1. NAME OF THE MEDICINAL PRODUCT

HALDOL 2mg/ml Drops® haloperidol

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

containing 2 mg haloperidol per ml. 1 ml=20 drops

For excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Oral drops, solution.

Appearance

Clear, colorless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Antipsychotic, psychomotor sedative. Additionally, in pediatrics , for short-term treatment of tics and vomiting (Gilles de la tourettes syndrome).

4.2 Phonology and Method of Administration

The dosages as suggested below are only averages, one should always try to tailor the dose to the patient's response. This often implies an upward titration in the acute phase, and a gradual reduction in the maintenance phase, in order to determine the minimal effective dose. Higher doses should only be given to patients responding poorly to lower dosages.

Adults

Moderate symptomatology: 0.5-2 mg, 2 or 3 times daily.
Severe symptomatology: 3-5 mg, 2 or 3 times daily.
Geriatric or debilitated patients: 0.5-2 mg, 2 or 3 times daily.
Chronic or resistant patients: 3-5 mg, 2 or 3 times daily.
Patients who remain severely disturbed or inadequately controlled may require dosage adjustment.
Daily dosages up to 100 mg may be necessary in some cases to achieve an optimal response.
Children 3-12 Years of Age (15-40 kg body weight)
The initial dosage is 0.5 mg/day. If required, dosage should be increased by an increment of 0.5 mg at 5- to 7-day intervals, until the desired therapeutic effect is achieved. The total dosage

may be administered in divided doses, 2-3 times daily.

Maintenance Dosage
After a satisfactory response has been achieved, dosage should then be gradually reduced to the lowest effective maintenance level.

Treatment withdrawal

Gradual withdrawal of haloperidol is advisable (see Warnings and Precautions – Additional considerations)

4.3 Contraindications

- Comatose states
- Central nervous system (CNS) depression due to alcohol or other depressant drug
- Parkinson's disease
- known hypersensitivity to haloperidol
- Lesion of the basal ganglia.

In common with other neuroleptics, haloperidol has the potential to cause rare prolongation of the QT interval. Use of haloperidol is therefore contra-indicated in patients with clinically significant cardiac disorders e.g. recent acute myocardial infarction, uncompensated heart failure, arrhythmias treated with class IA and III antiarrhythmic medicinal products, QTc interval prolongation, history of ventricular arrhythmia or torsades de pointes clinically significant bradycardia, second or third degree heart block and uncorrected hypokalaemia. Haloperidol should not be used concomitantly with other QT prolonging drugs (see section 4.5, Interactions)

4.4. Special Warnings and Special Precautions for Use

Increased Mortality in Elderly Patients with Dementia Related Psychosis

Rare cases of sudden death have been reported in psychiatric patients receiving antipsychotic drugs, including Haldol.

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.

The risk-benefit of haloperidol treatment should be fully assessed before treatment is commenced and patients with risk factors for ventricular arrhythmias such as cardiac disease, family history of sudden death and/or QT prolongation; uncorrected electrolyte disturbances, subarachnoid haemorrhage, starvation or alcohol abuse, should be monitored carefully (ECGs and potassium levels), particularly during the initial phase of treatment, to obtain steady plasma levels.

The risk of QT prolongation and/or ventricular arrhythmias may be increased with higher doses (see Sections 4.8 and 4.9) or with parenteral use, particularly intravenous administration. ECG monitoring should be performed for QT interval prolongation and for serious cardiac dysrhythmias if Haldol is administered intravenously.

Tachycardia and hypotension have also been reported in occasional patients.

Haloperidol should be used with caution in patients known to be slow metabolisers of CYP2D6, and during use of cytochrome P450 inhibitors. Concomitant use of antipsychotics should be avoided. (See Section 4.5)

Baseline ECG is recommended prior to treatment in all patients, especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination. During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual basis. Whilst on therapy, the dose should be reduced if QT is prolonged, and haloperidol should be discontinued if the QTc exceeds 500 ms.

