1. NAME OF THE MEDICINAL PRODUCT

HALDOL Decanoas 100 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

100 mg/ml solution:
Each ml of solution contains 141.04 mg of haloperidol decanoate, equivalent to 100 mg of haloperidol base.

Excipients with known effect:

100 mg/ml solution:
Each ml of solution contains 15 mg of benzyl alcohol and up to 1 ml of sesame oil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HALDOL DECANOAS is indicated for the maintenance therapy of chronic schizophrenic patients.

4.2 Posology and method of administration

Posology

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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Comatose state.
- Central nervous system (CNS) depression.
- Parkinson's disease.
- Dementia with Lewy bodies.
- Progressive supranuclear palsy.
- Known QTc interval prolongation or congenital long QT syndrome.
- Recent acute myocardial infarction.
- Uncompensated heart failure.
- History of ventricular arrhythmia or torsades de pointes.
- Uncorrected hypokalaemia.
- Concomitant treatment with medicinal products that prolong the QT interval (see section 4.5).

4.4 Special warnings and precautions for use

Increased mortality in elderly people with dementia

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

Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death. Analyses of seventeen placebo-controlled studies (modal duration of 10 weeks), largely in patients taking atypical antipsychotics, revealed a risk of death in treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10 week controlled study, the rate of death in patients treated with antipsychotics was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that treatment of elderly patients with haloperidol is also associated with increased mortality. This association may be stronger for haloperidol than for atypical antipsychotic medicinal products, is most pronounced in the first 30 days after the start of treatment, and persists for at least 6 months. The extent to which this association is attributable to the medicinal product, as opposed to being confounded by patient characteristics, has not yet been elucidated.

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

Cardiovascular effects

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

HALDOL Decanoate must not be administered intravenously.

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

A baseline ECG is recommended before 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.

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

Cerebrovascular events

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

Neuroleptic malignant syndrome

Haloperidol has been associated with neuroleptic malignant syndrome: a rare idiosyncratic response characterized by hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness and increased serum creatine phosphokinase levels. Hyperthermia is often an early sign of this syndrome. Antipsychotic treatment must be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Tardive dyskinesia

Tardive dyskinesia may appear in some patients on long-term therapy or after discontinuation of the medicinal product. The syndrome is mainly characterized by rhythmic involuntary movements of the tongue, face, mouth or jaw. The manifestations may be permanent in some patients. The syndrome may be masked when treatment is reinstituted, when the dose is increased or when a switch is made to a different antipsychotic. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics, including HALDOL Decanoate, must be considered.

Extrapyramidal symptoms

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

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

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

Seizures/convulsions

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

Hepatobiliary concerns

As haloperidol is metabolised by the liver, dose adjustment and caution is advised in patients with hepatic impairment (see sections 4.2 and 5.2). Isolated cases of liver function abnormalities or hepatitis, most often cholestatic, have been reported (see section 4.8).

Endocrine system concerns

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

Hormonal effects of antipsychotics include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligomenorrhea or amenorrhoea (see section 4.8). Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics and human breast tumours has been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. HALDOL Decanoate must be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours (see section 5.3).

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

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotics. 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.

Treatment initiation

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

Patients with depression

It is recommended that HALDOL Decanoate is not used alone in patients in whom depression is predominant. It may be combined with antidepressants to treat those conditions in which depression and psychosis coexist (see section 4.5).

Poor metabolisers of CYP2D6

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

Excipients of HALDOL Decanoate

HALDOL Decanoate contains benzyl alcohol, which may cause allergic reactions. HALDOL Decanoate must be used with caution in patients with renal or hepatic impairment, or in patients who are pregnant or breast-feeding, because of the risk of accumulation and toxicity (metabolic acidosis).

HALDOL Decanoate contains sesame oil, which may rarely cause severe allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Cardiovascular effects

HALDOL Decanoate is contraindicated in combination with medicinal products known to prolong the QTc interval (see section 4.3). Examples include:

- Class IA antiarrhythmics (e.g. disopyramide, quinidine).
- Class III antiarrhythmics (e.g. amiodarone, dofetilide, dronedarone, ibutilide, sotalol).
- Certain antidepressants (e.g. citalopram, escitalopram).
- Certain antibiotics (e.g. azithromycin, clarithromycin, erythromycin, levofloxacin, moxifloxacin, telithromycin).
- Other antipsychotics (e.g. phenothiazine derivatives, sertindole, pimozide, ziprasidone)
- Certain antifungals (e.g. pentamidine).
- Certain antimalarials (e.g. halofantrine).
- Certain gastrointestinal medicinal products (e.g. dolasetron).
- Certain medicinal products used in cancer (e.g. toremifene, vandetanib).
- Certain other medicinal products (e.g. bepridil, methadone).

