AUSTRALIAN PRODUCT INFORMATION

# HALDOL® DECANOATE

**Haloperidol decanoate**

**Solution for injection (IM OILY INJECTION)**

## 1. NAME OF THE MEDICINE

Haloperidol decanoate

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL injection contains 50 mg haloperidol (present as haloperidol decanoate 70.52 mg) and each 3 mL injection contains 150 mg haloperidol (present as haloperidol decanoate 211.56 mg).

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

For the full list of excipients, see Section 6.1 List of Excipients.

## 3. PHARMACEUTICAL FORM

The oily injection for intramuscular injection (IM) is a slightly amber, slightly viscous solution.

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

HALDOL DECANOATE 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 DECANOATE should be administered by deep intramuscular injection into the gluteal region. 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. It is recommended to alternate between the two gluteal muscles for subsequent injections.

**DO NOT ADMINISTER INTRAVENOUSLY**

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

Treatment initiation and dose titration must be carried out under close clinical supervision. The starting dose of HALDOL DECANOATE should be based on the patient's clinical history, 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

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|---|
| **Transition from oral haloperidol**<br>• A haloperidol decanoate dose of 10 to 15 times the previous daily dose of oral haloperidol is recommended.<br>• Based on this conversion, the haloperidol decanoate dose will be 25 to150 mg for most patients.<br>• However, the maximum recommended initial haloperidol decanoate dose should not exceed 100 mg. |
| **Continuation of treatment**<br>• 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.<br>• The most effective dose is expected to range between 50 and 200 mg.<br>• The maximum dosage is 300 mg every 4 weeks. |
| **Dosing interval**<br>• Usually 4 weeks between injections.<br>• Adjust the dosing interval as required (based on individual patient response). |
| **Supplementation with non-decanoate haloperidol**<br>• Consider supplementation with non-decanoate haloperidol during transition to HALDOL DECANOATE, dose adjustment or episodes of exacerbation of psychotic symptoms (based on individual patient response).<br>• 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 DECANOATE 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

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|---|
| **Transition from oral haloperidol**<br>• A low haloperidol decanoate dose of 12.5 to 25 mg is recommended. |
| **Continuation of treatment**<br>• 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.<br>• The maximum dosage is half that specified for adults. |
| **Dosing interval**<br>• Usually 4 weeks between injections.<br>• Adjust the dosing interval as required (based on individual patient response). |
| **Supplementation with non-decanoate haloperidol**<br>• Consider supplementation with non-decanoate haloperidol during transition to HALDOL DECANOATE, dose adjustment or episodes of exacerbation of psychotic symptoms (based on individual patient response).<br>• 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 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

subsequent adjustments at smaller increments and at longer intervals than in patients without renal impairment (see section 5.2 Pharmacokinetic Properties – 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 sections 4.4 Special Warnings and Precautions for Use – Hepatobiliary concerns and 5.2 Pharmacokinetic Properties – Special populations: Hepatic impairment).

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

## 4.3 CONTRAINDICATIONS

HALDOL DECANOATE is contraindicated in:

- in individuals who are hypersensitive to haloperidol or to any of the excipients (cross reactivity of sesame oil in patients with a peanut allergy may occur).
- comatose states from any cause.
- the presence of Central Nervous System (CNS) depression due to alcohol or other depressant drugs.
- patients with significant depressive states.
- Patients with previous spastic diseases.
- Parkinson's syndrome, except in the case of dyskinesias due to levodopa treatment.
- senile patients with pre-existing Parkinson-like symptoms.
- 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 drugs, including HALDOL DECANOATE (see section 4.8 Adverse Effects (Undesirable Effects)).

### Sudden Death in Elderly Patients with Dementia

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.

HALDOL DECANOATE is not indicated for the treatment of dementia-related behavioural disturbances.

### Cardiovascular Effects

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

Higher than recommended doses and intravenous administration of haloperidol appear to be associated with a higher risk of QTc-prolongation and/or ventricular arrhythmias, and Torsades de Pointes (see sections 4.5 Interactions with Other Medicines and Other Forms of Interaction; 4.8 Adverse Effects (Undesirable Effects) and 4.9 Overdose). Since QTc prolongation has been observed during HALDOL DECANOATE treatment, it is advised to be particularly cautious in patients with QTc-prolonging conditions (QTc-syndrome, electrolyte imbalance [especially hypokalaemia and hypomagnesaemia], drugs known to prolong QT, cardiovascular diseases, hypothyroidism, family history of QTc prolongation) (see section 4.5 Interactions with Other Medicines and Other Forms of Interaction).

