

1. NAME OF THE MEDICINAL PRODUCT

Haloperidol 10mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Haloperidol B.P. 10mg.

3. PHARMACEUTICAL FORM

Pink uncoated tablets intended for oral administration to human beings.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Psychotic conditions: Schizophrenia, paranoid psychoses, mania and hypomania.

Behavioural or mental disorders, including those associated with mental retardation, such as aggression, hyperactivity and self-mutilation.

Moderate to severe psychomotor agitation, excitement, violent or dangerous impulsive behaviour.

Gilles de la Tourette's syndrome and severe motor tics.

Restlessness and agitation in elderly patients.

Childhood behaviour disorders, especially with associated hyperactivity and aggression. As an adjunct to the short-term management of anxiety.

4.2. Posology and method of administration

Route of administration: oral.

There is considerable inter-patient variation in the dosage requirements and the dosage should be individualised to meet the needs and response of each patient. In determining the initial dose, consideration should be given to the patient's age, severity of symptoms and any previous response to other anti-psychotic therapy. The dosage may be administered in single or divided doses; administration twice daily is usually sufficient.

Adults:

Psychotic conditions, behavioural or mental disorders, moderate to severe psychomotor agitation or impulsive behaviour.

The usual initial dosage ranges from 1.5 to 20mg daily, depending on the individual patient's characteristics and the severity of symptoms. It may be necessary to increase the dosage, gradually, to obtain adequate control of symptoms. The maximum daily dose should not exceed 30mg.

The usual maintenance dosage ranges from 3 to 10mg daily, and this may be achieved by gradually reducing the dosage to the lowest effective maintenance level.

Gilles de la Tourette's syndrome.

The initial dosage is usually 2mg daily. This may be increased, gradually, during the acute phase of treatment and in order to obtain maximum control of symptoms a dosage of 6 to 30mg daily may be required.

When a satisfactory response has been achieved, the dosage should be gradually reduced to the lowest effective maintenance level, which is 4mg daily for most patients.

Elderly:

Half the recommended adult starting dose may be sufficient for therapeutic response. As elderly or debilitated patients may be much more sensitive to haloperidol, the maximum and maintenance doses will generally be lower.

Anxiety.

0.5mg twice daily.

Childhood behavioural disorders and schizophrenia

Total daily maintenance dose of 0.025-0.05 mg (25 to 50 micrograms)/kg body weight per day, up to a maximum of 10 mg daily. Half the dose should be given in the morning and the other half in the evening.

Gilles de la Tourette syndrome

Oral maintenance doses of up to 10 mg/day in most patients.

Adjunct to the short-term management of anxiety

Not recommended

4.3. Contraindications

Comatose states; Parkinson's Disease; hypersensitivity to haloperidol; breast-feeding, lesions of basal ganglia, clinically significant cardiac disorders (eg. 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, uncorrected hypokalaemia and other QT prolonging drugs.

4.4. Special warnings and precautions for use

Care is required when administering haloperidol to patients with hepatic disease, renal failure, pheochromocytoma, conditions predisposing to epilepsy (e.g. alcohol withdrawal or brain damage). Haloperidol may be given to patients with epilepsy but usual anticonvulsant therapy should be continued.

Caution is required when using haloperidol in thyrotoxic patients and those with arteriosclerosis who may have occult or manifest lesions of the basal ganglia; such patients may be more prone to develop extrapyramidal symptoms.

Haloperidol should be used with care in patients with severe cardiovascular disorders, because of the possibility of transient hypotension. Should hypotension occur and a vasopressor be required, adrenaline should not be used since haloperidol may block its vasopressor activity and paradoxical further lowering of the blood pressure may occur.

Cases of sudden death have been reported in psychiatric patients receiving antipsychotic drugs, including haloperidol.

There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. Those receiving concomitant therapy with such drugs should be monitored carefully (ECGs and potassium levels).

