NAME OF THE MEDICINAL PRODUCT

Tradename

HALDOL® Decanoas

International Non-Propriety Name (INN)

haloperidol decanoate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of HALDOL Decanoas 50 mg/ml is expressed in terms of the haloperidol content and is equivalent to 70.52 mg haloperidol decanoate.

Each ml of HALDOL Decanoas 100 mg/ml is expressed in terms of the haloperidol content and is equivalent to 141.04 mg haloperidol decanoate.

For excipients, see List of Excipients.

PHARMACEUTICAL FORM

Solution for injection.

Appearance:

50 mg/ml and 100 mg/ml injectable solutions

Slightly amber, slightly viscous solution. Free from visible foreign material.

CLINICAL PARTICULARS

Therapeutic Indications

HALDOL Decanoas is indicated for the maintenance treatment of chronic schizophrenia and other psychoses. It is also indicated in the treatment of other mental or behavioural problems where psychomotor unrest requires maintenance treatment.

Posology and Method of Administration

HALDOL Decanoas Injection is intended for use in chronic psychotic patients who require prolonged parenteral antipsychotic therapy. These patients should be previously stabilised on antipsychotic medication before considering a conversion to HALDOL Decanoas.

HALDOL Decanoas is for use in adults only and has been formulated to provide a one month's therapy for most patients following a single deep intramuscular injection in the gluteal region. HALDOL Decanoas should not be administered intravenously. As the administration of volumes greater than 3 ml are uncomfortable for the patient, such large injection volumes are not recommended.

Since individual response to neuroleptic drugs is variable, dosage should be individually determined and is best initiated and titrated under close clinical supervision. The individual starting dose will depend on both the severity of the symptomatology and the amount of oral medication required to maintain the patient before starting depot treatment.

It is recommended that the initial dose of HALDOL Decanoas be 10-15 times the previous daily dose of oral haloperidol. For most patients, this means a starting dose ranging between 25 and 75 mg of HALDOL Decanoas. A maximum starting dose of 100 mg should not be exceeded.

Depending on the individual patient's response the dose may gradually be increased by 50 mg until an optimal therapeutic effect is obtained. The most appropriate monthly dose of HALDOL Decanoas is often about 20 times the daily dose of oral

haloperidol. During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoas therapy can be supplemented with regular haloperidol.
The usual time interval between injections is four weeks. However, variation in patient response may dictate a need for adjustment of the dosing interval.
Use in elderly and in debilitated patients:
It is recommended to start with low doses, for example 12.5 mg-25 mg every 4 weeks, only increasing the dose according to the patient's response.

Contraindications

Comatose state; CNS depression due to alcohol or other depressant drug; Parkinson's disease; known hypersensitivity to HALDOL Decanoas or its excipients [contains sesame oil]; lesion of the basal ganglia.

Special Warnings and Special Precautions for Use

Rare cases of sudden death have been reported in psychiatric patients receiving antipsychotic drugs, including HALDOL Decanoas.
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.
Cardiovascular effects
Very rare reports of QT prolongation and/or ventricular arrhythmias, in addition to rare reports of sudden death, have been reported with haloperidol. They may occur more frequently with high doses and in predisposed patients.
As QT-prolongation has been observed during haloperidol treatment, caution is advised in patients with QT-prolonging conditions (long QT-syndrome, hypokalaemia, electrolyte imbalance, drugs known to prolong QT - see Interactions with Other Medicinal Products and Other Forms of Interaction, cardiovascular diseases, family history of QT prolongation), especially if haloperidol is given parenterally. The risk of QT prolongation and/or ventricular arrhythmias may be increased with higher doses or with parenteral use, particularly intravenous administration. **Haloperidol Decanoate must not be administered intravenously**.
Tachycardia and hypotension have also been reported in occasional patients.
Neuroleptic malignant syndrome
In common with other antipsychotic drugs, HALDOL Decanoas has been associated with neuroleptic malignant syndrome: a rare idiosyncratic response characterized by hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness. Hyperthermia is often an early sign of this syndrome. Antipsychotic

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

Tardive dyskinesia

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

Extrapyramidal symptoms

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

Antiparkinson drugs of the anticholinergic type may be prescribed as required, but should not be prescribed routinely as a preventive measure. If concomitant antiparkinson medication is required, it may have to be continued after stopping HALDOL Decanoas if its excretion is faster than that of haloperidol in order to avoid the development or aggravation of extrapyramidal symptoms. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including antiparkinson agents, are administered concomitantly with HALDOL Decanoas.