A baseline ECG is recommended before treatment. During therapy, the need for ECG monitoring for QTc interval prolongation and for ventricular arrhythmias must be assessed in all patients. 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.

**HALDOL DECANOATE MUST NOT BE ADMINISTERED INTRAVENOUSLY.**

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

## 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 DECANOATE must be used with caution in patients with risk factors for stroke.

## 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), and increased serum creatine phosphokinase levels. Additional signs may include 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. Dantrolene and bromocriptine have been used for the treatment of NMS.

Signs of autonomic dysfunction such as tachycardia, labile arterial pressure and sweating may precede the onset of hyperthermia thereby acting as early warning signs. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Hyperpyrexia and heat stroke not associated with the above symptom complex have also been reported with HALDOL DECANOATE.

## Extrapyramidal symptoms

Extrapyramidal reactions such as Parkinson-like symptoms, akathisia or dystonic reactions occur frequently with antipsychotics including oral and injectable haloperidol. These have been observed with HALDOL DECANOATE. In most patients, Parkinson-like symptoms, when first observed, were usually mild to moderately severe and usually reversible. They are more commonly observed during the first few days of treatment, however Parkinson rigidity, tremor and akathisia tend to appear less rapidly. They sometimes remit spontaneously as treatment continues or can be relieved by the use of anti-Parkinson medication or a reduction in dose. Anti-parkinson drugs of the anticholinergic type

should only be used when required because of their potential to impair the efficacy of HALDOL DECANOATE. If concomitant anti-parkinson medication is required, it may have to be continued after stopping HALDOL DECANOATE if its excretion is faster than that of HALDOL DECANOATE in order to avoid the development or aggravation of extrapyramidal symptoms. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including anti-parkinson agents, are administered.

Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crisis) have been reported far less frequently, but were often more severe.

Akathisia is best managed by a reduction in dosage in conjunction with the temporary use of an oral anti-parkinson drug. Dystonias, which can lead to laryngeal spasm or bronchospasm, may be controlled by amylobarbitone or injectable anti-parkinson agents. Extrapyramidal reactions appear to be dose-related.

## 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 (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of the extremities. Tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. The symptoms are persistent and 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. There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. Since there is a significant prevalence of this syndrome associated with the use of neuroleptic drugs, and 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. It is suggested that the dosage of all antipsychotic agents be progressively reduced with a view to discontinuation if possible. Should it be necessary to reinstitute treatment or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome, and, if the medication is stopped at that time, the full syndrome may not develop.

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.

## Tardive dystonia

Tardive dystonia, which might be observed in the absence of other symptoms of the above syndrome, has also been reported. Tardive dystonia is characterised by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible.

## 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 metabolised in the liver, dosage adjustment and careful observation of patients with hepatic impairment is recommended (see sections 4.2 Dose and Method of Administration – Special populations: Hepatic impairment and 5.2 Pharmacokinetic Properties – Special populations: Hepatic impairment). Impaired liver function and/or jaundice or hepatitis, most often cholestatic, has been reported (see section 4.8 Adverse Effects (Undesirable Effects)).

## Endocrine system concerns

Patients with thyrotoxicosis. Antipsychotic medication, including HALDOL DECANOATE, 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.

Hormonal effects of antipsychotic 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 Adverse Effects (Undesirable Effects)).

## 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 DECANOATE and preventive measures undertaken.

## Weight gain

Clinically significant weight gain has been reported in patients taking HALDOL DECANOATE. Patients taking antipsychotic medications, including HALDOL DECANOATE should undergo regular monitoring of weight and the testing of other parameters (e.g., blood glucose, haemoglobin A1C) that would be appropriate in the setting of significant weight gain. Clinicians should individualise treatment decisions based on such monitoring.

## Treatment initiation

It is recommended that patients to be treated with HALDOL DECANOATE must be treated initially with oral haloperidol to exclude the possibility of severe unexpected sensitivity to haloperidol.

**HALDOL DECANOATE 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 (norepinephrine) may be indicated if the resulting hypotension is prolonged and severe. Adrenaline (epinephrine) should 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 (see section 4.4 Special Warnings and Precautions for Use – Seizures/convulsions).
- 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 (see section 4.4 Special Warnings and Precautions for Use – Endocrine system concerns).
- Patients with known allergies or with a history of allergic reactions to drugs.
- Patients receiving anticoagulants (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

When HALDOL DECANOATE 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.

If concomitant anti-parkinson medication is required, it may have to be continued after HALDOL DECANOATE is discontinued because of the prolonged action of haloperidol decanoate. If both drugs are discontinued simultaneously, extrapyramidal symptoms may occur.

