

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Haloperidol 5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Haloperidol 5mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Blue, biconvex, circular tablets 8mm in diameter, marked with '267' and a breakline on one face and with the Clonmel logo on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the management of cases of schizophrenia, hypomania, mania, agitation, psychotic illness, paranoid psychosis, childhood behavior disorders especially associated with problems in mentally handicapped, and severe motor tics and Gilles de la Tourette syndrome, intractable hiccup, control of severe nausea and vomiting excluding that of hyperemesis gravidarum.

4.2 Posology and method of administration

Adults:

The usual initial dose is 1.5 to 20 mg daily depending on the individual patient's characteristics and the severity of the disorder, with increments until optimum response is obtained. Reduction of dosage can then be made to the usual maintenance dose of 3 to 10 mg daily.

In the elderly half the above doses are usually sufficient. Maximum and maintenance doses will usually be lower for geriatric and debilitated patients because of greater sensitivity.

Giles de la Tourette syndrome

The usual initial dose is 2 mg daily with increments to the level of optimal control, generally 6 to 50 mg followed by a gradual reduction to a maintenance level which is generally around 4 mg.

Children:

An initial dosage of 0.025 to 0.05 mg/kg body weight can be used with a maximum of 10 mg daily, with a subsequent maintenance level of 0.05 mg/kg body weight.

The higher dose levels generally should be avoided as much as possible especially in children and the elderly.

Adjustment of dosage should be on the basis of the individual patient's condition and response.

Route of administration

Oral

4.3 Contraindications

- i. Use in lactation in women breast-feeding infants.
- ii. Use in comatose states.
- iii. Use in patients with Parkinson's disease and/or where there is a lesion of the basal ganglia
- iv. Use in patients hypersensitive to Haloperidol and other butyrophenones.
- v. CNS depression due to alcohol or other depressant drugs.

4.4 Special warnings and precautions for use

- Haloperidol should only be used with great caution in patients with established or likely basal ganglial lesions or with throtoxicosis or phaeochromocytoma. It should be used only with care in patients with hepatic or renal dysfunction or epilepsy.
- Haloperidol may, particularly at high dose, induce side effects of the extrapyramidal type. It is therefore often necessary to administer anti-Parkinsonian drugs as a prophylactic measure. Prolonged use especially at high doses may result in tardive dyskinesia. If concomitant anti-parkinson medication is required, it may have to be continued for at least a couple of weeks after the last haloperidol dosage because of the very long half life haloperidol.
- In common with other antipsychotics haloperidol has been associated with persistent dyskinesia. Tardive dyskinesia may develop in some patients on long term therapy, possibly in relation to total cumulative dose or may develop after drug therapy has been discontinued. The risk is reported to be greater in elderly patients on high-dose therapy.
- 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, including QT-syndrome or a family history of QT prolongation, subarachnoid haemorrhage; metabolic abnormalities such as hypokalaemia, hypocalcaemia or hypomagnesemia, starvation, alcohol abuse or those receiving concomitant therapy with other drugs known to prolong QT interval, should be monitored carefully (ECGs and potassium levels), particularly during the initial phase of treatment, to obtain steady plasma levels.
- Characteristic symptoms are rhythmical involuntary movements of tongue, face, mouth or jaw sometimes accompanied by involuntary movements of the extremities. They may persist for many months or even years and, while they gradually disappear in some patients, they appear to be permanent in others.
- At the first signs of tardive dyskinesia which may be orofacial dyskinesia the benefit of continued treatment should be carefully assessed against the risk of the development of persistent dyskinesia. Withdrawal of treatment with careful observation of the dyskinesia and psychotic condition has been suggested in order to assess the need for continued neuroleptic therapy and to reveal persisting dyskinesia. Should it be necessary to reinstate treatment, the antipsychotic agent may mask the syndrome. Anti-Parkinsonian agents have proved of little value in this syndrome.
- Haloperidol should be used with caution in patients in whom transient hypotension might be detrimental such as those with severe cardiovascular disease. The hypotension may not respond to adrenaline. Haloperidol may block the vasopressor activity of adrenaline with a further lowering of blood pressure. Less commonly hypertension has also been reported. Cardiac effects such as QT-prolongation and/or ventricular arrhythmias have been reported very rarely. They may occur more frequently with high doses and in predisposed patients.
- Relatively high doses may lead to impaired body temperature control, malignant neuroleptic syndrome and hyperthermia, autonomic dysfunction, rigidity and coma. The drug should be withdrawn preferably in stages. Haloperidol may be a potential cause of rhabdomyolysis, even in the absence of symptoms of neuroleptic malignant syndrome.

- Rarely sudden death has been reported in psychotic patients usually on high dosage.
- Thyroxine may facilitate Haloperidol toxicity. Therefore it should only be used with great caution in patients with hyperthyroidism. Antipsychotic therapy in those patients must always be accompanied by an adequate thyreostatic treatment.
- 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.
- It has been reported that seizures can be triggered by Haloperidol. Therefore, caution is advised in patients with a known history of epilepsy or condition predisposing to convulsions, e.g. alcohol withdrawal or brain damage.
- Use with caution in patients with respiratory disorders. Haloperidol may cause potentiation of breathing impairment, and may possibly lead to 'silent pneumonia'.
- Avoid concomitant use with other antipsychotics.