Periodic electrolyte monitoring is recommended, especially for patients taking diuretics, or during intercurrent illness.

An approximately 3-fold increase risk of cerebrovascular adverse events have been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism

for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Haloperidol should be used with caution in patients with risk factors for stroke.

Neuroleptic malignant syndrome

In common with other antipsychotic drugs, Haldol has been associated with neuroleptic malignant syndrome: a rare idiosyncratic response characterized by hyperthermia, generalised muscle rigidity, autonomic instability, and 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 antipsychotics, 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 if its excretion is faster than that of Haldol 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.

Seizures/convulsions

It has been reported that seizures can be triggered by Haldol. 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 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 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 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 and preventive measures undertaken.

Additional considerations

In schizophrenia, the response to antipsychotic drug treatment may be delayed. Also, if drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months.

Acute withdrawal symptoms including nausea, vomiting and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Relapse may also occur and gradual withdrawal is advisable.

As with all antipsychotic agents, Haldol should not be used alone where depression is predominant. It may be combined with antidepressants to treat those conditions in which depression and psychosis coexist.

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

Concomitant use of haloperidol with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including torsade de pointes. Therefore concomitant use of these products is not recommended (see section 4.3-Contraindications).

Examples include certain antiarrhythmics, such as those of Class 1A (such as quinidine, disopyramide and

procainamide) and class III (such as amiodarone, sotalol and dofetilide), certain antimicrobials (sparfloxacin,

moxifloxacin, erythromycin IV), tricyclic antidepressants (such as amitriptyline), certain tetracyclic antidepressants (such as maprotiline), other neuroleptics (e.g. phenothiazines, pimozide and sertindole), certain antihistamines (such as terfenadine), cisapride, bretylium and certain antimalarials such as quinine and mefloquine. This list is not comprehensive.

Concurrent use of drugs causing electrolyte imbalance may increase the risk of ventricular arrhythmias and is not recommended (see section 4.4-Special Warnings and Precautions for Use). Diuretics, in particular those causing hypokalaemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred.

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 therapy, this results in a significant reduction of haloperidol plasma levels. Therefore, during combination treatment, the Haldol dose should be adjusted, when necessary. After stopping such drugs, it may be necessary to reduce the dosage of Haldol.

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

Effect of Haloperidol on Other Drugs

In common with all antipsychotics, Haldol 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 also been reported.

Haldol 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 may impair the antiparkinson effects of levodopa.

Haloperidol is an inhibitor of CYP 2D6. Haldol 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: 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, therapy should be stopped immediately if such symptoms occur.

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

The dosage of anticonvulsants may need to be increased to take account of the lowered seizure threshold.

4.6 Pregnancy and Breast-feeding

Pregnancy

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 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, mostly in combination with other drugs. Haldol should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Breast-feeding

Haldol is excreted in breast milk. If the use of Haldol 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 treated women.

4.7 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.

4.8 <u>Adverse Reactions</u>

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of haloperidol based on the comprehensive assessment of the available adverse event information. A causal relationship with haloperidol cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse

reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

Placebo-controlled double-blind data –adverse reactions reported at ≥1% incidence

The safety of HALDOL (2-20 mg/day) was evaluated in 566 subjects (of which 284 were treated with HALDOL, 282 were given placebo) who participated in 3 placebo-controlled, double-blind clinical trials, two in the treatment of schizophrenia and the third in the treatment of bipolar disorder.

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

Table 1. Adverse Reactions Reported by ≥1% of HALDOL-treated Subjects in 3 Double-Blind Parallel Placebo-Controlled Clinical Trials of HALDOL

System/Organ Class Adverse Reaction	**Haloperidol(n=284)** %	**Placebo (n=282)** %
Nervous System Disorders		
Extrapyramidal disorder	34.2	8.5
Hyperkinesia	10.2	2.5
Tremor	8.1	3.6
Hypertonia	7.4	0.7
Dystonia	6.3	0.4
Somnolence	5.3	1.1
Bradykinesia	4.2	0.4
Eye Disorders		
Visual disturbance	1.8	0.4
Gastrointestinal Disorders		
Constipation	4.2	1.8
Dry mouth	1.8	0.4
Salivary hypersecretion	1.2	0.7

Active comparator-controlled data –adverse eactions reported at ≥1% incidence

Sixteen double-blind active comparator-controlled trials were selected to determine the incidence of adverse reactions. In these 16 studies, 1295 subjects were treated with 1-45 mg/day HALDOL, in the treatment of schizophrenia.

