

1. NAME OF THE MEDICINAL PRODUCT

Haloperidol 5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Haloperidol B.P. 5mg.

3. PHARMACEUTICAL FORM

Light green 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, CNS depression, Parkinson's Disease; hypersensitivity to haloperidol; lesions of basal ganglia

In common with other neuroleptics, haloperidol has the potential to cause rare prolongation of the QT interval. Use of haloperidol is therefore contra-indicated in patients with clinically significant cardiac disorders (e.g. recent acute myocardial infarction, uncompensated heart failure, arrhythmias treated with class IA and III anti-arrhythmic medicinal products), QTc interval prolongation, history of ventricular arrhythmia or Torsades de pointes, clinically significant bradycardia, second or third degree heart block and uncorrected hypokalaemia.

Haloperidol should not be used concomitantly with other QT prolonging drugs (see section 4.5, Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

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.

Cardiovascular effects

Very rare reports of QT prolongation and/or ventricular arrhythmias, in addition to rare reports of sudden death, have been reported with haloperidol. They may occur more frequently with high doses and in predisposed patients.

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.

The risk of QT prolongation and/or ventricular arrhythmias may be increased with higher doses (see Sections 4.8 and 4.9) or with parenteral use, particularly intravenous administration. Continuous ECG monitoring should be performed for QT interval prolongation and for serious cardiac dysrhythmias if Haloperidol is administered intravenously.

Haloperidol should be used with caution in patients known to be slow metabolisers of CYP2D6, and during use of cytochrome P450 inhibitors. Concomitant use of antipsychotics should be avoided. (See Section 4.5).

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 (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 500 ms.

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

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 with caution in patients with risk factors for stroke.

Neuroleptic malignant syndrome

In common with other antipsychotic drugs, Haloperidol has been associated with neuroleptic malignant syndrome: a rare idiosyncratic response characterised by hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness. Hyperthermia is often an early sign of this syndrome. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Tardive dyskinesia

As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or after drug discontinuation. The syndrome is mainly characterised by rhythmic involuntary movements of the tongue, face, mouth or jaw. The manifestations

may be permanent in some patients. The syndrome may be masked when treatment is 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.

Extrapyramidal symptoms

In common with all neuroleptics, extrapyramidal symptoms may occur, e.g. tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia.

Anti-parkinson drugs of the anticholinergic type may be prescribed as required, but should not be prescribed routinely as a preventive measure. If concomitant anti-parkinson medication is required, it may have to be continued after stopping Haloperidol if its excretion is faster than that of Haloperidol in order to avoid the development or aggravation of extrapyramidal symptoms. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including anti-parkinson agents, are administered concomitantly with Haloperidol.

Seizures/Convulsions

It has been reported that seizures can be triggered by Haloperidol. Caution is advised in patients suffering from epilepsy and in conditions predisposing to convulsions (e.g., alcohol withdrawal and brain damage).

Hepato-biliary concerns

As Haloperidol is metabolised by the liver, caution is advised in patients with liver disease. Isolated cases of liver function abnormalities or hepatitis, most often cholestatic, have been reported.

Endocrine system concerns

Thyroxin may facilitate 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.

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.

Additional considerations

In schizophrenia, the response to antipsychotic drug treatment may be delayed. Also, if drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months.

Acute withdrawal symptoms including nausea, vomiting and insomnia have very rarely been described after abrupt cessation of high doses of anti-psychotic drugs. Relapse may also occur and gradual withdrawal is advisable.

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.

Caution is advised in patients with renal failure and pheochromocytoma.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of haloperidol with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including torsade de pointes. Therefore concomitant use of these products is not recommended (see section 4.3- Contraindications).

Examples include certain antiarrhythmics, such as those of Class 1A (such as quinidine, disopyramide and procainamide) and class III (such as amiodarone, sotalol and dofetilide), certain antimicrobials (sparfloxacin, moxifloxacin, erythromycin IV), tricyclic antidepressants (such as amitriptyline), certain tetracyclic antidepressants (such as maprotiline), other neuroleptics (e.g. phenothiazines, pimozide and sertindole), certain antihistamines (such as terfenadine), cisapride, bretylium and certain anti-malarials such as quinine and mefloquine. This list is not comprehensive.

