

New Zealand Data Sheet

1. PRODUCT NAME

SERENACE

Haloperidol tablets - 0.5mg; 1.5mg; 5mg

Haloperidol liquid – 2mg/mL

Haloperidol injection – 5mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Serenace tablets contains 0.5mg, 1.5mg and 5mg haloperidol respectively.

Serenace liquid contains 2mg/mL haloperidol

Serenace injection contains 5mg/mL haloperidol

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

SERENACE 0.5mg tablet: (1/4" diameter), green, biconvex, scored, uncoated, plain on one side, each containing haloperidol BP 0.5mg.

SERENACE 1.5mg tablet: (9/32" diameter), white, biconvex, scored, uncoated, plain on one side, each containing haloperidol BP 1.5mg.

SERENACE 5mg tablet: (5/16" diameter), red, biconvex, scored, uncoated, plain on one side, each containing haloperidol BP 5mg.

Liquid

Clear, colourless liquid containing 2mg haloperidol BP per ml, in a bottle.

Injection Ampoule

1ml amber coloured ampoule containing 5mg haloperidol BP per ml.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Chronic Therapy

The management of manifestations of psychotic disorders such as schizophrenia, psychosis due to organic brain damage or mental deficiency, senile psychosis, the manic phase of manic depressive illness, Gilles de la Tourette syndrome.

Short Term Therapy

The treatment of acute alcoholism for the relief of delusions, hallucinations and confused states, and for the control of accompanying tremulousness and aggressive behaviour.

In the treatment of intractable nausea and vomiting associated with radiation or malignancy and not responding to other therapy.
Neuroleptanalgesia.

4.2 Dosage and method of administration

Higher doses and intravenous administration of haloperidol appear to be associated with a higher risk of QT prolongation and Torsades de Pointes (See PRECAUTIONS and ADVERSE REACTIONS).

Where rapid control of an acutely disturbed patient is required, or where heavier than usual dosages are envisaged, or when parenteral administration, particularly repeated parenteral administration is required, then the patient should be transferred as soon as possible to a situation where ECG monitoring, parenteral antiparkinson medication and resuscitative measures are available.

There is considerable variation from patient to patient in the amount of medication required for therapy. As with all antipsychotic agents, it is important to titrate the dose of SERENACE in accordance with the clinical effect and the severity of the disease. Monitoring of blood levels is not a routine procedure. Children and debilitated or geriatric patients may be more sensitive to SERENACE, and the starting dose, maximum dose and maintenance doses are, therefore, generally lower for these patients. In all age groups, titration of dosage should be as rapid as possible and when therapy is commenced with parenteral SERENACE, a change to oral

medication should be made as soon as possible. Sedation should not be used as a control parameter, nor should SERENACE be used to achieve sedation, since it may lead to gross overdose. Once a satisfactory clinical response has been achieved by the titration method, the daily doses should be reduced to the lowest effective level.

No pharmacokinetic data are available to enable special recommendations to be given for patients with renal or hepatic impairment. Also, no information on the effects of meals on medicine absorption is available.

Parenteral Administration

The solution should be inspected for discolouration or the presence of particulate matter prior to administration. Each SERENACE injection is a single dose used in only one patient, and any remaining contents should be discarded.

Agitation and aggressiveness associated with acute psychosis (e.g. mania, hypomania, acute schizophrenia, toxic confusional states including delirium tremens).

0.5-10mg IM or IV initially. The amount will depend on the patient's age, physical status, and severity of symptoms. The initial dose may be given as a slow IV injection or as a bolus. Depending on the response of the patient, subsequent doses may be given as often as half hourly for IV injections or hourly for IM injections. In exceptional circumstances, a maximum daily dose of 30mg may be required. Doses above 10mg have not shown increased efficacy, but may be associated with increased adverse drug reactions.

This treatment approach is not without risk and high doses of antipsychotic agents should only be administered to the physically healthy adult.

Appropriate precautions should be taken in patients with a history or evidence of such conditions as cardiovascular disorders or epilepsy.

Parenteral total daily maintenance dose

Once continuous therapeutic control is achieved, there is a need to determine maintenance dosage. As pharmacokinetic studies to date have not addressed this problem, it is necessary to make an estimate, assuming that plasma levels are to be maintained, that the plasma half-life of haloperidol is approximately 24 hours, and that the initial control is attained within 24 hours. The maintenance dose may be calculated as half the total daily dose used to achieve control. This dose can then be given in divided doses morning and evening. To avoid excessive plasma levels, giving of the first maintenance dose should be delayed if possible until 4-8 hours after the last controlling dose.