Abrupt withdrawal of antipsychotic drugs after long-term therapy may be associated with acute withdrawal symptoms including nausea, vomiting and insomnia. Withdrawal from antipsychotics should always be gradual and closely monitored to avoid the risk of acute withdrawal syndromes or rapid relapse.

Like all other 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 co-exist. It must be kept in mind that antipsychotics are reported to increase plasma concentration of tricyclics, possibly increasing the risk of ventricular arrhythmias

Haloperidol may impair the antiparkinson effects of levodopa. If an antiparkinson agent is used concomitantly with haloperidol, both drugs should not be discontinued simultaneously, since extrapyramidal symptoms, previously controlled by antiparkinson agents, may occur due to the slower excretion rate of haloperidol.

The physician should keep in mind the possibility of additive antimuscarinic effects when haloperidol is used with antiparkinson drugs with antimuscarinic effects. Concomitant use of two or more drugs having antimuscarinic effects can increase side-effects such as dry mouth, urine retention, and constipation.

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

Haloperidol should be used in caution in patients known to be slow metabolisers of CYP2D6, and during the use of cytochrome P450 inhibitors. Concomitant use of anti-psychotics should be avoided.

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 diseases or abnormal findings on cardiac clinical examination. During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual basis. Whilst on therapy, the dose should be reduced if QT is prolonged, and haloperidol should be discontinued if the QTc exceeds 500ms.

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

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factor for VTE, all possible risk factors for VTE should be identified before and during treatment with Haloperidol and preventive measures undertaken.

Increased Mortality in Elderly people with Dementia

Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Haloperidol is not licensed for the treatment of dementia-related behavioural disturbances.

4.5 Interactions with other medicinal products and other forms of interaction

Following interactions have been reported with haloperidol:

Adrenergic blocking agents: Haloperidol may reverse the blood-pressure-lowering effects of adrenergic-blocking agents such as guanethidine.

Antiarrhythmics & other drugs that prolong QT interval: There is increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval given with anti-arrhythmics that prolong the QT interval. Concomitant use of haloperidol with amiodarone should be avoided. Amiodarone has a long half-life; there is a potential for drug interactions to occur for several weeks (or even months) after treatment with it has been stopped.

Anticonvulsant: Antipsychotics antagonise anticonvulsant effect of drugs such as carbamazepine, phenytoin, primidon which can result in lowering of convulsive threshold. Dosage of anticonvulsants may need to be increased.

Antimuscarinic drugs: Effects of haloperidol may be reduced by these drugs. There is also a possibility of increase in side-effects such as dry mouth, urine retention, and constipation due to additive antimuscarinic effects; concomitant use can also lead to confusion in the elderly.

Antidepressants, tricyclics: Haloperidol may impair the metabolism of tricyclic antidepressants and increase plasma concentration of tricyclics, possibly increasing risk of ventricular arrhythmia

CNS depressants: Haloperidol may enhance the central nervous system depressant effects of other CNS-depressant drugs including alcohol, hypnotics, sedatives or strong analgesics.

Enzyme inducers: Co-administration of enzyme-inducing drugs such as carbamazepine, phenobarbitone and rifampicin with haloperidol may result in a significant reduction of haloperidol plasma levels. Haloperidol dose may therefore need to be increased, according to the patient's response. After stopping such drugs, it may be necessary to re-adjust the dosage of haloperidol.

Levodopa: Haloperidol may impair the antiparkinson effects of levodopa.

Lithium: In rare cases, an encephalopathy-like syndrome has been reported in combination with lithium and haloperidol. Signs of encephalopathy-like syndrome include confusion, disorientation, headache, disturbances of balance and drowsiness. When lithium and haloperidol therapy are used concomitantly, haloperidol should be given in the lowest effective dose and lithium levels should

be monitored and kept below 1 mmol/l. If symptoms of encephalopathy-like syndrome occur, therapy should be stopped immediately.

Methyldopa: Enhanced CNS effects have been reported when haloperidol is used in combination with methyldopa.