This list is not exhaustive.

Caution is advised when HALDOL Decanoate is used in combination with medicinal products known to cause electrolyte imbalance (see section 4.4).

Medicinal products that may increase haloperidol plasma concentrations

Haloperidol is metabolised by several routes (see section 5.2). The major pathways are glucuronidation and ketone reduction. The cytochrome P450 enzyme system is also involved, particularly CYP3A4 and, to a lesser extent, CYP2D6. Inhibition of these routes of metabolism by another medicinal product or a decrease in CYP2D6 enzyme activity may result in increased haloperidol concentrations. The effect of CYP3A4 inhibition and of decreased CYP2D6 enzyme activity may be additive (see section 5.2). Based on limited and sometimes conflicting information, the potential increase in haloperidol plasma concentrations when a CYP3A4 and/or CYP2D6 inhibitor is coadministered may range between 20 to 40%, although in some cases, increases of up to 100% have

been reported. Examples of medicinal products that may increase haloperidol plasma concentrations (based on clinical experience or drug interaction mechanism) include:

- CYP3A4 inhibitors – alprazolam, fluvoxamine, indinavir, itraconazole, ketoconazole, nefazodone, posaconazole, saquinavir, verapamil, voriconazole.
- CYP2D6 inhibitors – bupropion, chlorpromazine, duloxetine, paroxetine, promethazine, sertraline, venlafaxine.
- Combined CYP3A4 and CYP2D6 inhibitors: fluoxetine, ritonavir.
- Uncertain mechanism – buspirone.

This list is not exhaustive.

Increased haloperidol plasma concentrations may result in an increased risk of adverse events, including QTc-prolongation (see section 4.4). Increases in QTc have been observed when haloperidol was given with a combination of the metabolic inhibitors ketoconazole (400 mg/day) and paroxetine (20 mg/day).

It is recommended that patients who take haloperidol concomitantly with such medicinal products be monitored for signs or symptoms of increased or prolonged pharmacologic effects of haloperidol, and the HALDOL Decanoate dose be decreased as deemed necessary.

Medicinal products that may decrease haloperidol plasma concentrations

Coadministration of haloperidol with potent enzyme inducers of CYP3A4 may gradually decrease the plasma concentrations of haloperidol to such an extent that efficacy may be reduced. Examples include:

- Carbamazepine, phenobarbital, phenytoin, rifampicin, St John's Wort (*Hypericum, perforatum*).

This list is not exhaustive.

Enzyme induction may be observed after a few days of treatment. Maximal enzyme induction is generally seen in about 2 weeks and may then be sustained for the same period of time after the cessation of therapy with the medicinal product. During combination treatment with inducers of CYP3A4, it is recommended that patients be monitored and the HALDOL Decanoate dose increased as deemed necessary. After withdrawal of the CYP3A4 inducer, the concentration of haloperidol may gradually increase and therefore it may be necessary to reduce the HALDOL Decanoate dose.

Sodium valproate is known to inhibit glucuronidation, but does not affect haloperidol plasma concentrations.

Effect of haloperidol on other medicinal products

Haloperidol can increase the CNS depression produced by alcohol or CNS-depressant medicinal products, including hypnotics, sedatives or strong analgesics. An enhanced CNS effect, when combined with methyldopa, has also been reported.

Haloperidol may antagonise the action of adrenaline and other sympathomimetic medicinal products (e.g. stimulants like amphetamines) and reverse the blood pressure-lowering effects of adrenergic-blocking medicinal products such as guanethidine.

Haloperidol may antagonise the effect of levodopa and other dopamine agonists.

Haloperidol is an inhibitor of CYP2D6. Haloperidol inhibits the metabolism of tricyclic antidepressants (e.g. imipramine, desipramine), thereby increasing plasma concentrations of these medicinal products.

