WARNING
Increased Mortality in Elderly Patients with Dementia-Related Psychosis – 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 1.5 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. Haloperidol Injection, USP is not approved for the treatment of patients with dementia-related psychosis (see WARNINGS).

DESCRIPTION:
Haloperidol is the first of the butyrophenone series of major antipsychotics. The chemical designation is 4-[4-(p-chlorophenyl)-4-hydroxypiperidino]-4-fluorobutyrophenone and it has the following structural formula:

![Chemical Structure](image)

Haloperidol Injection is a sterile parenteral form for intramuscular injection. The injection provides 5 mg haloperidol (as the lactate) with 1.8 mg methylparaben and 0.2 mg propylparaben per mL, and lactic acid for pH adjustment between 3.0 to 3.8.

ACTIONS:
The precise mechanism of action has not been clearly established.

INDICATIONS:
Haloperidol Injection is indicated for use in the treatment of schizophrenia. Haloperidol Injection is indicated for the control of tics and vocal utterances of Tourette’s Disorder.

CONTRAINDICATIONS:
Haloperidol Injection is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson’s disease.

WARNINGS:
Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Haloperidol Injection is not approved for the treatment of patients with dementia-related psychosis (see BOXED WARNING).

Cardiovascular Effects
Cases of sudden death, QT-prolongation, and Torsade de Pointes have been reported in patients receiving Haloperidol Injection. Higher than recommended doses of any formulation and intravenous administration of Haloperidol Injection appear to be associated with a higher risk of QT-prolonging and Torsade de Pointes. Although cases have been reported in the absence of predisposing factors, particular caution is advised in treating patients with other QT-prolonging conditions (including electrolyte imbalance [particularly hypokalemia and hypomagnesemia], drugs known to prolong QT, underlying cardiac abnormalities, hypothyroidism, and familial long QT-syn-
fully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with haloperidol.

Usage in Pregnancy

Rodents given 2-20 times the usual maximum human dose of haloperidol by oral or parenteral routes showed an increase in incidences of maternal toxicity, reduced fertility, delayed delivery, and pup mortality. No teratogenic effect has been reported in rats, rabbits or dogs at dosages within this range, but cleft palate has been observed in mice given 15 times the usual maximum human dose. Cleft palate in mice appears to be a nonspecific response to exposure of fetal life as well as to a variety of drugs, and there is no evidence to relate this phenomenon to predictably specific effects of these agents.

There are no well controlled studies with haloperidol in pregnant women. There are reports, however, of cases of limb malformations observed following maternal use of haloperidol along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy. The relationships have not been established in these cases. Since such experience does not exclude the possibility of fetal damage due to haloperidol, this drug should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the fetus. Infants should not be breastfed by mothers treated with haloperidol.

Combined Use of Haloperidol and Lithium

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and other extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN, and FBS) followed by irreversible brain damage has occurred in a few patients treated with lithium plus haloperidol. A causal relationship between these events and the concomitant administration of lithium and haloperidol 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 appear.

General

A number of cases of bronchopneumonia, some fatal, have followed the use of antipsychotic drugs, including haloperidol. It has been postulated that lethargy and decreased sensation of thirst due to central inhibition may reduce compensatory bronchodilation, hemococoncentration and reduced pulmonary ventilation. Therefore, if the above signs and symptoms appear, especially in the elderly, the physician should institute supportive therapy promptly.

Although not reported with haloperidol, decreased serum cholesterol and/or cutaneous hyperpigmentation have been reported in patients receiving chemically-related drugs. Haloperidol may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be warned accordingly.

The use of haloperidol with this drug should be avoided due to possible additive effects and hypotension.

PRECAUTIONS:

Haloperidol 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, ephrinephrine should be administered. Low blood pressure may block its vasopressor action and paradoxical further lowering of the blood pressure may occur. Instead, metaraminol, phenyl- ephrine, or other similar agents should be administered.

— receiving anticonvulsant medications, with a history of seizures, or with EEG abnor- malities. The patient may be at risk for the convulsive threshold. If indicated, adequate anticonvulsant therapy should be continued.

— with known allergies, or with a history of aller- gic reactions to drugs.

— receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione).

If concomitant antiparkinson medication is required, it may have to be continued after haloperidol is administered because of the difference in excretion rates. If both are discontinued simultaneously, extrapyramidal symptoms may appear. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including antihistamines, are adminis- tered concomitantly with haloperidol.