Phenindione: Antagonism of the effect of phenindione has been reported.

Sympathomimetics: Haloperidol may antagonize the action of adrenaline and other sympathomimetic agents.

In pharmacokinetic studies, increased haloperidol levels have been reported when haloperidol was given concomitantly with the following drugs: *quinidine*, *bupirone* and *fluoxetine*. Haloperidol plasma levels should therefore be monitored and reduced if necessary.

Use of haloperidol with concomitant QT prolonging drugs could induce torsade de pointes and is contraindicated. These include class IA and III anti arrhythmics, neuroleptics, antidepressive agents (tricyclics and venlafaxine), certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, antimalarials, certain non-sedating antihistaminics (terfenadine, astemizole), 5-HT₃ receptor antagonists, arsenic trioxide. See section 4.3.

Concomitant use of drugs that cause electrolyte imbalance or that are metabolic inhibitors of cytochrome CYP2D6 may increase the risk of ventricular arrhythmias. If the benefit is considered to outweigh the risk in the individual patient, co-administration should be undertaken with caution and ECG monitoring should be considered. (See section 4.4)

4.6. Pregnancy and lactation

The safety of haloperidol in pregnancy has not been established. There is some evidence of harmful effects in some but not all animal studies. There are no well controlled studies of haloperidol in pregnant women; experience suggests that there may be teratogenic effects, although a causal relationship has not been established. Haloperidol should not be used during pregnancy unless the anticipated benefit clearly outweighs the potential risk to the foetus.

Haloperidol is excreted in breast milk and breast-feeding should be discontinued if the use of haloperidol is considered essential.

4.7. Effects on ability to drive and use machines

Haloperidol may cause some degree of sedation or impaired alertness, particularly at higher doses and at the start of treatment. Patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8. Undesirable effects

Central Nervous System: In common with all neuroleptics, extrapyramidal symptoms may occur, eg tremor, oculogyric crisis and laryngeal dystonia. Anti-Parkinson agents should not be prescribed routinely.

As with all antipsychotics agents, tardive dyskinesia may appear in some patients on long term therapy or after drug discontinuation. The syndrome is mainly characterised by rhythmical 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 reinstated, when the dosage is increased or when a switch is made to a different antipsychotic drug. Treatment should be discontinued as soon as possible. However, since its occurrence may be related to duration of treatment, as well as daily dose, Haloperidol should be given in the minimum effective dose for the minimum possible time, unless it is established that long term administration for the treatment of schizophrenia is required.

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

The following effects have been reported rarely; confusional states or epileptic fits, depression, sedation, agitation, insomnia, headache, vertigo and apparent exacerbation of psychotic symptoms.

In common with other antipsychotic drugs, haloperidol has been associated with neuroleptic malignant syndrome (NMS). An idiosyncratic response characterised by hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness, coma and elevated CPK. Signs of autonomic dysfunction such as tachycardia, labile arterial pressure and sweating may precede onset of hyperthermia, acting as early warning signs. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted. Haloperidol, even in low dosage in susceptible (especially non-psychotic) individuals may cause unpleasant subjective feelings of being mentally dulled or slowed down, dizziness, headache or paradoxical effects of excitement, agitation or insomnia.

Gastro-intestinal System: gastro-intestinal symptoms, nausea, loss of appetite, constipation and dyspepsia have been reported.

Endocrinal System: Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligo- or amenorrhoea. Hypoglycaemia and the syndrome of inappropriate antidiuretic hormone secretion have been reported rarely. Impairment of sexual function including erection and ejaculation has also been occasionally reported.

Cardiovascular System: Tachycardia and dose related hypotension are uncommon, but can occur, particularly in the elderly, who are more susceptible to the sedative and hypotensive effects. Less commonly, hypertension has also been reported.

