janssen

Haldol® *decanoas*
haloperidol decanoate

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.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
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A resocializing effect has been observed in emotionally withdrawn patients.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 in the liver.

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.

CLINICAL PARTICULARS
Therapeutic indications
Haldol Decanoas is indicated for the maintenance treatment of chronic schizophrenia and other psychoses.

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 stabilized 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.

Maintenance therapy
The maintenance dosage of haloperidol decanoate must be individualized with titration upward or downward based on therapeutic response. The usual maintenance range is 10 to 15 times the previous daily dose in oral haloperidol equivalents dependent on the clinical response of the patients.

SPECIAL WARNINGS AND SPECIAL PERCAUTIONS FOR USE
Rare cases of sudden death have been reported in psychiatric patients receiving antipsychotic drugs, including Haldol Decanoas.
Since QT-prolongation has been observed during Haldol Decanoas treatment, it is advised to be cautious in patients with QT-prolonging conditions (QT-syndrome, hypokalaemia, electrolyte imbalance, drugs known to prolong QT, cardiovascular diseases, family history of QT prolongation, see section Interactions with Other Medicinal Products and Other Forms of Interaction).
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.
Since haloperidol is metabolized in the liver, caution is advised in patients with liver disease.
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).
Thyroxin may facilitate Haldol Decanoas toxicity. Therefore, it should only be used with great caution in patients with hyperthyroidism. Antipsychotic therapy in those patients must always be accompanied by an adequate thyreostatic treatment.
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.
If concomitant antiparkinson medication is required, it may have to be continued for at least a couple of weeks after the last Haldol Decanoas injection because of the very long half-life of Haldol Decanoas.
If a patients requires antipsychotic drug treatment after recovery from Neuroleptic Malignan Syndrome (NMS), the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since the recurrences of NMS have been reported.
Hyperpyrexia and heat stroke, have also been reported with HALDOL.
HALDOL DECANOAS should be administered cautiously to patients :
- With severe cardiovascular disorders, because of the possibility of transient hypotension and/or precipitation of anginal pain. Should hypotension occur and a vasopressor be required, epinephrine should not be used since HALDOL may block its vasopressor activity, and paradoxical further lowering of the blood pressure may occur. Instead, metaraminol, phenylephrine or norepinephrine should be used.
- Receiving anticoagulants, since an isolated instance of interference occured with the effects of one anticoagulant (Phenindione).

In patients with thyrotoxicosis who are also receiving antipsychotic medication, including haloperidol decanoate, severe neurotoxicity (rigidity, inability to walk or talk) may occur.
When HALDOL is used to control mania in bipolar disorder, there may be a rapid mood swing to depression.
The use of alcohol with this drug should be avoided due to possible additive effects and hypotension.
Due to the fact that elderly patients are more sensitive to neuroleptic effects, the dosage must be carefully determined.
Safety and effectiveness of haloperidol decanoate in children have been established.

UNDESIRABLE EFFECTS
Any adverse reactions following the administration of Haldol Decanoas are generally those of Haldol.
As with all injectable medications, local tissue reactions have been reported with Haldol Decanoas.

Cardiovascular effects
Tachycardia and hypotension have been reported in occasional patients. With haloperidol very rare reports of QT prolongation and/or ventricular arrhythmias, in addition to rare reports of sudden death, have been reported. They may occur more frequently with high doses and in predisposed patients.

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 should not be prescribed routinely.
In cases of muscle cramps by injecting a hypnosedative when switching from an existing neuroleptic treatment to HALDOL DECANOAS treatment, the antiparkinson medication can only be reduced or stopped if the HALDOL DECANOAS treatment has been stabilized.

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 rhythmical 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.

Tardive dystonia
Tardive dystonia, not associated with the above syndrome, have been reports. Tardive dystonia is characterized by delayed onset of choreic or dyctonic movements, is often persisten, and has the potential becoming irreversible.

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, 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.

Other CNS effects
These are occasionally reported and include: depression, sedation, agitation, drowsiness, insomnia, headache, confusion, vertigo, grand mal seizures, and apparent exacerbation of psychotic symptoms including hallucination and catatonic like behaviour states which may be responsive drug withdrawal and/or treatment with anticholinergic drugs.