### Patients with depression

As with all antipsychotic agents, HALDOL DECANOATE should not be used alone where depression is predominant.

### Use in the elderly

Lower initial doses and more gradual adjustments are recommended for elderly or debilitated patients (see section 4.2 Dose and Method of Administration)

### Paediatric use

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

### Effects of laboratory tests

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

**Cardiovascular effects**

As with other antipsychotic medicines, caution is advised when HALDOL DECANOATE is used in combination with medications known to prolong the QTc interval (see section 4.4 Special Warnings and Precautions for Use – Cardiovascular effects). 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. 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 DECANOATE is used in combination with medicines known to cause electrolyte imbalance (see section 4.4 Special Warnings and Precautions for Use – Cardiovascular effects)

**Medicines that may increase haloperidol plasma concentrations**

Haloperidol is metabolised by several routes, (see section 5.2 Pharmacokinetic Properties – 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 Pharmacokinetic Properties – 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, duloxetine 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 Special Warnings and Precautions for Use – 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 DECANOATE 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.

### Effects of HALDOL DECANOATE on other medicines

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

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

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

Haloperidol decanoate may impair the antiparkinsonian effects of levodopa and other dopamine agonist medicines.

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 must be discontinued should such signs appear.

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

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

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

There are no human data on the effects of haloperidol on male and female fertility. In female rats, administration of haloperidol induced estrus cycle disruptions, and in female mice, subcutaneous administration of haloperidol prior to ovulation induced delays in implantation, cleavages and blastocoele formation. In male rats, oral administration of haloperidol prior to mating reduced fertility, increased preimplantation loss and induced histopathological changes in the reproductive organs. Following intraperitoneal administration of haloperidol to female rats from early pregnancy to weaning, the frequency of ejaculation in offspring was reduced. These studies used various dose levels and in some cases a no-effect level was not established. The significance of these findings for human exposure to therapeutic doses of haloperidol decanoate is unknown.

### Use in pregnancy – Category C

There have been isolated case reports of birth defects following foetal exposure to haloperidol in combination with other drugs.

Non-teratogenic class effect: Neonates exposed to antipsychotic medicines (including HALDOL DECANOATE) 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 DECANOATE 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.

Withdrawal-emergent syndromes in neonates, following long-term, in utero exposure to haloperidol, have been reported.

In pregnant rodents, administration of haloperidol during the period of organogenesis has produced adverse effects including embryolethality, gross malformations (cleft palate, neural tube defects), and reduced brain and body weight and behavioural effects in offspring. The significance of these findings for human exposure to therapeutic doses of haloperidol decanoate is unknown.

### Use in lactation

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. 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 HALDOL DECANOATE therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

HALDOL DECANOATE 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.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

### Clinical trial data

### Comparator and open-label trial data – adverse drug reactions reported at ≥1% incidence

The safety of HALDOL DECANOATE (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 DECANOATE-treated subjects in these trials are shown in **Table 3**.

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

| **System/Organ Class**<br>Adverse Reaction | **Haloperidol decanoate (n=410)**<br>**%** |
|---|---|
| **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

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 below:

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

## Post-marketing data

Adverse events first identified as adverse reactions during post-marketing experience with haloperidol, presented by frequency category based on spontaneous reporting rates, are included in **Table 5.** The post-marketing review was based on review of all cases including haloperidol and haloperidol decanoate products. In each table, 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 5:** 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, Injection site abscess |
| **Investigations** | |
| Very rare | Electrocardiogram QT prolonged, Weight decreased |

### Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

### 4.9 OVERDOSE

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

### Symptoms

In general, the symptoms of over dosage would be an exaggeration of known pharmacological effects and adverse reactions, the most prominent of which would be severe extrapyramidal reactions, hypotension or sedation.

The patient would appear comatose with respiratory depression and hypotension that could be severe enough to produce a shock-like state. The extrapyramidal reaction would be manifest by muscular weakness or rigidity and generalised or localised tremor, as demonstrated by akinetic or agitans types respectively. With accidental over dosage, hypertension rather than hypotension occurred in a two-year-old child.

There is a possibility of ventricular arrhythmias, sometimes associated with QTc-interval prolongation.

### 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 Pharmacokinetic Properties – Special populations: Renal impairment). A patent airway must be established by use of an oropharyngeal airway or endotracheal tube or, in prolonged cases of coma, by tracheostomy. Respiratory depression may be counteracted by artificial respiration and mechanical respirators.