Adverse reactions reported by ≥1% of HALDOL-treated subjects noted in the active-comparator controlled clinical trials are shown in Table 2.

Table 2. Adverse Reactions Reported by ≥1% of HALDOL-treated Subjects in 16 Double-Blind Active Comparator Clinical Trials of HALDOL

System/Organ Class Adverse Reaction	**Haloperidol (n=1295)** %
Nervous System Disorder	
Dizziness	4.8
Akathisia	2.9
Dyskinesia	2.5
Hypokinesia	2.2
Tardive dyskinesia	1.62
Eye Disorders	
Oculogyric crisis	1.24
Vascular Disorders	
Orthostatic hypotension	6.6
Hypotension	1.47
Reproductive system and breast Disorders	
Erectile dysfunction	1.0
Investigations	
Weight increased	7.8

Placebo- and active comparator-controlled Data –dverse reactions reported at <1%-incidence

Additional adverse reactions that occurred in <1% of HALDOL-treated subjects either of the above 2 clinical datasets are listed below in Table 3.

Table 3. Adverse Reactions Reported by <1% haloperidol-treated Subjects in Either the Placebo- or Comparator-controlled Clinical Trials.

Endocrine Disorders
Hyperprolactinaemia
Psychiatric Disorders
Libido decreased
Loss of libido
Restlessness
Nervous System Disorders
Motor dysfunction
Muscle contractions involuntary
Neuroleptic malignant syndrome
Nystagmus
Parkinsonism
Sedation
Eye Disorders
Vision blurred
Cardiac Disorders
Tachycardia
Musculoskeletal and Connective Tissue Disorders
Trismus
Torticollis
Muscle rigidity
Muscle Spasms
Musculoskeletal stiffness
Muscle Twitching
Reproductive System and Breast Disorders
Amenorrhoea
Breast discomfort
Breast pain
Galactorrhoea
Dysmenorrhoea
Sexual dysfunction
Menstrual disorder
Menorrhagia
General Disorders and Administration Site Conditions
Gait disturbance

Postmarketing data

Adverse events first identified as adverse reactions during postmarketing experience with haloperidol are included in Tables 4 .The postmarketing review was based on review of all cases where there was a use of the active moiety haloperidol (both Haloperidol and Haloperidol decanoate).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 4: Adverse 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
Investigations	
Very rare	Electrocardiogram QT prolonged, Weight decreased

Additional adverse events:

Nervous system disorders:

Common: Masked facies

Uncommon: Akinesia, Cogwheel rigidity

4.9 Overdose

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, 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

There is no specific antidote. Treatment is largely supportive. Activated charcoal may be administered. For comatose patients, a patent airway should be established by use of an oropharyngeal airway or endotracheal tube. Respiratory depression may necessitate artificial respiration.

ECG and vital signs should be monitored and monitoring should continue until the ECG is normal. Severe arrhythmias should be treated with appropriate anti-arrhythmic measures.

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

In cases of severe extrapyramidal reactions, antiparkinson medication (e.g. benztropine mesylate 1 to 2 mg IM or IV) should be administered parenterally.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: antipsychotics, ATC code: N05AD01

Mechanism of action

Haloperidol is an antipsychotic, belonging to the group of the butyrophenones. Haloperidol is a potent central dopamine receptor antagonist and, therefore, is classified among the very incisive antipsychotics. Haloperidol has no antihistaminergic or anticholinergic activity.