Concurrent use of drugs causing electrolyte imbalance may increase the risk of ventricular arrhythmias and is not recommended (see section 4.4-Special Warnings and Precautions for Use). Diuretics, in particular those causing hypokalaemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred.

Haloperidol is metabolised by several routes, including glucuronidation and the cytochrome P450 enzyme system (particularly CYP 3A4 or CYP 2D6). Inhibition of these routes of metabolism by another drug or a decrease in CYP 2D6 enzyme activity may result in increased haloperidol concentrations and an increased risk of adverse events, including QT-prolongation. In pharmacokinetic studies, mild to moderately increased haloperidol concentrations have been reported when haloperidol was given concomitantly with drugs characterised as substrates or inhibitors of CYP 3A4 or CYP 2D6 isozymes, such as, itraconazole, buspirone, venlafaxine, alprazolam, fluvoxamine, quinidine, fluoxetine, sertraline, chlorpromazine, and promethazine. A decrease in CYP2D6 enzyme activity may result in increased haloperidol concentrations. Increases in QTc and extrapyramidal symptoms have been observed when haloperidol was given with a combination of the metabolic inhibitors ketoconazole (400 mg/day) and paroxetine (20 mg/day). It may be necessary to reduce the haloperidol dosage.

Effect of Other Drugs on Haloperidol

When prolonged treatment with enzyme-inducing drugs such as carbamazepine, phenobarbital, rifampicin is added to Haloperidol therapy, this results in a significant

reduction of haloperidol plasma levels. Therefore, during combination treatment, the Haloperidol dose should be adjusted, when necessary. After stopping such drugs, it may be necessary to reduce the dosage of Haloperidol.

Sodium valproate, a drug known to inhibit glucuronidation, does not affect haloperidol plasma concentrations.

Effect of Haloperidol on Other Drugs

In common with all neuroleptics, Haloperidol can increase the central nervous system depression produced by other CNS-depressant drugs, including alcohol, hypnotics, sedatives or strong analgesics. An enhanced CNS effect, when combined with methyl dopa, has also been reported.

Haloperidol may antagonise the action of adrenaline and other sympathomimetic agents and reverse the blood-pressure-lowering effects of adrenergic-blocking agents such as guanethidine.

Haloperidol may impair the antiparkinson effects of levodopa.

Haloperidol is an inhibitor of CYP 2D6. Haloperidol inhibits the metabolism of tricyclic antidepressants, thereby increasing plasma levels of these drugs.

Other Forms of Interaction

In rare cases, an encephalopathy-like syndrome has been reported in combination with lithium and haloperidol. It remains controversial whether these cases represent a distinct clinical entity or whether they are in fact cases of NMS and/or lithium toxicity. Signs of encephalopathy-like syndrome include confusion, disorientation, headache, disturbances of balance and drowsiness. One report showing symptomless EEG abnormalities on the combination has suggested that EEG monitoring might be advisable. 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.

Antagonism of the effect of the anticoagulant phenindione has been reported.

The dosage of anticonvulsants may need to be increased to take account of the lowered seizure threshold.

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 have been a number of reports of birth defects following foetal exposure to haloperidol for which a causal role for haloperidol cannot be excluded. Reversible extrapyramidal symptoms have been observed in neonates exposed to haloperidol in utero during the last trimester of pregnancy. Haloperidol should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

Haloperidol is excreted in breast milk. There have been isolated cases of extrapyramidal symptoms in breast-fed children. If the use of Haloperidol is essential, the benefits of breast-feeding should be balanced the potential risks.

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

The data provided below covers all haloperidol formulations including the Haloperidol Decanoate formulations.