Other forms of interaction

In rare cases the following symptoms were reported during the concomitant use of lithium and haloperidol: encephalopathy, extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, acute brain syndrome and coma. Most of these symptoms were reversible. It remains unclear whether this represents a distinct clinical entity.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (more than 400 pregnancy outcomes) indicate no malformative or foeto/ neonatal toxicity of haloperidol. However, there have been isolated case reports of birth defects following foetal exposure to haloperidol in combination with other medicinal products. Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of HALDOL Decanoate during pregnancy.

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

Breastfeeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

HALDOL Decanoate has a moderate influence on the ability to drive and use machines. Some degree of sedation or impairment of alertness may occur, particularly with higher doses and at the start of treatment and may be potentiated by alcohol. It is recommended that patients be advised not to drive or operate machines during treatment, until their susceptibility is known.

4.8 Undesirable effects

The safety of haloperidol decanoate was evaluated in 410 patients who participated in 3 comparator studies (1 comparing haloperidol decanoate versus fluphenazine and 2 comparing the decanoate formulation to oral haloperidol), 9 open label studies and 1 dose response study.

Based on pooled safety data from these clinical studies, the most commonly reported adverse reactions were: extrapyramidal disorder (14%), tremor (8%), parkinsonism (7%), muscle rigidity (6%) and somnolence (5%).

In addition, the safety of haloperidol was evaluated in 284 haloperidol-treated patients who participated in 3 placebo-controlled clinical studies and in 1295 haloperidol-treated patients who participated in 16 double-blind active comparator-controlled clinical studies.

Table 3 lists adverse reactions as follows:

- Reported in clinical studies with haloperidol decanoate.
- Reported in clinical studies with haloperidol (non-decanoate formulations) and relate to the active moiety.
- From postmarketing experience with haloperidol decanoate and haloperidol.

Adverse reaction frequencies are based on (or estimated from) clinical trials or epidemiology studies with haloperidol decanoate, and classified using the following convention:

Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000
Not known: cannot be estimated from the available data.

The adverse reactions are presented by System Organ Class and in order of decreasing seriousness within each frequency category.

Table 3: Adverse reactions

System Organ Class	**Adverse Reaction**				
	Frequency				
	Very Common	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and lymphatic system disorders					Pancytopenia Agranulocytosis Thrombocytopenia Leukopenia Neutropenia
Immune system disorders					Anaphylactic reaction Hypersensitivity
Endocrine disorders					Inappropriate antidiuretic hormone secretion Hyperprolactinaemia
Metabolic and nutritional disorders					Hypoglycaemia

System Organ Class	Adverse Reaction				
	Frequency				
	Very Common	Common	Uncommon	Rare	Not known
Psychiatric disorders		Depression Insomnia			Psychotic disorder Agitation Confusional state Loss of libido Libido decreased Restlessness
Nervous system disorders	Extrapyramidal disorder	Akathisia Parkinsonism Masked facies Tremor Somnolence Sedation	Akinesia Dyskinesia Dystonia Cogwheel rigidity Hypertonia Headache		Neuroleptic malignant syndrome Tardive dyskinesia Convulsion Bradykinesia Hyperkinesia Hypokinesia Dizziness Muscle contractions involuntary Motor dysfunction Nystagmus
Eye disorders			Oculogyric crisis Vision blurred Visual disturbance		
Cardiac disorders			Tachycardia		Ventricular fibrillation Torsade de pointes Ventricular tachycardia Extrasystoles
Vascular disorders					Hypotension Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders					Laryngeal oedema Bronchospasm Laryngospasm Dyspnoea
Gastrointestinal disorders		Constipation Dry mouth Salivary hypersecretion			Vomiting Nausea
Hepatobiliary disorders					Acute hepatic failure Hepatitis Cholestasis Jaundice Liver function test abnormal
Skin and subcutaneous tissue disorders					Angioedema Dermatitis exfoliative Leukocytoclastic vasculitis Photosensitivity reaction Urticaria Pruritus Rash Hyperhidrosis
Musculoskeletal and connective tissue disorders		Muscle rigidity			Rhabdomyolysis Torticollis Trismus Muscle spasms Muscle twitching Musculoskeletal stiffness

System Organ Class	Adverse Reaction				
	Frequency				
	Very Common	Common	Uncommon	Rare	Not known
Renal and urinary disorders					Urinary retention
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders		Sexual dysfunction			Priapism Amenorrhoea Galactorrhoea Dysmenorrhoea Menorrhagia Erectile dysfunction Gynaecomastia Menstrual disorder Breast pain Breast discomfort
General disorders and administration site conditions		Injection site reaction			Sudden death Face oedema Oedema Hyperthermia Hypothermia Gait disturbance Injection site abscess
Investigations		Weight increased			Electrocardiogram QT prolonged Weight decreased

Electrocardiogram QT prolonged, ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia), torsade de pointes and sudden death have been reported with haloperidol.