Oral total daily maintenance dose

May be calculated in the same manner if transferring directly from parenteral controlling dose. A transfer from parenteral maintenance dose to oral maintenance dose would use the same daily dose.

Oral Administration

Adults

Moderate symptomatology

0.5-5mg (0.25 – 2.5mL) per day.

Severe symptomatology

5-15mg (2.5 – 7.5mL) per day. Daily oral dosages should be titrated against patient response and may be increased up to a maximum daily dose of 30mg (15mL) in exceptional circumstances. Doses above 10mg (5mL) have not shown increased efficacy, but may be associated with increase adverse drug reactions . Once a satisfactory clinical response has been achieved by the titration method, the daily doses should be reduced to the lowest effect level.

Geriatric or Debilitated Patients

0.5-3mg (0.25 – 1.5mL) per day is usually sufficient.

Children

For severely aggressive or hostile children or for the rare Gilles de la Tourette Syndrome, the initial dose should be 0.5-3mg (0.25 – 1.5mL) per day and SERENACE liquid is recommended. Maintenance dose is usually 0.05mg (0.025mL)/kg body weight.

4.3 Contraindications

- Comatose states;
- In the presence of central nervous system depression due to alcohol and other depressant agents;
- Severe depressive states;
- Previous spastic diseases;
- Senile patients with pre-existing parkinsonian symptoms;

- Parkinson's disease;
- Known hypersensitivity to haloperidol or other ingredients in the dosage form (see Excipients);
- In patients with manifest occult lesions of the basal ganglia;
- In patients with prolactin dependent tumours;

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 Interactions)

4.4 Special warnings and precautions for use

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal syndrome known as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic agents. Clinical manifestations of this syndrome are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated creatine phosphokinase (CPK), myoglobinuria and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated.

The management of NMS should include immediate discontinuation of antipsychotic agents, intensive symptomatic treatment and monitoring, and treatment of any serious medical problems for which specific treatments are available. Dantrolene and bromocriptine have been used for the treatment of NMS. The reintroduction of antipsychotic therapy after recovery from NMS should be carefully considered since recurrences of NMS have been reported. Haloperidol should be used cautiously in patients exposed to high temperatures. Hyperpyrexia and heat stroke have been reported to be associated with haloperidol, not associated with other manifestations of NMS (see Adverse Effects).

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary dyskinetic movements may develop in patients treated with antipsychotic agents (see Adverse Effects). Although the dyskinetic syndrome may remit partially or completely if the medication is withdrawn, it is irreversible in some patients. The prevalence of this syndrome appears to be highest among the elderly, particularly elderly women.

At the present time, it is uncertain whether neuroleptic agents differ in their potential to cause tardive dyskinesia. Since there is a significant prevalence of this syndrome associated with the use of neuroleptic agents, and since there is no known effective treatment, chronic use of these agents should generally be restricted to patients for whom there is no alternative therapy available with better risk acceptability. The risk of developing irreversible tardive dyskinesias increases the duration of treatment and total cumulative doses, although in some instances, tardive dyskinesia may develop after relatively short periods of treatment at low doses.

The risk of developing tardive dyskinesia may therefore be minimised by reducing the dose of the neuroleptic agent used and its duration of administration, consistent with the effective management of the patient's condition. There is no known effective treatment. If manifestations of tardive dyskinesia are noted, the neuroleptic agent should be discontinued.

Cardiovascular effects

Higher doses and intravenous administration of haloperidol appear to be associated with a higher risk of QT prolongation and Torsades de Pointes. Rare cases of sudden death have been reported even in the absence of predisposing factors. (see Contraindications)

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, or risk factors for QT prolongation, such as hypothyroidism, should be monitored carefully (ECGs and potassium levels), particularly during the initial phase of treatment.

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 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.

Cerebrovascular Adverse Events (CVAE), including Stroke, in Elderly Patients with Dementia

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 in caution in patients with risk factors for stroke.

Safety Experience in Elderly Patients with Dementia-related Psychosis:

Observational studies suggest that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Risk factors that may predispose this patient population to increased risk of death when treated with antipsychotics include age >80 years, sedation, concomitant use of benzodiazepines, or presence of pulmonary conditions (e.g. pneumonia, with or without aspiration).

Active Alcoholism

CNS depression may be potentiated and risk of stroke may be increased. Increased hypotensive effects and the potential for alcohol intoxication may also occur.