Cardiac effects such as QT-interval prolongation, Torsade de Pointes, ventricular arrhythmias, including ventricular fibrillation and ventricular tachycardia and cardiac arrest have been reported rarely. Cases of sudden unexpected death have also occurred. These effects may occur more frequently with high doses, intravenous administration and in predisposed patients (see 4.4. Special Warnings and Special Precautions for use).

Autonomic Nervous System: Dry mouth as well as excessive salivation, blurred vision, urinary retention and hyperhidrosis have been reported.

Other Adverse Reactions: The following effects have been reported rarely: Jaundice, cholestatic hepatitis, or transient abnormalities of liver function in the absence of jaundice; priapism and weight changes. Temperature disorders may also occur, characteristically hyperthermia associated with NMS, although hypothermia has also been reported. The following have been reported very rarely: blood dyscrasia, including agranulocytosis, thrombocytopenia and transient leucopenia, hypersensitivity reactions including anaphylaxis.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs-
Frequency unknown

4.9. Overdose

Overdosage causes intensification of the pharmacological and adverse effects of the drug. Severe extrapyramidal symptoms, hypotension or sedation are likely to be most prominent. Coma with respiratory depression may occur and hypotension may be present. Extrapyramidal reactions may include muscle weakness or rigidity and localised or generalised tremor. With accidental overdosage in young children, hypothermia, bradycardia, sinus arrhythmia and hypertension have been reported.

There is no specific antidote. Treatment is symptomatic and supportive. The stomach should be emptied by gastric aspiration and lavage. A patent airway and artificial ventilation may need to be established. Hypotension may be treated by

placing the patient in the head-down position and by use of a plasma expander and careful use of a vasopressor drug such as noradrenaline. Adrenaline should not be used. Extrapyramidal reactions should be treated with parenteral antiparkinsonian or antihistamine drugs.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Haloperidol is a member of the butyrophenone class of neuroleptic drugs and has antipsychotic, anti-anxiety and anti-emetic effects. Although the precise central mechanism of action has not been elucidated, antagonism of dopamine-mediated synaptic neurotransmission appears to be an important action of haloperidol and may be the primary action through which the antipsychotic and extrapyramidal neurologic effects are mediated.

Within the autonomic nervous system, haloperidol displays less α -adrenergic antagonism than chlorpromazine and shows little anti-adrenergic activity in treated patients. The cholinergic blocking effects of antipsychotic drugs are relatively weak and anti-cholinergic effects are infrequent with haloperidol, relative to other neuroleptic agents.

Orthostatic hypotension, seen with chlorpromazine and resulting from a combination of central actions and peripheral α -adrenergic blockade, occurs much less frequently during therapy with haloperidol.

5.2. Pharmacokinetic properties

Haloperidol is readily absorbed from the gastro-intestinal tract. It is metabolised in the liver and is excreted in the urine and faeces. There is wide inter-subject variation in plasma concentrations of haloperidol. The drug is very extensively bound to plasma proteins. It is widely distributed in the body and it crosses the blood-brain barrier. The plasma half-life of haloperidol is reported to range from about 13 to nearly 40 hours.

5.3. Preclinical safety data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose B.P.
Polyvinylpyrrolidone B.P. \ Povidone
Starch B.P.
Magnesium Stearate B.P.
Stearic Acid B.P.C.
Aerosil B.P.
Ponceau 4R (Dispersed Red 11652) E124
Water

6.2. Incompatibilities

Nil.

6.3. Shelf life

3 years (36 months).

6.4. Special precautions for storage

Store below 20°C.
Protect from light.

6.5 Nature and contents of container

Polypropylene securitainers with tamper evident polypropylene caps.
Pack size: 25, 28, 50, 100, 250, 500 and 1000 tablets.

6.6. Instruction for use and handling

Use as directed by the physician.
Keep out of reach of children.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Ltd
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Croydon
Surrey
CR0 0XT
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 12762/0115

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25th July 2001

10. DATE OF REVISION OF THE TEXT

25/02/2010