Class effects of antipsychotics

Cardiac arrest has been reported with antipsychotics.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health, according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

4.9 Overdose

While overdose is less likely to occur with parenteral than with oral medication, the following details are based on oral haloperidol, also taking into account the extended duration of action of HALDOL Decanoate.

Symptoms and signs

The manifestations of haloperidol overdose are an exaggeration of the known pharmacological effects and adverse reactions. The most prominent symptoms are severe extrapyramidal reactions, hypotension and sedation. An extrapyramidal reaction is manifest by muscular rigidity and a generalised or localised tremor. Hypertension rather than hypotension is also possible.

In extreme cases, the patient would appear comatose with respiratory depression and hypotension that could be severe enough to produce a shock-like state. The risk of ventricular arrhythmias, possibly associated with QTc prolongation, must be considered.

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).

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

It is recommended that ECG and vital signs be monitored, and that monitoring continues until the ECG is normal. Treatment of severe arrhythmias with appropriate anti-arrhythmic measures is recommended.

Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma or concentrated albumin and vasopressor agents, such as dopamine or noradrenaline. Adrenaline must not be used because it might cause profound hypotension in the presence of haloperidol.

In cases of severe extrapyramidal reactions, it is recommended that an antiparkinson medicinal product be administered, and continued for several weeks. Antiparkinson medicinal products must be withdrawn very cautiously as extrapyramidal symptoms may emerge.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics; antipsychotics; butyrophenone derivatives, ATC code: N05AD01.

Mechanism of action

Haloperidol decanoate is an ester of haloperidol and decanoic acid, and as such, a depot antipsychotic 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 is a potent central dopamine type 2 receptor antagonist, and at recommended doses, has low alpha-1 antiadrenergic activity and no antihistaminergic or anticholinergic activity.

Pharmacodynamic effects

Haloperidol suppresses delusions and hallucinations as a direct consequence of blocking dopaminergic signalling in the mesolimbic pathway. The central dopamine blocking effect has activity on the basal ganglia (nigrostriatal bundles). Haloperidol causes efficient psychomotor sedation, which explains the favourable effect on mania and other agitation syndromes.

The activity on the basal ganglia probably underlies the undesirable extrapyramidal motor effects (dystonia, akathisia and parkinsonism).

The antidopaminergic effects of haloperidol on lactotropes in the anterior pituitary explain hyperprolactinaemia due to inhibition of dopamine-mediated tonic inhibition of prolactin secretion.

Clinical studies

In clinical studies, patients were mostly reported to have received prior treatment with orally administered haloperidol before converting to haloperidol decanoate. Occasionally, patients had previously been treated orally with another antipsychotic medicinal product.

5.2 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.

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.

Biotransformation

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

Elimination

The terminal elimination half-life of haloperidol 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 after oral administration and 21 hours after intramuscular administration.

Haloperidol apparent clearance after extravascular administration ranges from 0.9 to 1.5 l/h/kg and is reduced in poor metabolisers of CYP2D6. Reduced CYP2D6 enzyme activity may result in increased concentrations of haloperidol. The inter-subject variability (coefficient of variation, %) in haloperidol clearance was estimated to be 44% in a population pharmacokinetic analysis in patients with schizophrenia. After intravenous haloperidol administration, 21% of the dose was eliminated in the faeces and 33% in the urine. Less than 3% of the dose is excreted unchanged in the urine.

Linearity/non-linearity

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 dose. Results from small clinical studies suggest a lower clearance and a longer elimination half-life of haloperidol in elderly patients. The results are within the observed variability in haloperidol pharmacokinetics. Dose adjustment is recommended in elderly patients (see section 4.2).

Renal impairment

The influence of renal impairment on the pharmacokinetics of haloperidol has not been evaluated. About one-third of a haloperidol dose is excreted in urine, mostly as metabolites. Less than 3% of administered haloperidol is eliminated unchanged in the urine. Haloperidol metabolites are not considered to make a significant contribution to its activity, although for the reduced metabolite of haloperidol, back-conversion to haloperidol cannot be fully ruled out. Even though impairment of renal function is not expected to affect haloperidol elimination to a clinically relevant extent, caution is advised in patients with renal impairment, and especially those with severe impairment, due to the long half-life of haloperidol and its reduced metabolite, and the possibility of accumulation (see section 4.2).