Severe Cardiovascular Diseases

Haloperidol in therapeutic doses does not usually affect blood pressure significantly but care should be exercised in patients with severe cardiovascular disorders or being treated with antihypertensive agents because of the possibility of unexpected hypotension, and/or precipitation of angina. Severe or prolonged hypotension may require vasopressors. Adrenaline should not be used since haloperidol may block its vasopressor

activity and cause further decrease in blood pressure. Therefore, noradrenaline or metaraminol should be used instead.

Anginal pain may be provoked in patients with ischaemic heart disease. Caution should be observed in patients with arteriosclerosis who may have occult lesions of the basal ganglia (see **Contraindications**).

Epilepsy

Haloperidol may be given to epileptics but adequate anticonvulsant therapy should be maintained as haloperidol may decrease the seizure threshold. It has been reported that haloperidol can trigger seizures in known epileptics that were previously controlled. Caution is therefore advised in patients receiving anticonvulsants, with a history of seizures, or with EEG abnormalities and in conditions predisposing to convulsions (e.g. alcohol withdrawal and brain damage).

Glaucoma

Glaucoma or a predisposition to glaucoma may be triggered because of the secondary anticholinergic effects of haloperidol.

Hepatic Function

Impairment of hepatic function may alter metabolism of haloperidol.

Hyperthyroidism or Thyrotoxicosis

Severe neurotoxicity such as rigidity and inability to walk or talk may result when these patients are treated with antipsychotics. Thyrotoxic patients may be more prone to develop extrapyramidal symptoms. Antipsychotic treatment in these patients should always be accompanied by appropriate monitoring and therapy.

Endocrine System Concerns

Thyroxin may facilitate haloperidol 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.

Hyperprolactinaemia

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 haloperidol and preventive measures undertaken.

Pulmonary Insufficiency

A number of cases of bronchopneumonia, sometimes fatal, have been reported following the use of antipsychotic agents. Haloperidol should be used with caution in patients with pulmonary insufficiency such as asthma, emphysema or acute pulmonary infections. Haloperidol may cause potentiation of breathing impairment and may possibly lead to 'silent pneumonia'.

Renal Function Impairment

Renal function impairment is mostly a concern at higher dosage since renal clearance of unchanged medicine is relatively low.

Urinary Retention

Urinary retention may be potentiated due to secondary anticholinergic effects.

Elderly or Debilitated Patients

Elderly or debilitated patients receiving haloperidol should be observed for evidence of over-sedation which, unless alleviated, could result in complications such as terminal stasis pneumonia.

Bipolar Mood Disorders

When haloperidol is used to control mania in cyclic disorders, a rapid mood swing to depression may occur. As with all antipsychotic agents, haloperidol 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. However, it should be noted that haloperidol may impair the metabolism of tricyclic antidepressants (see **Interactions**).

Suicide

The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high-risk patients should accompany therapy.

Dental

Patients should be instructed in proper oral hygiene, including caution in use of regular toothbrushes, dental floss and toothpicks as the leukopenic and thrombocytopenic effects of haloperidol may result in an increased incidence of microbial infection, delayed healing and gingival bleeding. If leukopenia or thrombocytopenia occurs, dental work should be deferred until blood counts have returned to normal. The peripheral anticholinergic effects of haloperidol may decrease or inhibit salivary flow, especially in middle-aged or elderly patients, thus contributing to the development of caries, periodontal disease, oral candidiasis and discomfort.

Other Precautions

It should be borne in mind that the antiemetic action of haloperidol may relieve

nausea and vomiting, and so obscure the diagnosis of an underlying organic disorder which was causing these symptoms.

Ocular or cutaneous changes and decreases in serum cholesterol have occurred following administration of a butyrophenone structurally related to haloperidol. In the same study which reported these changes, haloperidol was shown to be free of these side effects; however, it is advisable to carefully observe patients who receive haloperidol for a prolonged period in order to identify any changes in the skin or eyes.

Haloperidol should be used with caution in patients with known allergies or with a history of allergic reactions to medicines.

Caution is advised in patients 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 discontinued, because of the different excretion rates. Extrapyramidal symptoms may occur if both haloperidol and the antiparkinson agent are discontinued simultaneously. The physician should keep in mind the possible anticholinergic effects associated with antiparkinson agents.

Caution is advised in patients with phaeochromocytoma.

In schizophrenia, the response to antipsychotic agent treatment may be delayed. If medicines are withdrawn, recurrence of symptoms may not become apparent for several weeks or months. With parenteral haloperidol in the acute situation, the use of a prophylactic anticholinergic agent (e.g. benztropine) is recommended to cover the period of parenteral administration and for several days afterwards.