Seizures/Convulsions

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

Hepatobiliary concerns

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

Endocrine system concerns

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

Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligo- or amenorrhoea. Very rare cases of hypoglycaemia and of Syndrome of Inappropriate ADH Secretion have been reported.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with HALDOL Decanoas and preventive measures undertaken.

Additional considerations

It is recommended that patients being considered for HALDOL Decanoas therapy be initially put on oral haloperidol to exclude the possibility of an unexpected adverse sensitivity to haloperidol.

As with all antipsychotic agents, HALDOL Decanoas 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.

Interactions with Other Medicinal Products and Other Forms of Interaction

As with other antipsychotics, caution is advised when prescribing haloperidol with medications known to prolong the QT interval.

Haloperidol is metabolized by several routes, including glucuronidation and the cytochrome P450 enzyme system (particularly CYP 3A4 or CYP 2D6). Inhibition of these routes of metabolism by another drug or a decrease in CYP 2D6 enzyme activity may result in increased haloperidol concentrations and an increased risk of adverse events, including QT-prolongation. In pharmacokinetic studies, mild to moderately increased haloperidol concentrations have been reported when haloperidol was given concomitantly with drugs characterized as substrates or inhibitors of CYP 3A4 or CYP 2D6 isozymes, such as, itraconazole, nefazodone, buspirone, venlafaxine, alprazolam, fluvoxamine, quinidine, fluoxetine, sertraline, chlorpromazine, and promethazine. A decrease in CYP2D6 enzyme activity may result in increased haloperidol concentrations. Increases in QTc have been observed when haloperidol was given with a combination of the metabolic inhibitors ketoconazole (400 mg/day) and paroxetine (20 mg/day). It may be necessary to reduce the haloperidol dosage.

Caution is advised when used in combination with drugs known to cause electrolyte imbalance.

Effect of Other Drugs on Haloperidol

When prolonged treatment with enzyme-inducing drugs such as carbamazepine, phenobarbital, rifampicine is added to HALDOL Decanoas therapy, this results in a significant reduction of haloperidol plasma levels. Therefore, during combination treatment, the HALDOL Decanoas dose or the dosage interval should be adjusted, when necessary. After stopping such drugs, it may be necessary to reduce the dosage of HALDOL Decanoas.

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

Effect of Haloperidol on Other Drugs

In common with all neuroleptics, HALDOL Decanoas can increase the central nervous system depression produced by other CNS-depressant drugs, including alcohol, hypnotics, sedatives or analgesics. An enhanced CNS effect, when combined with methyldopa, has been reported.

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

HALDOL Decanoas may impair the antiparkinsonian effects of levodopa.

Haloperidol is an inhibitor of CYP 2D6. HALDOL Decanoas inhibits the metabolization of tricyclic antidepressants, thereby increasing plasma levels of these drugs.

Other Forms of Interaction

In rare cases the following symptoms were reported during the concomitant use of lithium and haloperidol decanoate: encephalopathy, extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, brain stem disorder, acute brain

syndrome and coma. Most of these symptoms were reversible. It remains unclear whether this represents a distinct clinical entity.
Nonetheless, it is advised that in patients, who are treated concomitantly with lithium and HALDOL Decanoas, therapy should be stopped immediately if such symptoms occur.
Antagonism of the effect of the anticoagulant phenindione has been reported.

