hyperglycaemia
Psychiatric Disorders	
Very rare	Psychotic disorder, Agitation, Confusional state, Depression, Insomnia
Nervous System Disorders	
Very rare	Convulsion, Headache
Cardiac Disorders	
Very rare	Torsade de pointes, Ventricular fibrillation, Ventricular tachycardia, Extrasystoles
Respiratory, thoracic and mediastinal disorders	
Very rare	Bronchospasm, Laryngospasm, Laryngeal oedema, Dyspnoea
Gastrointestinal Disorders	
Very rare	Vomiting, Nausea
Hepatobiliary Disorders	
Very rare	Acute Hepatic Failure, Hepatitis, Cholestasis, Jaundice, Liver function test abnormal
Skin and subcutaneous tissue disorders	
Very rare	Angioedema, Leukocytoclastic vasculitis, Dermatitis exfoliative, Urticaria, Photosensitivity reaction, Rash, Pruritus, Hyperhidrosis
Musculoskeletal and Connective Tissue Disorders	
Very rare	Rhabdomyolysis
Renal and Urinary Disorders	
Very rare	Urinary retention
Pregnancy, Puerperium and Perinatal Conditions	
Very rare	Drug withdrawal syndrome neonatal
Reproductive System and Breast Disorders	
Very rare	Priapism, Gynaecomastia
General Disorders and Administration Site Conditions	
Very rare	Sudden Death, Face oedema, Oedema, Hypothermia, Hyperthermia
Investigations	
Very rare	Electrocardiogram QT prolonged, Weight decreased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https//nzphvc.otago.ac.nz/reporting/

4.9 Overdose

While overdose is less likely to occur with parenteral than with oral medication, information pertaining to oral is presented, modified only to reflect the extended duration of action of HALDOL.

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 interval prolongation, should be considered.

Treatment

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 – Special populations: Renal impairment**)

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 must not be used.

In case of severe extrapyramidal reactions, anti-parkinson medication should be administered and continued for several weeks. Anti-parkinson medication must be withdrawn very cautiously as extrapyramidal symptoms may emerge.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Butyrophenone Derivatives, ATC Code: N05AD01

Mechanism of Action

Haloperidol decanoate is an ester of haloperidol and decanoic acid, and as such, a depot neuroleptic belonging to the butyrophenones group. After intramuscular injection, haloperidol decanoate is gradually released from muscle tissue and hydrolysed slowly into free haloperidol which enters the systemic circulation.

Haloperidol decanoate is a potent central dopamine type 2 receptor antagonist and at recommended dosages, 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 effective psychomotor sedation, which explains the favourable effect on mania.

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.

5.2 Pharmacokinetic properties

Absorption

Administration of haloperidol decanoate as a depot intramuscular injection results in a slow and sustained release of haloperidol. The plasma concentrations rise gradually, usually peaking within the first week after injection.

Steady state plasma levels are reached within 2 to 4 months in patients receiving monthly injections.

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.

Metabolism

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. 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.

Excretion

The terminal elimination half-life of haloperidol after intramuscular injection with haloperidol decanoate is on average 3 weeks. This is longer than for the non-decanoate formulations, where the haloperidol terminal elimination half-life is on average 24 hours. Haloperidol apparent clearance after extravascular administration ranges from 0.9 to 1.5 L/h/kg and is reduced in poor metabolisers of CYP2D6 substrates. 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

The pharmacokinetics of haloperidol following intramuscular injections of haloperidol decanoate are dose related. The relationship between dose and plasma haloperidol level is approximately linear for doses below 450 mg.

Special populations

Elderly

Haloperidol plasma concentrations in elderly patients were higher than in younger adults administered the same dosage. 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. Dosage adjustment is recommended in elderly patients (see **section 4.2 – Special populations: Elderly**).

Renal impairment

The influence of renal impairment on the pharmacokinetics of haloperidol has not been evaluated. Since less than 3% of administered haloperidol is eliminated unchanged in the urine, impairment of renal function is not expected to affect its elimination. Therefore, dosage adjustment is not required in patients with renal impairment, but caution is advised when treating patients with renal impairment.

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 metabolized in the liver. Therefore, dosage adjustment and caution is advised in patients with hepatic impairment (see **section 4.2 – Special populations: Hepatic impairment** and **section 4.4 – Hepatobiliary concerns**).

Pharmacokinetic/pharmacodynamics relationships

Therapeutic Concentrations

Based on clinical studies with haloperidol, therapeutic response is obtained in most patients with acute or chronic schizophrenia at plasma concentrations of 1 to 10 ng/mL, while some patients may require concentrations up to 17 ng/mL.

In patients with first episode schizophrenia treated with short acting haloperidol formulations, therapeutic response may be obtained at concentrations as low as 0.6 to 3.2 ng/mL, as estimated based on measurements of D_2 receptor occupancy and assuming that a D_2 receptor occupancy level of 60 to 80% is most appropriate for obtaining therapeutic response and limiting extrapyramidal symptoms.

Due to the high inter-subject variability in haloperidol pharmacokinetics and the concentration-effect relationship, it is recommended to adjust the individual haloperidol decanoate dose based on the patient's response. This must take into account the time after a change in dose to achieve a new steady state plasma concentration and the additional time to elicit a therapeutic response.

Cardiovascular effects

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

5.3 Preclinical safety data

Carcinogenicity, genotoxicity, impairment of fertility, teratogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sesame oil

Benzyl alcohol

6.2 Incompatibilities

Due to the oily base, this injectable solution may not be used in infusions.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

50 mg/mL: 1mL amber glass ampoules, in boxes of 5s.
100 mg/mL: 1mL ampoules, in boxes of 5s.

6.6 Special precautions for disposal and other handling

Before use, roll the ampoule between the palms of the hands for a moment to warm up.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd
Auckland, NEW ZEALAND
Telephone: 0800 800 806
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9. DATE OF FIRST APPROVAL

15 December 1988 (HALDOL)
24 September 1991 (HALDOL CONCENTRATE)

10. DATE OF REVISION OF TEXT

29 October 2021

Summary table of changes

Section changes	Summary of new information
2	Excipient of known effect added.