As with other antipsychotic agents, it should be noted that haloperidol may be capable of potentiating the hypotensive effects of agents such as anesthetics, opiates, and alcohol.

In a study of 12 schizophrenic patients coad- ministered haloperidol and rifampin, plasma haloperidol levels were decreased by a mean of 70% and mean scores on the Brief Psychiat- ric Rating Scale were increased from baseline. In 5 other schizophrenic inpatients treated with haloperidol and rifampin, discontinuation of rifampin produced a mean 3.3-fold increase in haloperidol-tolerated plasma levels. Thus, careful monitoring of clinical status is warranted when rifampin is administered or discontinued in haloperidol-treated patients.

When haloperidol is used to control mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurolepticytosis (rigidity, inactivity of voluntary movement or talk) may occur in patients with thyrotoxicosis who are also receiving antipsychotic medication, including haloperidol.

No mutagenic potential of haloperidol was found in the Ames Salmonella microsomal acti- vation assay. However, some inconsistent posi- tive findings have been obtained in in vitro and in vivo studies of effects of haloperidol on chromosome structure and number. The available cytogenetic data considered too inconsistent to be conclusive at this time. Carcinogenicity studies using oral haloperi- dol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than 50% in both dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater incidence of tumors was seen in control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol-related increase in the incidence of neoplasia in rats at dosages below the usual daily human dose for chronic or resistant patients.

In female mice at 5 and 20 times the highest initial daily dose, and in male resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence, at doses equivalent to the usual daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no sta- tistically significant differences in incidences of total tumors or specific tumor types were noted. Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic admin- istration. Testosterone levels in rats indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a fac- tor of potential importance if the prescription of these drugs is continued in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. In patients treated with haloperidol, prolactin levels in mammary neoplasias has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic admin- istration of these drugs and mammary tumor- genesis; the evidence has not been considered too limited to be conclusive at this time.

There are no well-controlled studies with haloperidol along with other drugs. There are reports, however, of cases of limb malfor- mations observed following maternal use of haloperidol along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy. Causal relationships were not established in these cases. Since such experience does not exclude the possibility of fetal damage due to haloperidol, this drug should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the fetus. Infants should not be breastfed by mothers treated with haloperidol.

Pregnancy

Non-teratogenic Effects

Neonates exposed to antipsychotic drugs, particularly the third trimester of pregnancy, are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hyperpyrexia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity and in some cases symptoms have been self-limited, in other cases neonates have required inten- sive care unit support and prolonged hospitaliza- tion.

Haloperidol should be used during preg- nancy only if the potential benefit justifies the possible risk to the fetus.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of haloperidol did not include sufficient numbers of older subjects over 65 to determine whether they respond dif- ferentially from younger subjects. Other reported clinical experience has not consistently identi- fied differences in responses between the elderly and younger patients. However, the prevalence of tardive dyskinesia appears to be highest among the elderly, especially elderly women (see WARNINGS: Tardive Dyskinesia). Also, the pharmacokinetics of haloperidol in geriatric patients generally warrants the use of lower doses (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS:

Cardiovascular Effects

Tachycardia, hypotension, and hypertension have been reported. QT prolongation and/or ventricular arrhythmias have also been reported, in addition to ECG pattern changes compatible with the polymorphous configur- ation of torsade de pointes, and may occur more frequently with high doses and in pre- disposed patients (see WARNINGS and PRE- CAUTIONS).

Cases of sudden and unexpected death have been reported in association with antipsychotic administration of Haloperidol Injection. The nature of the evidence makes it impossible to determine definitively whether the haloperidol injection played in the outcome of the reported cases. The possibility that Haloperidol Injection may have contributed to such deaths cannot be excluded, but it is to be kept in mind that sud- den and unexpected death may occur in psy- chotic patients when they go untreated or when they are treated with other antipsychotic drugs.

CNS Effects

Extrapyramidal Symptoms (EPS)

EPS during the administration of haloperidol have been reported frequently during the first few days of treatment. EPS can be categorized generally as Parkinson-like sympt- omatology, akathisia, or dyskinesias (i.e., dystonias and oculogyric crises). While all can occur at relatively low doses, they occur more frequently and with greater severity at higher doses. The symptoms may be alleviated by dose reductions or administration of antiparkinson drugs such as benztpine mesylate USP or tetrabenazine hydrochloride USP. It should be noted that persistent EPS have been reported; the drug may have to be discontin- ued in such cases.