Pharmacodynamic effects

As a direct consequence of the central dopamine blocking effect, haloperidol has an incisive activity on delusions and hallucinations (probably due to an interaction in the mesocortical and limbic tissues) and an activity on the basal ganglia (nigrostriatal bundles). Haloperidol causes efficient psychomotor sedation, which explains the favourable effect on mania and other agitation syndromes (see "Indications").

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

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).

5.2 Pharmacokinetic Properties

Absorption

Following oral administration, the bioavailability of the drug is 60 to 70%. Peak plasma levels of haloperidol occur within two to six hours of oral dosing and about twenty minutes after intramuscular administration.

Distribution

Plasma protein binding is 92%. The volume of distribution at steady state (VDss) is large (7.9 ± 2.5 L/kg). Haloperidol crosses the blood-brain barrier easily.

Metabolism

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

Elimination

The mean plasma half-life (terminal elimination) is 24 hours (range 12 to 38 hours) after oral administration and 21 hours (range 13 to 36 hours) after intramuscular administration. Excretion occurs with the faeces (60%) and the urine (40%). About 1% of the ingested haloperidol is excreted unchanged with the urine.

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.

5.3 NON-CLINICAL INFORMATION

Nonclinical data reveal no special hazards for humans based on conventional studies of 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.

Non-clinical evaluations testing haloperidol revealed no clinically relevant toxic effects in rats or dogs following chronic toxicity studies up to 18 months in rats and 12 months in dogs. A no adverse effect level (NOAEL) of about 2 mg/kg/day day (~2x Maximum Recommended Oral Chronic Human Dose {MROCHD}) and a NOAEL / low adverse effect level (LOAEL) of about 0.65 to 2 mg/kg/day (~.65-2x MROCHD), has been determined for dogs and rats, respectively. Several in-vitro and in-vivo tests for mutagenesis of haloperidol showed no relevant information on any mutagenic effect. Short-term (6 to 12 month) alternative carcinogenicity studies in various mouse models have shown no carcinogenic potential. Long-term (18 to 24 month) carcinogenicity studies in rats, up to 50 mg/kg/day (diet) (~50x MROCHD) showed no increase in a tumor-generating potential, although in female mice increases in mammary tumors and pituitary gland adenomas, as well as overall increases in neoplasia were observed at the mid- (6.3 mg/kg/day - diet) (~6.3x MROCHD) and high-dose (25 mg/kg/day - diet) (~25x MROCHD) groups. Mammary tumors can be a consequence of increased prolactin concentrations in the blood. Numerous antipsychotics also cause hyperprolactinemia in humans. In rodents, haloperidol administration showed limited teratogenic effects (cleft palate at 5 mg/kg/day) (~5x MROCHD), changes in skeletal ossification (0.5 mg/kg/day) (~0.5x MROCHD), as well as embryo-toxicity (0.5 mg/kg/day) (~0.5x MROCHD). After administration of haloperidol, the fertility of female mice and rats was decreased, possibly due to the sedative effect of the compound.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactic acid, methyl parahydroxybenzoate, purified water.

6.2 Incompatibilities

None known.

6.3 Storage Conditions

Store below 30°C.

Do not freeze.

Keep out of the sight and reach of children

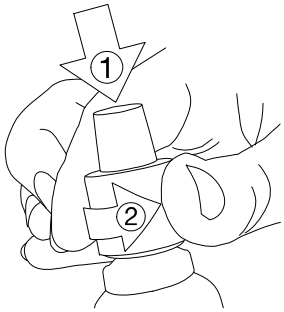
6.4 Nature and Contents of Container

- 15 ml LDPE dropper bottle (0.1 mg per drop)

6.5 Instructions for Use and Handling <and Disposal>

*Oral drops:***-15 ml LDPE dropper bottle**

Haldol is supplied in a 15 ml LDPE dropper bottle with a child-proof cap and is opened as follows: push the plastic screw cap down while turning it counter clockwise.
After removal of the screw cap, the required number of drops can be obtained by means of the drop counter, which is fitted on the bottle.



Manufacturer:

Janssen Pharmaceutica, Beerse, Belgium.

Registration Holder:

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