4.5 Interaction with other medicinal products and other forms of interaction

- Haloperidol will potentiate the effects of central nervous system depressants including alcohol, hypnotics, sedatives or strong analgesics.
- Concomitant use of lithium salts and haloperidol may result in an encephalopathy-like syndrome, a severe neuromuscular syndrome with impaired consciousness and fever. Such a combination is best avoided. When lithium and haloperidol therapy are used concomitantly, haloperidol should be given in the lowest effective dosage and lithium levels should be monitored and kept below 1 mmol/litre. If symptoms of encephalopathy-like syndrome occur, therapy should be stopped immediately.
- Combination with methyldopa may lead to enhanced sedation and mental disturbances. Haloperidol may antagonise the effects of sympathomimetic agents and the anti-parkinsonian effects of levodopa.
- Concurrent use with anti convulsants may require an increase in their dosage.
- Concomitant administration of rifampicin and haloperidol may lead to a decrease in plasma haloperidol concentration. Dosage adjustment of haloperidol should be administered according to careful monitoring of plasma drug concentration and/or clinical responses of haloperidol when co-administration or discontinuation of rifampicin is necessary in schizophrenic patients.
- Caution is required when administering haloperidol to patients taking fluoxetine as this combination may precipitate anti-cholinergic and extra-pyramidal effects.
- Haloperidol may antagonise the action of adrenaline and other sympathomimetic agents and reverse the hypotensive effects of adrenergic blocking agents such as guanethidine.
- Haloperidol inhibits the metabolism of tricyclic antidepressants, thereby increasing plasma levels of these drugs.
- Antagonism of the effect of phenindione has been reported.
- In pharmacokinetic studies, increased haloperidol levels have been reported when haloperidol was given concomitantly with the following drugs: quinidine, buspirone and fluoxetine. Haloperidol plasma levels should therefore be monitored and the dosage should be reduced if necessary.

- Co-administration of enzyme-inducing drugs such as carbamazepine, phenobarbitone and rifampicin with haloperidol may result in a significant reduction of haloperidol plasma levels during prolonged treatment. The haloperidol plasma during prolonged treatment. The haloperidol dose may therefore need to be increased or the dosage interval reduced, according to the patient's response. After stopping such drugs, it may be necessary to readjust the dose of haloperidol.
- The effect of haloperidol on QTc interval is likely to be potentiated by concurrent use of other drugs that also prolong the QTc interval, therefore concurrent use of these drugs and haloperidol requires careful monitoring.
- Electrolyte imbalance, particularly hypokalaemia, greatly increases the risk of QTc interval prolongation. Patients receiving haloperidol concomitantly with drugs that cause electrolyte imbalance should be closely monitored.
- The plasma concentrations of haloperidol may be increased by drugs which inhibit the drug metabolizing enzyme CYP3A4 and CYP2D6 such as terbinafine, erythromycin, fluoxetine and paroxetine. Where co-administration of such drugs is required, it may be necessary to adjust the dose of Haloperidol accordingly.

4.6 Fertility, pregnancy and lactation

Pregnancy

Haloperidol should not be used during pregnancy unless considered essential by the physician. Some teratogenesis has been demonstrated in mice, but not in other species. There are reports of two cases of limb malformations observed following maternal use of haloperidol along with other drugs which have suspected teratogenic potential. A casual relationship was not established.

Lactation

The drug is excreted in breast milk reaching levels comparable to maternal plasma. If the use of Haloperidol is essential, the benefits of breast feeding should be balanced against its potential risks.

4.7 Effects on ability to drive and use machines

Haloperidol may cause drowsiness or affect mental concentration and these may be potentiated by alcohol. The user should not drive or operate machinery unless the drug has been shown not to interfere with his physical or mental ability. Occasionally paradoxical excitement has been reported.

4.8 Undesirable effects

In common with all neuroleptics, extrapyramidal symptoms may occur e.g. tremor, rigidity, hypersalivation, bradykinesia, akathisia and acute dystonia. Oculogyric crises and laryngeal dystonic reactions have been reported. Antiparkinson drugs of the anticholinergic type should not be prescribed routinely.

As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long term therapy or after drug discontinuation. The syndrome is mainly characterized 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. It has been reported that fine vermicular movements of the tongue may be an early sign of tardive dyskinesia. If the medication is stopped at that time, the full syndrome may not develop.

In common with other antipsychotic drugs, Haloperidol has been associated with cases of neuroleptic malignant syndrome (NMS), an idiosyncratic response characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, coma and elevated plasma CPK levels. Signs of autonomic dysfunction such as tachycardia, labile arterial pressure and sweating may precede the onset of hyperthermia, thereby acting as early warning signs. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring

instituted.

Tachycardia and hypotension have been reported in occasional patients. Hypotension may occur particularly in the elderly.