Pregnancy and Lactation

Animal studies have demonstrated a teratogenic effect of haloperidol (see Preclinical Safety Data).
Neonates exposed to antipsychotic drugs (including haloperidol) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may vary in severity following delivery. These symptoms in the neonates may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder.
HALDOL Decanoas has shown no significant increase in fetal anomalies in large population studies. There have been isolated case reports of birth defects following fetal exposure to HALDOL Decanoas in combination with other drugs. HALDOL Decanoas should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.
HALDOL Decanoas is excreted in breast milk. If the use of HALDOL Decanoas is considered essential, the benefits of breast-feeding should be balanced against its potential risks. Extrapyramidal symptoms have been observed in breast-fed infants of HALDOL Decanoas treated women.

Effects on 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. Patients should be advised not to drive or operate machinery during treatment, until their susceptibility is known.

Undesirable Effects

Clinical Trial Data

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

The safety of HALDOL Decanoas (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 Drug Reactions (ADRs) reported by ≥1% of HALDOL Decanoas-treated subjects in these trials are shown in Table 1.

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

System/Organ Class Adverse Reaction	HALDOL Decanoas (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 ADRs that occurred in <1% of HALDOL Decanoas-treated subjects either of the above trial data are listed below in Table 2.

Table 2. Adverse Drug Reactions Reported by <1 % of HALDOL Decanoas-treated Subjects in Comparator and Open-Label Clinical Trials of HALDOL Decanoas

Nervous System Disorders
Akinesia
Dyskinesia
Hypertonia
Dystonia
Cogwheel rigidity
Eye Disorders
Vision blurred
Visual disturbance
Oculogyric crisis
Cardiac Disorders
Tachycardia

The following is a list of additional ADRs that have been identified in clinical trials with other formulations of haloperidol (non decanoate):

Endocrine Disorders: Hyperprolactinaemia

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: Amenorrhoea; Galactorrhoea; Menstrual disorder; Erectile dysfunction; Breast discomfort; Breast pain; Dysmenorrhoea; Menorrhagia

General Disorders and Administration Site Conditions: Gait disturbance

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with haloperidol are included in Table 3. The postmarketing review was based on review of all cases including haloperidol and haloperidol decanoate containing products. In the table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000, including isolated reports

In Table 3, ADRs are presented by frequency category based on spontaneous reporting rates.

Table 3: Adverse Drug Reactions Identified During Postmarketing 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
Metabolic and Nutritional Disorders	
Very rare	Hypoglycaemia
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	Leukocytoclastic vasculitis, Dermatitis exfoliative, Urticaria, Photosensitivity reaction, Rash, Pruritis, Hyperhidrosis
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

Overdose

While overdosage 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 HALDOL Decanoas.

Symptoms:

The manifestations 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 QT-prolongation, should be considered.

Treatment:

Since there is no specific antidote, treatment is primarily supportive. For comatose patients, a patent airway should be established by use of an oropharyngeal airway or endotracheal tube. Respiratory depression may necessitate artificial respiration. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as dopamine or noradrenaline. Adrenaline should not be used.

In case of severe extrapyramidal reactions, antiparkinsonian medication of the anticholinergic type should be administered and be continued for several weeks.

They must be withdrawn very cautiously as extrapyramidal symptoms may emerge.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

ATC Code N05AD01

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 dopamine antagonist and, therefore, a very incisive neuroleptic.

In the brain, haloperidol has an incisive action on delusions and hallucinations (probably through an interaction with dopamine receptors in the mesocortical and limbic tissues) and an inhibitory effect through its activity on the basal ganglia, i.e. nigrostriatal bundles, which also underlies the extrapyramidal motor side-effects (namely dystonia, akathisia and parkinsonism).

Haloperidol presents an effective psychomotor sedative effect, which also explains the favourable effect on mania and other agitation syndromes.

A resocializing effect has been observed in emotionally withdrawn patients.

The more peripheral antidopaminergic effects explain the activity against nausea and vomiting (via the chemoreceptor-trigger zone), the relaxation of the gastro-intestinal

sphincters and the increased prolactin release (through an inhibition of the activity of the prolactin inhibiting factor, PIF, at the level of the adenohypophysis).