Dystonia

Ocular Effect: Symptoms of dystonia, pro- longed abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dys- tonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness

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of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Withdrawal Emergent Neurological Signs
Generally, patients receiving short-term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under “Tardive Dyskinesia” except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of haloperidol.

Tardive Dyskinesia
As with all antipsychotic agents haloperidol has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially reversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on long-term therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia. Antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop.

Tardive Dystonia
Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible.

Other CNS Effects
Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to a drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with haloperidol (see WARNINGS for further information concerning NMS).

Hematologic Effects: Reports have appeared citing the occurrence of mild and usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphocytosis. Agranulocytosis has rarely been reported to have occurred with the use of haloperidol, and then only in association with other medications.

Liver Effects: Impaired liver function and/or jaundice have been reported.

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

Endocrine Disorders: Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hypogonadism, hypoglycemia and hypothyroidism.

Gastrointestinal Effects: Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting.

Autonomic Reactions: Dry mouth, blurred vision, urinary retention, diaphoresis and priapism.

Respiratory Effects: Laryngospasm, bronchospass and increased depth of respiration.

Special Senses: Cataracts, retinopathy and visual disturbances.

Postmarketing Events
Hyperammonemia has been reported in a 5½ year old child with citrullinemia, an inherited disorder of ammonia excretion, following treatment with haloperidol.

OVERDOSE: Manifestations
In general, the symptoms of overdose would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) severe extrapyramidal reactions, 2) hypotension, or 3) sedation. The patient may appear comatose with respiratory depression and hypotension which could be severe enough to produce a shock-like state. The extrapyramidal reaction would be manifest by muscular weakness or rigidity and a generalized or localized tremor as demonstrated by the akinetic or agitans types respectively. With accidental overdose, hypotension rather than hypotension occurred in a two-year old child. The risk of ECG changes associated with torsade de points should be considered. (For further information regarding torsade de points, please refer to ADVERSE REACTIONS).

Treatment
Since there is no specific antidote, treatment is primarily supportive. A patent airway must be established by use of an oropharyngeal airway or endotracheal tube or, in prolonged cases of coma, by tracheostomy. Respiratory depression may be counteracted by artificial respiration and mechanical respirators. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. ECG and vital signs should be monitored especially for signs of QT prolongation or torsade de points. Since the ECG is normal. Severe arrhythmias should be treated with appropriate antiarrhythmic medications.

DOSE AND ADMINISTRATION:
There is considerable variation from patient to patient in the amount of medication required for treatment. As with all drugs used to treat schizophrenia, dosage should be individualized according to the needs and response of each patient. Dosage adjustments, either upward or downward, should be carried out as rapidly as practicable to achieve optimum therapeutic control.

To determine the initial dosage, consideration should be given to the patient’s age, severity of illness, previous response to other antipsychotic drugs, and any concomitant medication or disease state. Debilitated or geriatric patients, as well as those with a history of adverse reactions to antipsychotic drugs, may require less Haloperidol Injection. The optimal response in such patients is usually obtained with more gradual dosage adjustments to achieve low levels.

Parenteral medication, administered intramuscularly in doses of 2 to 5 mg, is utilized for prompt control of the acutely agitated schizophrenic patient with moderately severe to very severe symptoms. 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.

Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Switchover Procedure
An oral form should supplant the injectable as soon as practicable. In the absence of bioavailability studies establishing bioequivalence between these two dosage forms the following guidelines for dosage are suggested. For an initial approximation of the total daily dose required, the parenteral dose administered in the preceding 24 hours may be used. Since this dose is only an initial estimate, it is recommended that careful monitoring of clinical signs and symptoms, including clinical efficacy, sedation, and adverse effects, be carried out periodically for the first several days following the initiation of switchover. In this way, dosage adjustments, either upward or downward, can be quickly accomplished. Depending on the patient’s clinical status, the first oral dose should be given within 12 to 24 hours following the last parenteral dose.

HOW SUPPLIED:
Product
NDC
No.
No.
5AB

45850F

457401
53323-474-01
Haloperidol Injection, USP. 5 mg/mL, 2 mL
vial, packaged in trays of 25.

457410
53323-474-10
Haloperidol Injection, USP. 5 mg/mL, 10 mL
multiple dose vial, packaged individually.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature] Do not freeze.

PROTECT FROM LIGHT.
Vial stoppers do not contain natural rubber latex.