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אוגוסט 2013

רופא/ה נכבד/ה
רוקח/ת נכבד/ת

ברצוננו להביא לידיעתכם את העדכונים בעלון לרופא של התכשיר:
Haldol Ampoules

העלון לרופא מפורסם במאגר התרופות שבאתר משרד הבריאות.

כמו כן ניתן לקבלם מודפסים על ידי פניה אלינו לטלפון 09-9591111 .

להלן העדכונים.

בברכה,

ליליאנה בלטר
רוקחת ממונה

1. NAME OF THE MEDICINAL PRODUCT

~~Tradename~~

HALDOL AMPOULES® (haloperidol)

~~International Non-Proprietary Name (INN)~~

~~haloperidol~~

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains 5 mg haloperidol per ml.

For excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Solution for injection.

~~*5 mg/ml injectable solution*~~

Clear, colorless solution, free from visible foreign material containing 5mg haloperidol per ml.

For excipients, see List of Excipients.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Psychomotor agitation encountered in different neuropsychotic affections. Prophylaxis and therapy of acute and chronic vomiting.

4.2. Posology and Method of Administration

There is considerable variation from patient to patient in the amount of medication required for treatment. As with all antipsychotic drugs, dosage should be individualized according to the needs and response of the individual patient. When initiating treatment, consideration should be given to the following factors: age of the patient, severity of the disease, history of response to other antipsychotic drugs, concomitant medication or disease state.

Haldol Injection is reserved for prompt control of the acutely agitated patient with moderately severe to very severe symptoms.

Haldol Injection is recommended for IM administration only.

Haldol Injection should be substituted by Haldol Tablets as soon as feasible.

The usual dosage is 2-5 mg (0.4-1 ml of a Haldol ampoule) administered intramuscularly.

Depending on the response of the patient, subsequent doses may be given, administered as often as every hour, although 4- to 8-hour intervals may be satisfactory.

Acute and Chronic Vomiting:

5 mg administered IM.

Treatment withdrawal

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

4.3. Contraindications

Comatose state; CNS depression due to alcohol or other depressant drug; Parkinson's disease; known hypersensitivity to Haldol; 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.

Haldol Ampoules is not approved for treatment of patients with Dementia-related psychosis.

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 Haldol treatment, caution is advised in patients with QT-prolonging conditions (long QT-syndrome, hypokalaemia, electrolyte imbalance, drugs known to prolong QT, cardiovascular diseases, family history of QT prolongation), especially if Haldol is given parenterally (see Section 4.5). 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. Continuous ECG monitoring should be performed for QT interval prolongation and for serious cardiac dysrhythmias if Haldol is administered intravenously.

Haldol Injection is recommended for IM administration only.

Tachycardia and hypotension have also been reported in occasional patients.

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 ~~neuroleptics~~ 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 ~~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 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.

~~Caution is advised in patients with renal failure and phaeochromocytoma~~.

4.5. 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 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 ~~neuroleptics~~ 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.

4.6. Pregnancy ~~and Lactation~~ and Breast-feeding

~~Animal studies have demonstrated a teratogenic effect of haloperidol (see Section 5.3).~~

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. Animal studies have demonstrated a teratogenic effect of haloperidol (see Non-Clinical Information) 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 or other CNS depressants. Patients should be advised not to drive or operate machinery during treatment, until their susceptibility is known.

4.8. ~~Undesirable Effects~~ Adverse Reactions

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.

4.9. Clinical trial data

4.9.1. Placebo-controlled double-blind data – adverse ~~Drug~~ 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 ~~Drug~~ reactions (ADRs) reported by ≥1% of HALDOL-treated subjects in these trials are shown in Table 1.

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

System/Organ Class Adverse Reaction	**HALDOL (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

4.9.1. Active comparator-controlled data – adverse ~~Drug~~ reactions reported at ≥1% incidence

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

~~ADRs~~ 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 ~~Drug~~ Reactions Reported by ≥1% of HALDOL-treated Subjects in 16 Double-Blind Active Comparator Clinical Trials of HALDOL

System/Organ Class Adverse Reaction	**HALDOL** **(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

4.9.1. Placebo- and active comparator-controlled data – adverse ~~Drug~~ reactions reported at <1% incidence

Additional ~~ADRs~~ 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 ~~Drug~~ Reactions Reported by <1% of HALDOL-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 ~~ADRs~~ 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 HALDOL and HALDOL DECANOATE). In the table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000, including isolated reports

In Table 4, ~~ADRs~~ adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 4: 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
Reproductive System and Breast Disorders	
Very rare	Priapism, Gynaecomastia
Pregnancy, Puerperium and Perinatal Conditions	
Very rare	Drug withdrawal syndrome neonatal
General Disorders and Administration Site Conditions	
Very rare	Sudden Death, Face oedema, Oedema, Hypothermia, Hyperthermia
Investigations	
Very rare	Electrocardiogram QT prolonged, Weight decreased

4.10. Overdose

Symptoms

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. ~~but gastric lavage or induction of emesis is advised (unless the patients is obtunded, comatose or convulsing), followed by administration of activated charcoal~~.

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 ~~a neuroleptic~~ 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 ~~neuroleptics~~

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").

~~On the basis of its limbic activity, haloperidol exerts a neuroleptic sedative activity and has been shown to be useful as an adjuvant in the treatment of chronic pain.~~

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. ~~Preclinical Safety Data~~ NON-CLINICAL INFORMATION

Non-clinical 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.

~~*Pre*~~ 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

Water for injection.

6.2. Incompatibilities

None known.

6.3. Special Precautions for Storage

Store below 30°C.

Protect from light.

Keep out of the sight and reach of children.

6.4. Nature and Contents of Container

~~Injectable solution is supplied in~~ 1 ml amber colored glass ampoules Type I.

6.5. Instructions for Use and Handling

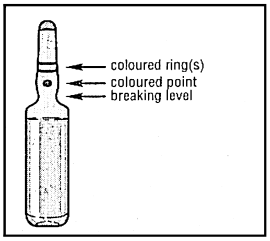
Solution for injection – ampoules

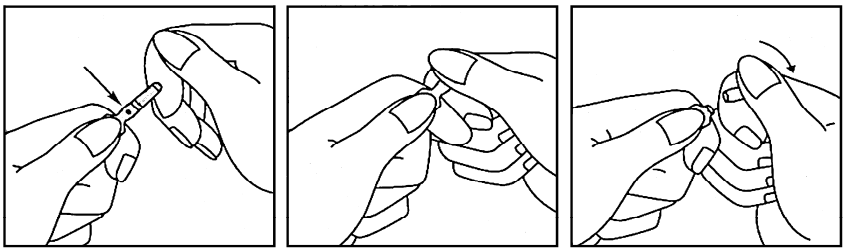
1. Hold the ampoule between the thumb and index finger, leaving the tip of the ampoule free.

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.





Manufacturer: GlaxoSmithkline Manufacturing S.p.A Torrile, Italy
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