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 compared to placebo-treated patients. The increased mortality in placebo-treated patients was consistently greater than that in treatment groups. The findings of increased mortality in observational studies may be attributed to the antipsychotic treatment itself, to the use of antipsychotic drugs to treat symptoms of the disease for which they were not indicated, or to other characteristics of elderly patients with dementia. Studies have shown that the risk of death in elderly patients with dementia is increased by 1.3 to 1.4 times in those treated with antipsychotics compared to those not treated. 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 among patients taking antipsychotics 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 antipsychotics, treatment with conventional antipsychotics 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 is not approved for the treatment of patients with dementia-related psychosis (see WARNINGS).

Indications and Usage

Haloperidol Injection is indicated for the control of tics and vocal utterances of Tourette’s Disorder. Haloperidol Injection is a sterile, nonpyrogenic, water-soluble, and water-dispersible concentrate for intramuscular or intravenous injection. It is available as a sterile solution for injection containing 10 mg/mL of haloperidol. The solution is clear, colorless, and has a pH of 3.5 to 5.0.

Combined use of Haloperidol and Lithium

In patients with bipolar disorder, the coadministration of lithium and haloperidol has been associated with an increased risk of toxicity. Lithium is contraindicated in patients with a history of renal failure, hepatic failure, cardiopulmonary disease, or a history of seizures. Haloperidol appears to be associated with a higher risk of QT-prolongation and Torsades de Pointes. Although haloperidol injection is contraindicated in severe toxic or stressful situations, haloperidol may be used to treat acute agitation and extrapyramidal symptoms in patients with acute and severe psychiatric illness when other treatments are not feasible. The use of haloperidol injection should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

General

In patients with a history of bronchopneumonia, some fatal, have followed the use of antipsychotic drugs, including haloperidol injection. Agranulocytosis has also been reported in patients receiving chemically-related drugs. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their WBC monitored frequently during the first few months of therapy and discontinuation of haloperidol injection should be considered after the first sign of a clinically significant decrease in WBC in the absence of other causative factors. Patients with a history of leukopenia/neutropenia should be carefully monitored for signs of infection and treatment discontinued promptly if such signs or symptoms occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm3) should discontinue haloperidol injection and have their WBC followed closely.

Usage in Pregnancy

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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 indicating the occurrence of mild and usually transient leukopenia and leucocytopagia, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphocytomonychosis. Agranulo- 

cytosis has rarely been reported to have occurred with the use of haloperidol, and then only in association with other medication.

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

Dermatologic Reactions  
Tachyphylaxis and acniform skin reactions and isolated cases of photosensitivity and loss of hair.

Endocrine Disorders  
Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypothyroidism, hyperlipemia.

Gastrointestinal Effects  
Anorexia, constipation, diarreha, hypertransaminemia, nausea and vomiting.

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

Respiratory Effects  
Laryngospasm, bronchospasm and increased depth of respiration.

Special Senses  
Blurred vision, diplopia, asthenopia and visual disturbances.

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

OVERDOSAGE  
Parenteral Administration  
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) hypoten- 
sion, or 3) sedation. The patient would 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 dyskinesia, weakness or rigidity and a generalized or localized tremor as demonstrated by the akinetic or agitated 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 antitoxin, 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 respirations. Hypoten- 
sion 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 admin- istered. ECG and vital signs should be monitored especially for signs of Q1 prolongation or dysrhythmias and myocardial damage should continue until the ECG is normal. Severe arthrythmias should be treated with ap- propriate anti-arhythmic measures.

DOSEAGE 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, previ- ous 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. The optimal response in such patients is usually obtained with more gradual dosage adjustments and at lower dosage levels.

Carcinogenicity  
Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg 
per day) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high-dose male rats, there was no apparent increased incidence of tumors compared to controls. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasms and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antiparkinson effects of low and moderate doses of antipsychotic drugs. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro; a factor of potential importance if the prescription of these drugs is contemplated in a patient with a potential requirement for pregnancy. Although distantly related cancers, breast, prostate, cervix, ovary, lung, melano- 
masia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown. Studies on human breast cancers have been found in rodent models to differ in their clinical significance of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumori- 
genesis, the available evidence is considered too limited to be conclusive at this time.

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. 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 beneficial effect justifies a potential risk to the fetus. Infants should not be nursed during drug treatment.

Pediatric Use  
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use  
Clinical studies of haloperidol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other clinical experience has not consist- ently demonstrated increased sensitivity to antipsychotic drugs. Therefore, the recommended dosages and moni-
toring should continue until the ECG is normal. Severe arrhythmias should be treated with ap- proper anti-arhythmic measures.

Adverse Reactions  
Cardiovascular Effects  
Tachycardia, hypotension, and hypertension have been reported. QT prolongation and/or ventricular ar- rhythmias have been reported. In addition to ECG pattern changes compatible with the polymorphous variation of torsade de pointes, and may occur more frequently with high doses and in predisposed patients (see WARNINGS and PRECAUTIONS).

Cases of sudden and unexpected death have been reported in association with the administration of halo- peridol. The nature of the evidence makes it impossible to determine definitively what role, if any, haloperidol may have played in the outcome of the reported cases. The possibility that haloperidol caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic 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, often during the first few days of treatment. EPS can be categorized generally as Parkinson-like symptoms, akathisia, or dystonia (increased movement of the body or limbs). In male patients, dystonia is more frequently and with greater severity at higher doses. The symptoms may be controlled with dose reductions or administration of antiparkinson drugs such as benzztropine mesylate USP or trihexyphenidyl hydrochloride USP. It should be noted that persistent EPS have been reported: the drug may have to be discontinued in such cases.

Dystonia  
Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: squam of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and speech disorders. These symptoms may occur at relatively low doses, occur more frequently and with greater severity at higher doses. The symptoms may be controlled with dose reductions or administration of antiparkinson drugs such as benzztropine mesylate USP or trihexyphenidyl hydrochloride USP. It should be noted that persistent EPS have been reported: the drug may have to be discontinued in such cases.

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 dyskinesias when abruptly withdrawn. In certain of these cases the dyskinesic movements are in all probability due to the disease process.

Tardive Dyskinesia  
As with all antipsychotic agents haloperidol has been associated with persistent dyskinesias. Tardive dys- kinesia, a syndrome consisting of potentially irreversible, 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-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movement of the mouth or jaw (e.g., protrusion of tongue, puckering of lips, 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 allevi- ate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reintroduce 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 Dyskinesia  
Tardive dyskinesia, not associated with the above syndrome, has also been reported. Tardive dyskinesia 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, con- fusion, vertigo, ringing of the ears, neck stiffness, seizures, exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anti- 
cholinergic drugs.