Rarely sudden unexplained death has been reported in psychotic patients receiving antipsychotic drugs, including haloperidol.

Cardiac Effects such as cardiac arrest, QT-Interval prolongation Torsade de Pointes and /or ventricular arrhythmias (ventricular fibrillation and ventricular tachycardia) have been reported rarely. They may occur more frequently with high doses, intravenous administration and in predisposed patients (*see 4.4 Special Warnings and Special Precautions for Use*).

Nausea, vomiting, dyspepsia and loss of appetite have been reported. Weight changes may occur.

Hormonal effects include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligo- or amenorrhoea.

Very rare cases of hypoglycaemia, and a syndrome of inappropriate ADH secretion have been reported.

Autonomic effects, such as blurring of vision, dry mouth as well as excessive salivation, urinary retention and excessive perspiration may occur occasionally.

Jaundice, abnormalities of liver function and hepatitis (most often cholestatic) have rarely been reported.

Skin rashes, urticaria, anaphylaxis and photosensitisation have rarely been reported.

Blood dyscrasias including mild and transient leucopenia have occasionally been reported. Agranulocytosis and thrombocytopenia have only been reported rarely.

Other side effects occasionally reported include: bodytemperature dysregulation, constipation, impairment of sexual function including erection and ejaculation, priapism and peripheral oedema.

Other side effects occasionally reported include: depression, sedation, agitation, drowsiness, insomnia, headache, confusion, vertigo, grand mal seizures, apparent exacerbation of psychotic symptoms and paradoxical effects of excitement.

4.9 Overdose

In general, the signs and symptoms of overdosage would be an exaggeration of known pharmacological effects, the most prominent of which would be severe extrapyramidal symptoms, hypotension or sedation. In extreme cases 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.

The patient may appear comatose with respiratory depression and hypotension which could be severe enough to produce a shock-like state. The risk of ventricular arrhythmias possibly associated with QT prolongation should be considered.

Treatment

Since there is no specific antidote, treatment is primarily supportive.

For comatose patients a patent airway should be established and if necessary, mechanically assisted respiration is advised.

Electrocardiographic monitoring should commence immediately and continue until the patient is clinically recovered or any abnormalities that may have shown disappeared.

Hypotension and circulatory collapse may be counteracted by the use of intravenous fluids, plasma or concentrated albumin and vasopressor agents such as dopamine or noradrenaline.

Adrenaline should not be used.

In cases of severe extrapyramidal symptoms, anti-parkinsonian medication should be administered and be continued for several weeks. They must be withdrawn very cautiously as extrapyramidal symptoms, manifested by muscle rigidity and tremor may emerge.

Severe arrhythmias should be treated with appropriate anti-arrhythmic measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Haloperidol is a butyrophenone which is widely used in the management of psychotic conditions. Its actions and uses are similar to those of the phenothiazine, chlorpromazine. Many of the antipsychotic drugs have sedative effects but patients usually develop tolerance rapidly to this sedation. The term neuroleptic is used to contrast the effect of these drugs with those of the classical C.N.S. depressants such as general anaesthetics, sedatives and hypnotics, and opioids. The neuroleptic syndrome consists of suppression of spontaneous movements and complex behaviour, while spinal reflexes and unconditioned nociceptive avoidance behaviour remain intact.

In man the neuroleptic drugs reduce initiative and interest in the environment and they reduce displays of emotion or affection. Initially there may be some slowness in response to external stimuli and drowsiness. However, subjects are easily aroused, capable of giving appropriate answers to direct questions and seem to have intact intellectual functions. There is no ataxia, incoordination or dysarthria at ordinary doses. Psychotic patients become less agitated and restless and withdrawn or autistic patients sometimes become more responsive and communicative. Aggressive and impulsive behaviour diminishes. Gradually (usually over a period of days) psychotic symptoms of hallucinations, delusions and disorganised or incoherent thinking tend to disappear.

Antipsychotic drugs are considered to act by interfering with dopaminergic transmission in the brain by blocking dopamine receptors and may give rise to extrapyramidal effects and to hyperprolactinaemia.

5.2 Pharmacokinetic properties

Haloperidol is readily absorbed from the gastrointestinal tract. It is metabolised in the liver and is excreted in the urine and in the faeces. There is evidence of enterohepatic recycling. Paths of metabolism of haloperidol include oxidative N-dealkylation. Haloperidol has been reported to have a half-life cycle ranging from about 13 to nearly 40 hours. Its half-life is prolonged during the night. Haloperidol is extensively bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier.

5.3 Preclinical safety data

No further information provided.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium Hydrogen Phosphate Dihydrate
Maize Starch
Povidone

Magnesium Stearate
Sodium Starch Glycolate
Indigo Carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the container tightly closed.

6.5 Nature and contents of container

Polypropylene tubes with low density polyethylene caps.

High density polyethylene film is used as packing material.

Pack sizes: 100, 250, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Limited,
Waterford Road,
Clonmel,
Co. Tipperary,
Ireland.

8 MARKETING AUTHORISATION NUMBER

PA 126/55/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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