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

System Organ Class	Adverse Drug Reactions				
	Frequency Category				
	Very Common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)	Not Known
Blood and lymphatic System Disorders			Leukopenia		Agranulocytosis; Neutropenia; Pancytopenia; Thrombocytopenia
Immune System Disorders			Hypersensitivity		Anaphylactic reaction
Endocrine Disorders				Hyperprolactinaemia	Inappropriate antidiuretic hormone secretion
Metabolic and Nutritional Disorders					Hypoglycaemia
Psychiatric Disorders	Agitation; Insomnia	Depression; Psychotic disorder	Confusional state; Libido Decreased; Loss of libido;		

			Restlessness		
Nervous System Disorders	Extrapyramidal disorder; Hyperkinesia; Headache	Tardive dyskinesia; Oculogyric Crisis; Dystonia; Dyskinesia; Akathisia; Bradykinesia; Hypokinesia; Hypertonia; Somnolence; Masked Facies, Tremor; Dizziness	Convulsion; Parkinsonism; Akinesia; Cogwheel rigidity; Sedation; Muscle Contractions Involuntary	Motor dysfunction; Neuroleptic malignant syndrome; Nystagmus;	
Eye Disorders		Visual disturbance;	Vision blurred		
Cardiac Disorders			Tachycardia		Ventricular Fibrillation; Torsade de pointes; Ventricular Tachycardia; Extrasystoles
Vascular Disorders		Orthostatic Hypotension; Hypotension			
Respiratory, thoracic and mediastinal Disorders			Dyspnoea	Bronchospasm	Laryngeal Oedema; Laryngospasm
Gastrointestinal Disorders		Constipation; Dry mouth; Salivary hypersecretion; Nausea; Vomiting			
Hepatobiliary Disorders		Liver function test abnormal	Hepatitis; Jaundice		Acute Hepatic Failure; Cholestasis
Skin and subcutaneous tissue disorders		Rash	Photosensitivity Reaction; Urticaria; Pruritis; Hyperhidrosis		Leukocytoclastic Vasculitis; Dermatitis Exfoliative
Musculoskeletal and Connective Tissue Disorders			Torticollis; Muscle rigidity; Muscle Spasms; Musculoskeletal	Trismus; Muscle Twitching	

			stiffness		
Renal and Urinary Disorders		Urinary retention			
Reproductive System and Breast Disorders		Erectile dysfunction	Amenorrhoea; Dysmenorrhoea; Galactorrhoea; Breast Discomfort; Breast Pain;	Menorrhagia; Menstrual Disorder; Sexual Dysfunction	Gynaecomastia, Priapism
General Disorders and Administration Site Conditions		Injection Site Reaction	Gait disturbance; Hyperthermia; Oedema		Sudden Death; Face Oedema; Hypothermia
Investigations		Weight increased; Weight decreased		Electrocardiogram QT prolonged	

Additional Information

Cardiac effects such as QT-interval prolongation, torsade de pointes, ventricular arrhythmias, including ventricular fibrillation and ventricular tachycardia), and cardiac arrest have been reported. These effects may occur more frequently with high doses, and in predisposed patients.

Toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported in patients taking haloperidol. The true incidence of these reports is not known.

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

Symptoms:

In general, the manifestations of haloperidol overdose are an extension of its pharmacological actions, the most prominent of which would be severe extrapyramidal symptoms, hypotension and psychic indifference with a transition to sleep. The risk of ventricular arrhythmias possibly associated with QT-prolongation should be considered. The patient may appear comatose with respiratory depression and hypotension which could be severe enough to produce a shock-like state. Paradoxically hypertension rather than hypotension may occur. Convulsions may also occur.

Treatment:

There is no specific antidote to haloperidol. A patent airway should be established and maintained with mechanically assisted ventilation if necessary. In view of isolated reports of arrhythmia, ECG monitoring is strongly advised. Hypotension and circulatory collapse

should be treated by plasma volume expansion and other appropriate measures. Adrenaline should not be used. The patient should be monitored carefully for 24 hours or longer, body temperature and adequate fluid intake should be maintained.

In cases of severe extrapyramidal symptoms, appropriate anti-Parkinson medication should be administered.

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.
Dispersed Green 18834 (E142/E102/E131/E122)
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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12-16 Addiscombe Road
Croydon
Surrey
CR0 0XT
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 12762/0114

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

25th July 2001

10. DATE OF REVISION OF THE TEXT

10/09/2010