Gastro-intestinal symptoms
Nausea, vomiting and loss of appetite have been reported. Weight changes may occur.

Endocrine effects
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.

Cardiovascular effects
Tachycardia, hypertension and hypotension have been reported in occasional patients. QT-interval prolongation, ECG pattern changes : compatible with the polymorphous configuration of torsade de pointes and/or ventricular arrhythmias have been reported very rarely.

Miscellaneous
There have been occasional reports of mild and usually transient decreases in blood cell counts. Agranulocytosis and thrombocytopenia have only rarely been reported, and then usually in association with other medication.
Isolated cases of liver function abnormalities or hepatitis, most often cholestatic, have been reported.
Hypersensitivity reactions such as skin rash, urticaria and anaphylaxis are exceptional.
Other side effects occasionally reported are: constipation, blurred vision, dry mouth, urinary retention, priapism, erectile dysfunction, peripheral oedema, excessive perspiration or salivation and body temperature disregulation.

Dermatologic reaction
Maculopapular and acneiform skin reactions and isolated cases of photosensitivity and loss of hair.

Respiratory effect
Laryngospasm, bronchospasm and increased depth of respiration.

Special sense
Cataracts, retinopathy and visual disturbances.

CONTRAINDICATIONS
Comatose state; CNS depression due to alcohol or other depressant drug; Parkinson's disease; known hypersensitivity to Haldol Decanoas; lesion of the basal ganglia.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
As with other antipsychotics, caution is advised when prescribing with medications known to prolong the QT interval.
Haloperidol is metabolized by several routes, including glucuronidation and the cytochrome P450 enzyme system. Inhibition of these route of metabolism by another drug may result in increased haloperidol concentrations and a risk 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. Increases in QTc have been observed when haloperidol was given in combination with the metabolic inhibitors ketoconazole (400 mg/day) or paroxetine (20 mg/day). It may be necessary to reduce the haloperidol dosage.
Sodium valproate, a drug known to inhibit glucuronidation, does not affect haloperidol plasma concentrations.
Caution is advised when used in combination with drugs known to cause electrolyte imbalance.
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 strong 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.
Haldol Decanoas inhibits the metabolization of tricyclic antidepressants, thereby increasing plasma levels of these drugs.
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.
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.
An encephalopatic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leucocytosis, elevated serum enzymes, BUN and FBS) followed by irreversible brain damage has occured in a few patients treated with lithium plus HALDOL. A causal relationship between these events and the concomitant administration of lithium and HALDOL has not been established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appears

Pregnancy and Lactation
Animal studies have demonstrated a teratogenic effect of haloperidol (see section Preclinical Safety Data).
Reversible extrapyramidal symptoms have been observed in neonates exposed to haloperidol in utero during the last trimester of pregnancy.
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.

Overdose
While overdosage is less likely to occur with parenteral than with oral medication, information pertaining to oral Haldol 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, sedation. An extrapyramidal reaction is manifest by muscular rigidity and a generalized or localized 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.

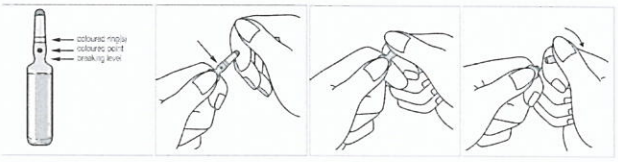
Treatment
Since there is no specific antidote, treatment is primarily supportive. For comatose patients, a patent airway should be established by use of an oropharyngeal airway or endotracheal tube. Respiratory depression may necessitate artificial respiration. Hypotension and circulatory collapse may 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.

Special Precautions For Storage
Store below 30°C.
Protect from light.
Keep out of reach of children.

Shelf Life
3 years

Instructions for use/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.



HOW SUPPLIED
Haldol Decanoas 50 mg/ml
Box @ 5 ampoule @ 1 ml Reg.No.: DKI1055202043A1

Haldol Decanoas 100 mg/ml
Box @ 5 ampoule @ 1 ml Reg.No.: DKI1055202043B1

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