There is considerable variation from patient to patient in the amount of medication required for therapy. Close observation is required during dosage titration in order to minimise the risk of overdose or emergence of psychotic manifestations prior to the next dose. This is particularly important in patients with impaired liver or renal function.

Carcinogenicity and Mutagenicity

There was no evidence of carcinogenicity in Wistar rats following oral administration of haloperidol for 24 months at doses up to 5mg/kg/day (about five folds the maximum recommended human dose based on body surface area). In female mice, there was a statistically significant increase in mammary gland neoplasia and total tumour incidence following oral administration of haloperidol at doses of 1.25 and 5mg/kg/day (less than, and about twice, the maximum recommended human dose based on body surface area), and a statistically significant increase in pituitary gland neoplasia at 5mg/kg/day. In male mice, there were no carcinogenic effects. Haloperidol increases prolactin levels, which may affect human breast cancers, one-third of which are prolactin dependent *in vitro*. Although clinical studies have not shown a clear association between chronic administration of antipsychotic agents (including haloperidol) and an increase in the incidence of breast cancers, it may be a factor of importance when prescribing haloperidol for patients in which breast cancer was previously detected.

Use in Paediatrics

As the safety and effectiveness of haloperidol has not been generally established in children, the medicine is not recommended for use in the paediatric age group except in severely aggressive and hostile children or for the treatment of the rare Gilles de la Tourette syndrome. Haloperidol should not be used in children under 3 years of age. Children are highly susceptible to the extrapyramidal side effects of haloperidol, especially dystonias.

Use in the Elderly

Elderly patients tend to develop higher plasma concentrations of haloperidol because of changes in distribution due to decreases in lean body mass, total body water, and albumin, and often an increase in total body fat composition. These patients usually require lower initial dosage and a more gradual titration of dose (see **Dosage and Administration**). Elderly patients exhibit an increased sensitivity to the anticholinergic, sedative and extrapyramidal side effects of haloperidol. Careful observation during haloperidol therapy for early signs of tardive dyskinesia and reduction of dosage or discontinuation of medication may prevent a more severe manifestation of the syndrome.

4.5 Interaction with other medicines and other forms of interaction***Pharmacokinetic Interactions***

There is evidence to suggest that haloperidol is a substrate of CYP3A4 and CYP2D6, and inhibitor, as well as a stimulator of CYP2D6. Studies also suggested that reduced haloperidol, one of the metabolites of haloperidol, is a substrate of CYP3A4 and an inhibitor of CYP2D6. Involvement of these isoforms in the biotransformation of haloperidol may explain some of the medicine interactions observed.

Haloperidol inhibits the metabolism of tricyclic antidepressants, increasing the blood levels of these medicines. This may result in increased tricyclic antidepressant toxicity as well as increased anticholinergic effects. It is thought that inhibition of CYP2D6 by haloperidol or reduced haloperidol is responsible for this inhibitory effect. On the other hand, it is not known whether the metabolism of haloperidol is affected when tricyclic antidepressants is co-administered.

In pharmacokinetic studies, mild to moderately increased haloperidol levels have been reported when haloperidol was given concomitantly with quinidine, buspirone or fluoxetine. It may be necessary to reduce the dosage of haloperidol when any of these medicines are used concomitantly with haloperidol. The exact mechanism responsible for the interactions is not known but may be secondary to inhibition of CYP2D6 by quinidine, competition with CYP3A4 by buspirone and inhibition of CYP2D6 and CYP3A4 by fluoxetine. It is not known whether haloperidol affects the levels of quinidine or buspirone whereas fluoxetine levels appear to be unaffected when used concomitantly with haloperidol. Antidepressants such as fluvoxamine, nefazodone, paroxetine and venlafaxine may increase haloperidol concentrations by possibly inhibiting CYP2D6 mediated metabolism of haloperidol similarly to that seen with fluoxetine.

Due to competitive inhibition of CYP2D6-mediated haloperidol metabolism and increased dopamine₂ blockade, co-administration of haloperidol and olanzapine may result in an increased risk of Parkinsonism.