Pharmacokinetic Properties

Absorption

Administration of haloperidol decanoate as a depot intramuscular injection results in a slow and sustained release of free haloperidol. The plasma concentrations rise gradually, usually peaking within 3 to 9 days after injection. The pharmacokinetics of haloperidol decanoate following intramuscular injections are dose-related. The relationship between dose and plasma haloperidol level is roughly linear for doses below 450 mg.

Distribution

Haloperidol crosses the blood-brain barrier easily. Plasma protein binding is 92%.

Metabolism

Haloperidol is metabolized by several routes including the cytochrome P450 enzyme system (particularly CYP 3A4 or CYP 2D6) and glucuronidation.

Elimination

After reaching peak plasma concentrations, levels fall with an apparent half-life of about 3 weeks. Haloperidol is excreted in the urine (40%) and faeces (60%). About 1% of the dose is excreted unchanged with the urine.

Multiple-Dose Pharmacokinetics

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

Therapeutic Concentrations

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

Preclinical Safety Data

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.

Haloperidol has been shown to block the cardiac hERG channel in several published studies *in vitro*. In a number of *in vivo* studies intravenous administration of haloperidol in some animal models has caused significant QTc prolongation, at doses around 0.3 mg/kg i.v., giving C_{max} plasma levels 3 to 7 times higher than the effective human plasma concentrations of 4 to 20ng/ml These intravenous doses which prolonged QTc did not cause arrhythmias. In some studies higher intravenous doses of 1 to 5 mg/kg haloperidol i.v. caused QTc prolongation and/or ventricular arrhythmias at C_{max} plasma levels 19 to 68 times higher than the effective human plasma concentrations.

PHARMACEUTICAL PARTICULARS

List of Excipients

Benzyl alcohol, sesame oil refined.

Incompatibilities

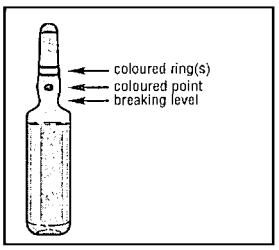
Due to the oily base, this injectable solution must not be used in infusions.

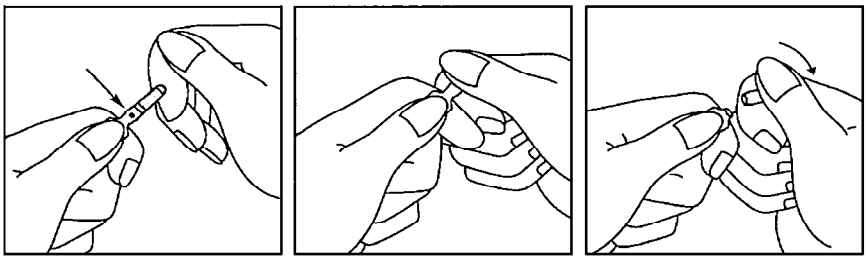
Shelf Life

Observe expiry date on the outer pack.

Special Precautions for Storage
Store between 15° and 30°C. Protect from light.
Keep out of reach of children.
Nature and Contents of Container
HALDOL Decanoas 50 mg/ml is supplied in 1 ml and 3 ml amber colored glass Type I ampoules.
HALDOL Decanoas 100 mg/ml is supplied in 1 ml amber colored glass Type I ampoules.
Instructions for Use and Handling
Before use, roll the ampoule between the palms of the hands for a moment to warm it up.

1. Hold the ampoule between the thumb and index finger, leaving the tip of the ampoule free.
2. With the other hand, hold the tip of ampoule putting the index finger against the neck of ampoule, and the thumb on the coloured point in parallel to the identification coloured ring(s).
3. Keeping the thumb on the point, sharply break the tip of ampoule while holding firmly the other part of the ampoule in the hand.





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DATE OF REVISION OF THE TEXT
August 2011