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 noradrenaline (norepinephrine). Adrenaline (epinephrine) must not be used as it may cause profound hypotension in the presence of haloperidol. In case of severe extrapyramidal reactions anti-parkinson medication should be administered and continued for several weeks. Anti-parkinson medication must then be withdrawn very cautiously as extrapyramidal symptoms may emerge.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

ATC Code N05AD01

### Mechanism of action

Haloperidol decanoate is a long-acting form of haloperidol. The basic effects of haloperidol decanoate are the same as those of haloperidol with the exception of duration of action. When it is administered as an intramuscular depot injection in sesame oil, esterases present in the blood and tissues hydrolyse haloperidol decanoate to provide a slow release of the active neuroleptic haloperidol from the depot into the systemic circulation.

Haloperidol 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.

### Clinical trials

No data available.

### 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 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.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

Administration of haloperidol decanoate as a depot IM injection results in a slow and sustained release of haloperidol. The plasma concentrations rise gradually, usually peaking within 3 to 9 days after injection and falling thereafter with an apparent half-life of about 3 weeks. Steady state plasma levels were reached in 2-4 months in chronic psychotic 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; however, the reduction pathway accounts for some 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 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 Dose and Method of Administration – Special populations: Elderly).

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. 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 Dose and Method of Administration – Special populations: 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 metabolised in the liver. Therefore, dosage adjustment and caution is advised in patients with hepatic impairment (see sections 4.2 Dose and Method of Administration – Special populations: Hepatic impairment and 4.4 Special Warnings and Precautions for Use – 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 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.

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.

# 5.3 PRECLINICAL SAFETY DATA

## Genotoxicity

Haloperidol and haloperidol decanoate were negative in bacterial gene mutation assays, and haloperidol was also negative in a mammalian forward mutation assay and in assays for chromosomal damage in human lymphocytes in vitro and in vivo and in rat bone marrow in vivo.

## Carcinogenicity

There was no evidence of carcinogenicity in Wistar rats following oral administration of haloperidol for 24 months at doses up to 5mg/kg/day. In female mice, there was an increase in mammary gland neoplasia and total tumour incidence following oral administration of haloperidol at doses of 1.25 and 5mg/kg/day and an increase in pituitary gland neoplasia at 5mg/kg/day. There were no

carcinogenic effects in male mice. Haloperidol increases prolactin levels, which may affect human breast cancers, one-third of which are prolactin dependent in vitro. Although clinical studies have not shown an association between chronic treatment with antipsychotic drugs (including haloperidol) and an increase in breast cancer incidence, it may be a factor of importance when prescribing haloperidol for patients with a history of breast cancer.

In four alternative short-term carcinogenicity models using neonatal or transgenic mice, there was no evidence of carcinogenicity at systemic exposures (plasma AUC) from one to eleven times the clinical exposure, at the maximal recommended human intramuscular dose of haloperidol decanoate.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

The inactive ingredients are benzyl alcohol and sesame oil.

Each mL contains 1.5% w/v benzyl alcohol as a preservative i.e. each mL contains 15 mg benzyl alcohol.

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25˚C. Protect from light.

## 6.5 NATURE AND CONTENTS OF CONTAINER

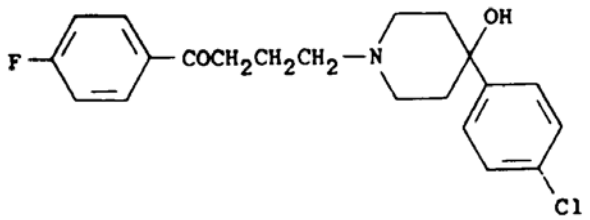
HALDOL DECANOATE is supplied as either 50 mg/1 mL or 150 mg/3 mL in glass ampoules. Each pack contains 5 ampoules.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical structure




--- [decanoate]

4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-4-piperidinyl decanoate

Haloperidol decanoate is the decanoate ester of haloperidol. Haloperidol decanoate is almost insoluble in water but is soluble in most organic solvents.

### CAS number

74050-97-8

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

## 8. SPONSOR

Janssen-Cilag Pty Ltd
1-5 Khartoum Road,
Macquarie Park,
NSW, 2113, AUSTRALIA
Telephone: 1800 226 334

NZ Office:
Auckland, NEW ZEALAND
Telephone: 0800 800 806

## 9. DATE OF FIRST APPROVAL

28 August 1991

## 10. DATE OF REVISION

20 September 2021

### Summary Table of Changes

| Section changed | Summary of new information |
|---|---|
| 2 | Description of the product reworded. Excipient of known effect added. |
| 3 | Description of the visual ID added. |
| 6.4 | Storage condition text aligned to registered details |
| 6.5 | Add registered pack size |