A significant fall in haloperidol plasma levels occurs when prolonged treatment with enzyme inducing agents such as carbamazepine, phenobarbitone, phenytoin or rifampicin is added to haloperidol therapy. This is thought to be the result of the ability of these agents to induce CYP3A4, thereby accelerating the metabolism of haloperidol; serum concentrations of haloperidol may be significantly reduced. Therefore, during therapy with this combination, the dosage of haloperidol may need to be increased. Conversely, after stopping therapy with such agents, it may be necessary to reduce the dosage of haloperidol. Haloperidol does not appear to influence the pharmacokinetics of carbamazepine and phenobarbitone. Whether or not haloperidol affects the plasma level of rifampicin is at present unclear.

The clearance of haloperidol is greater in tobacco smokers as compared with non-smokers, and serum concentrations of haloperidol are lower in smoking patients. It is suggested that plasma concentrations of haloperidol be monitored in patients who either start or stop smoking.

Pharmacodynamic Interactions

Haloperidol may block the vasopressor activity of adrenaline and related sympathomimetic agents, and cause a paradoxical further lowering of blood pressure in hypotensive patients. Haloperidol may also reverse the blood pressure lowering effects of adrenergic blocking agents such as guanethidine. Concomitant use of propranolol and haloperidol therapy has been reported to result in hypotension and cardiopulmonary arrest. This is due to alpha- receptor binding and intrinsic relaxant effects on peripheral blood vessels by haloperidol and relaxant effects on peripheral vessels by propranolol.

Medicines known to prolong the QT interval and/or to be associated with torsades de pointes, such as quinidine, disopyramide, amiodarone, tricyclic antidepressants, terfenadine, and certain quinolone antibiotics may affect haloperidol therapy (see Contraindications & Warnings and Precautions - Cardiovascular effects). Concurrent use of haloperidol with antiarrhythmic agents may result in additive cardiac effects (see Contraindications & Warnings and Precautions - Cardiovascular effects).

Use of drugs that cause electrolyte imbalance may increase the risk of ventricular arrhythmias during concomitant use of haloperidol (see Warnings and Precautions - Cardiovascular effects)

High doses of haloperidol may potentiate the action of methyl dopa. This combination has reportedly resulted in dementia and enhanced CNS effects (e.g. disorientation, memory loss, slowed or difficult thought, aggression, irritability, and mental retardation) in several patients.

Haloperidol blocks dopamine receptors. Haloperidol may therefore interfere with the anti-Parkinsonian effects of levodopa. Cabergoline, a long-acting dopamine-2 receptor agonist, should not be used concurrently with haloperidol, a dopamine-2 antagonist, due to the antagonistic pharmacologic effects and therefore, decreased

therapeutic effect of both agents.

Parkinsonian syndrome has been reported with concomitant use of tacrine and haloperidol due to increased acetylcholine activity in the striatal region of the brain. Alcohol may potentiate the sedative effect of haloperidol thereby impairing the ability of patients to perform activities requiring mental alertness. Concurrent use of alcohol and haloperidol may cause hypotension and increase alcohol intoxication (see **Warnings and Precautions**).

Haloperidol will potentiate the action of other central nervous system depressants (e.g. anaesthetics, opiates, barbiturates and alcohol).

The combination of lithium with an antipsychotic agent such as haloperidol, has occasionally produced an acute encephalopathic syndrome characterised by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leucocytosis, elevated serum enzymes and serum urea and followed by irreversible brain damage. Although a causal relationship has not been established, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity, and treatment discontinued should such signs appear.

Dextromethorphan is metabolised by CYP2D6. Concomitant use of dextromethorphan and haloperidol, an inhibitor of this isoenzyme, may result in elevated concentrations of dextromethorphan and increased adverse effects (CNS excitement, mental confusion, respiratory depression, nervousness, tremors, insomnia, and diarrhoea). A reduction of dextromethorphan doses may reduce or resolve adverse effects.

Haloperidol has been reported to antagonise the anticoagulant activity of phenindione and coumarin anticoagulants.

Increases in intraocular pressure may occur in patients receiving anticholinergic agents, including anti-Parkinsonian agents, concurrently with haloperidol.

Concurrent use of amphetamines and haloperidol may decrease both the stimulant effects of amphetamines as well as the antipsychotic effects of haloperidol.

The anticholinergic effects of other agents may be intensified when used concurrently with haloperidol e.g. anticholinergic agents, antihistamines, tricyclic antidepressants, MAO inhibitors and antidyskinetic agents.

4.6 Fertility, pregnancy and lactation

Impairment of Fertility

The animal data falls into three broad areas: female fertility, male fertility and effects in offspring.