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

Hepatic impairment

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

Pharmacokinetic/pharmacodynamics relationships

Therapeutic concentrations

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

In patients with first-episode schizophrenia 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. On average, concentrations in this range would be obtained with doses of 1 to 4 mg daily.

Due to the high inter-subject variability in haloperidol pharmacokinetics and the concentration-effect relationship, it is recommended to adjust the individual haloperidol 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. Measurement of haloperidol blood concentrations may be considered in individual cases.

Cardiovascular effects

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

Extrapyramidal symptoms

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

5.3 Preclinical safety data

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

In a carcinogenicity study of haloperidol, dose-dependent increases in pituitary gland adenomas and mammary gland carcinomas were seen in female mice. These tumours may be caused by prolonged dopamine D2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.

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, producing C_{max} plasma levels at least 7 to 14 times higher than the therapeutic plasma concentrations of 1 to 10 ng/ml that were effective in the majority of patients in clinical studies. These intravenous doses, which prolonged QTc, did not cause arrhythmias. In some animal studies, higher intravenous haloperidol doses of 1 mg/kg or greater caused QTc prolongation and/or ventricular arrhythmias at C_{max} plasma levels at least 38 to 137 times higher than the therapeutic plasma concentrations that were effective in the majority of patients in clinical studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol, sesame oil.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C.
Store in the original package to protect from light.
Keep out of the sight and reach of children.

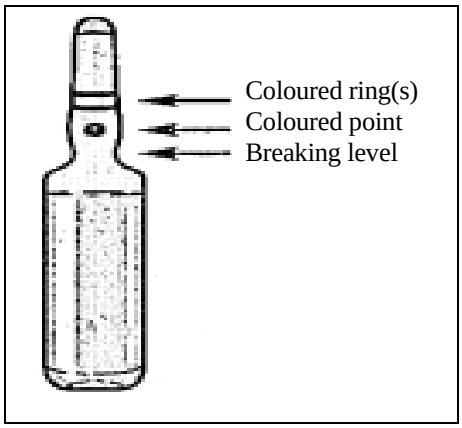
6.5 Nature and contents of container

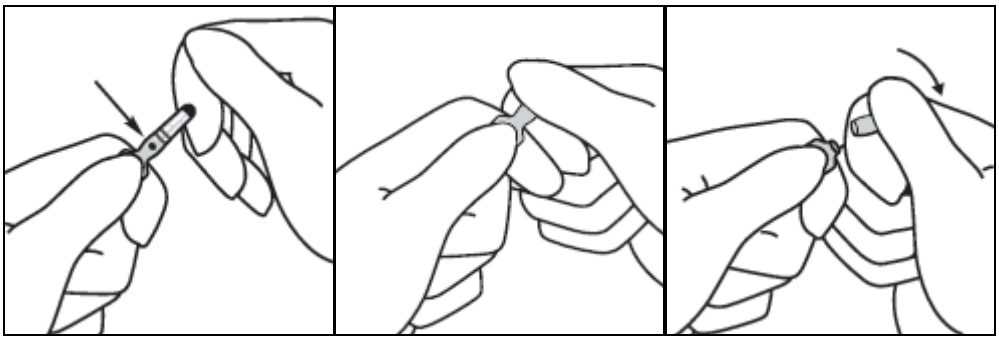
100 mg/ml solution:
1 ml of solution in an amber glass ampoule.

Packs of 5 ampoules.

6.6 Special precautions for disposal and other handling

- Before using the ampoule, roll it briefly between both hand palms to warm up the product.
- Hold the ampoule between the thumb and index finger, leaving the tip of the ampoule free.
- 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 parallel to the identification coloured rings.
- Keeping the thumb on the point, sharply break the tip of ampoule while holding firmly the other part of the ampoule in the hand.





Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. IMPORTER and REGISTRATION HOLDER

J-C Health Care Ltd., Kibbutz Shefayim, 6099000, Israel

8. MARKETING AUTHORISATION NUMBER(S)

032-5022745-01

9. DATE OF REVISION OF THE TEXT

Revised in February 2021 according to MOHs guidelines