There are no human data on the effects of haloperidol on male or female fertility. In female rats, administration of haloperidol induced oestrus cycle disruptions. In female mice, delays in the implantation, cleavages, and blastocoele formation followed subcutaneous administration of haloperidol prior to ovulation. In male rats, oral administration of haloperidol prior to mating

reduced fertility, increased pre-implantation loss, and induced histopathological changes in the reproductive organs. Following intraperitoneal administration of haloperidol to female rats from early pregnancy to weaning, the frequency of ejaculation in offspring was reduced.

Various dose levels were used in the above animal studies and in some studies a no effect level was not established. The relationship between the effects at the given dose levels in mice and rats and potential toxicity in humans is unknown.

Pregnancy

Category C definition: Medicines which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

When given in high doses during late pregnancy, butyrophenones may cause prolonged neurological disturbances in the newborn infant. In pregnant mice, rats and hamsters, administration of haloperidol during the period of organogenesis has produced a range of adverse effects, including embryoletality, gross malformations such as cleft palate and neuronal tube defects, and reduced brain and body weight and behavioural effects in offspring. The significance of these findings for human exposure to therapeutic doses of haloperidol is unknown. Haloperidol should be used during pregnancy only if the anticipated benefit outweighs the risk. The administered dose and duration of treatment should be as low, and as short, as possible.

Lactation

Haloperidol is distributed into breast milk. Safe use of haloperidol by nursing mothers has not been established; therefore, its use is not recommended. The frequency of ejaculation in offspring was reduced following intraperitoneal administration of haloperidol to female rats from early pregnancy to weaning (see **Impairment of Fertility**).

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

In the low dosage range (1-2mg daily), adverse effects from haloperidol have been infrequent, mild and transitory. In patients receiving higher doses, some adverse effects are seen more frequently. Neurological effects are the most common.

Central Nervous System Effects Common (≥1% and <10%) Extrapyramidal reactions

- Akathisia
- Dystonia
- Parkinsonian effects

Uncommon (≥0.1% and <1%)

- Hallucinations

- Unusual tiredness or weakness
- Persistent tardive dyskinesia

Rare ($\geq 0.01\%$ and $< 0.1\%$)

- Neuroleptic Malignant Syndrome (NMS)
- Tardive dystonia

Akathisia may appear within the first 6 hours after dose; often indistinguishable from psychotic agitation. Akathisia is best managed by a reduction in dosage in conjunction with the temporary use of an oral antiparkinson agent.

Dystonias appear most often in children and young adults and early in treatment; may subside within 24 to 48 hours after discontinuation of haloperidol. Dystonias, which can produce laryngeal spasm or bronchospasm may be controlled by intravenous or intramuscular administration of benztropine mesylate (1-2mg IM or IV) or biperiden (2-10mg IM or IV), or intravenous diazepam (10mg IV). A pseudo Parkinson rigidity syndrome may occur later during the course of treatment and may respond to antiparkinson agents.

Parkinsonian effects are characterised by difficulty in speaking or swallowing; loss of balance control; mask-like face; shuffling gait; stiffness of arms or legs; trembling and shaking of hands and fingers. *Parkinsonian effects* are more frequent in the elderly; symptoms may be seen in the first few days of treatment or after prolonged treatment, and can recur after even a single dose. They sometimes remit spontaneously as treatment continues, or can be relieved by a reduction in dose or the temporary use of antiparkinson medication.

It has been reported that some extrapyramidal reactions may persist even after a reduction in dosage and/or treatment with antiparkinson agents. In such cases, the medicine should be discontinued.

Tardive dyskinesia (lip smacking or puckering; puffing of cheeks; rapid or worm-like movements of tongue; uncontrolled chewing movements; uncontrolled movements of the arms and legs) is more frequent in elderly patients, women, and patients with brain damage. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of the medicine increases. Less commonly, the syndrome can develop after relatively brief treatment periods at low doses. It may persist after discontinuation of haloperidol.

The syndrome may become clinically recognisable either during treatment, upon dosage reduction, or upon withdrawal of treatment. The dosage of antipsychotic agent should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder, since the syndrome may be masked by a higher dose. In patients requiring long-term treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be prescribed. The need for continued treatment should be reassessed periodically.

There is no known effective treatment for tardive dyskinesia. Antiparkinson agents usually do not alleviate the symptoms. It is suggested that antipsychotic agents be discontinued if symptoms of tardive dyskinesia appear.

Neuroleptic Malignant Syndrome (NMS) characterised by difficult or unusually fast breathing; fast heartbeat or irregular pulse; high fever; high or low blood pressure; increased sweating; loss of bladder control; severe muscle stiffness; seizures; unusual tiredness or weakness; unusually pale skin. Additional signs may include elevated creatinine phosphokinase, rhabdomyolysis and acute renal failure. May occur at any time during neuroleptic therapy, but is most commonly seen after start of therapy, or after patient has switched from one neuroleptic to another, during combination therapy with other psychotropic medication, or after a dosage increase.

The management of neuroleptic malignant syndrome should include immediate discontinuation of antipsychotic agents, intensive monitoring and treatment of symptoms, and treatment of any associated medical problems (e.g. pneumonia, systemic infection).

Tardive dystonia increased blinking or spasm of eyelid; unusual facial expressions or body positions; uncontrolled twisting movements of neck, trunk, arms, or legs.

Other Central Nervous System Effects

Drowsiness, depression, anxiety, euphoria, lethargy, agitation, insomnia, headache, confusion, sedation, anorexia, vertigo, restlessness, apprehension, grand mal seizures. Toxic psychosis may occur with overdose.

Cardiovascular Effects -(See Contraindications & Warnings and Precautions - Cardiovascular effects)

- Orthostatic hypotension
- Tachycardia
- Increased respiratory rate
- QT prolongation
- Ventricular arrhythmias
- Polymorphous configuration of torsade de pointes
- Cardiac arrest

Haematological Effects

- Agranulocytosis (sore throat and fever; unusual bleeding or bruising)
- Mild and usually transient leukopenia and leukocytosis
- Minor decreases in red blood cell counts
- Anaemia
- Tendency toward lymphocytosis and monocytosis

Hepatobiliary Effects

- Impaired liver function and/or jaundice or cholestatic hepatitis "No causal relationship has been established"

Respiratory Effects

- Laryngospasm

- Bronchospasm
- Increased depth of respiration
- Bronchopneumonia, sometimes fatal

Dermatological and Hypersensitivity Reactions

- Hypersensitivity reactions
- Local reactions as erythema, swelling or tender lumps
- Maculopapular and acneiform skin reactions and isolated cases of photosensitivity and loss of hair, urticaria, exfoliative dermatitis and erythema multiforme

Endocrine Effects

- Hyperprolactinaemia
- Gynaecomastia
- Menstrual irregularities including oligo or amenorrhoea
- Mastalgia
- Breast engorgement
- Impotence or increased libido
- Lactation
- Hyperglycaemia
- Hypoglycaemia
- Hyponatraemia
- Inappropriate anti-diuretic hormone secretion (very rare)

Gastrointestinal Effects

- Constipation
- Anorexia
- Nausea
- Vomiting
- Diarrhoea
- Dyspepsia
- Heartburn
- Hypersalivation

Autonomic Effects

- Blurred vision
- Dryness of mouth
- Urinary retention
- Excessive perspiration or salivation
- Priapism and erectile dysfunction

Ocular Effects

- Cataract
- Retinopathy
- Visual disturbances

Other Effects

- Heat stroke (hot, dry skin; inability to sweat; muscle weakness;

confusion)

- Increased sensitivity of skin to sun
- Weight gain
- Peripheral oedema
- Sudden unexplained death

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Symptoms and Findings

The manifestation would be an exaggeration of the known pharmacologic effects and adverse reactions. The most prominent symptoms would be:

1. Severe extrapyramidal reactions
2. Hypotension
3. Sedation

Sometimes coma with respiratory depression and hypotension, which could be severe enough to produce a shock-like state, can occur. Extrapyramidal reactions may consist of muscular weakness or rigidity and a generalised or localised tremor. Hypertension, rather than hypotension, is also possible. Convulsions, QT prolongation and ventricular arrhythmias including torsade de pointes may occur.

Treatment of Overdosage

There is no specific antidote. Treatment is largely symptomatic and supportive. Activated charcoal may be administered to decrease medicine absorption. Note: Dialysis is NOT effective in removing excessive systemic haloperidol.

For comatose patients, establish a patent airway by use of an oropharyngeal airway or endotracheal tube. Respiratory depression may necessitate artificial respiration.

Convulsions may be treated with IV diazepam, however, respiratory status should be monitored during its administration.

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 haloperidol may reverse its action and cause profound hypotension.

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

ECG and vital signs should be monitored. Hypothermia should be managed with external warming.

For advice on the management of overdose please contact the National

Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Although the complex mechanism of the therapeutic effect of haloperidol is not clearly established, it is known that it produces a selective effect on the central nervous system by competitive blockade of postsynaptic dopamine (D₂) receptors in the mesolimbic dopaminergic system, and an increased turnover of brain dopamine to produce its tranquillising effects. With subchronic therapy, depolarisation blockade, or diminished firing rate of the dopamine neurone (decreased release) along with D₂ postsynaptic blockade, results in the antipsychotic action. Blockade of dopamine receptors in the nigrostriatal dopamine pathway produces extrapyramidal motor reactions; blockade of dopamine receptors in the tuberoinfundibular system decreases growth hormone release and increases prolactin release by the pituitary. There is also some blockade of alpha-adrenergic receptors of the autonomic system.

5.2 Pharmacokinetic properties

Absorption

Haloperidol is rapidly absorbed from the gastrointestinal tract following oral administration but appears to undergo first-pass metabolism in the liver. Peak plasma levels of haloperidol occur within two to six hours of oral dosing and about twenty minutes after intramuscular administration.

Distribution

Haloperidol is approximately 92% bound to plasma proteins. The distribution of haloperidol into the human body tissues and fluids has not been fully determined. In animal studies, the medicine is mainly distributed into the liver, with lower concentrations being distributed into the brain, lungs, kidneys, spleen and heart. Haloperidol is also distributed into breast milk.

Metabolism

Metabolism of haloperidol occurs in the liver. Haloperidol is metabolised by oxidative *N*-dealkylation of the piperidine nitrogen to form fluorenylcarboxylic acids and piperidine metabolites which appeared to be inactive, and by reduction of the butyrophenone carbonyl to the carbinol, forming the alcohol hydroxyhaloperidol. Limited data suggest that the reduced metabolite, hydroxyhaloperidol, has some pharmacological activity, although its activity appears to be less than that of haloperidol. There is evidence of enterohepatic recycling and due to the influence of the first-pass effect of metabolism in the liver, plasma concentrations following oral administration are lower than those following intramuscular administration. Haloperidol and its metabolites are excreted in the urine, via the bile and in the faeces. The plasma half-life of haloperidol after oral administration ranges from 12 to 38 hours. Studies have shown that CYP3A4 and/or CYP2D6 are involved in the metabolic biotransformation of haloperidol.

Excretion

The mean plasma half-life (terminal elimination) has been determined as 20.7 ± 4.6 (SD) hours, and although excretion begins rapidly, only 24 to 60% of ingested radioactive medicine is excreted (mainly as metabolites in urine; some in faeces) by the end of the first week, and very small but detectable levels of radioactivity persist in the blood and are excreted for several weeks after dosing. In humans, haloperidol glucuronide is a major metabolite excreted in the urine. About 1% of the ingested dose is recovered unchanged in the urine. The slow excretion may be related to a high degree of plasma protein binding. Haloperidol is highly lipid-soluble and may remain in fatty tissue for some weeks.

6. PHARMACEUTICAL PRECAUTIONS

6.1 List of excipients

SERENACE tablets contain the following excipients: lactose, starch - maize, acacia, magnesium stearate, calcium hydrogen phosphate. SERENACE 0.5mg tablets also contain quinoline yellow CI47005 and green s CI44090. SERENACE 5mg tablets also contain brilliant scarlet 4R CI16255.

SERENACE liquid contains the following excipients: lactic acid, water, methyl hydroxybenzoate and propyl hydroxybenzoate as preservatives. Purchase of a measuring device is required to dispense liquid.

SERENACE ampoules contain the following excipients: (s) lactic acid, sodium hydroxide and water for injections.

6.3 Shelf life

Tablets: 2 years

Ampoules: 3 years

Liquid: 3 years

6.4 Special precautions for storage

Store below 30°C.

Ampoules – protect from light

6.5 Nature and contents of container

Liquid – glass bottle

Tablets - HDPE bottle with PP CR closure

Ampoules – glass

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pharmacy Retailing (NZ) Limited
 Trading as Healthcare Logistics
 58 Richard Pearse Drive
 Airport Oaks
 Auckland
 New Zealand
 Ph: (09) 915 9500
aspen@aspenpharma.co.nz

9. DATE OF FIRST APPROVAL

Injection: 31/12/1969
 0.5mg & 1.5mg Tablets: 31/12/1969
 5mg Tablet: 25/06/1971
 Liquid: 31/12/1969

10. DATE OF REVISION OF TEXT

15 June 2017

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections revised	Update to the SPC-style format
Section 4.8	Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/
Section 4.9	For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766)
A contact telephone number for the sponsor.	Phone number and email address included.
Section 6: Inclusion of 'measuring device' statement Section 4.2: dosing instructions in mLs.	June 2017

