

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Haloperidol Injection BP 5 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains Haloperidol 5 mg.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless sterile solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of anxiety states, behavioural disorders, schizophrenia, hypomania, mania and allied psychoses. It is an antiemetic and it may be used to control nausea and vomiting. It is also of use in the treatment of motor tics, including Gilles de la Tourette syndrome, and in the management of alcohol withdrawal.

4.2 Posology and method of administration

For intramuscular or intravenous administration.

Adults:

For the prompt control of acutely agitated patients with moderate to severe symptoms, an initial dose of 2 - 10mg intramuscularly may be adequate, although up to 30mg intramuscularly may be required to control severely agitated patients. Depending on the response of the patients, subsequent intramuscular doses of 5mg may be given as frequently as every hour if required, although intervals of 4 to 8 hours may be adequate.

To control nausea and vomiting, the usual dose is 1 - 2mg, intramuscularly every 12 hours. For pre-anaesthetic medication a single intravenous or intramuscular dose of 1-5mg may be given to control tension and apprehension preoperatively, and to reduce the incidence of post operative nausea and vomiting.

For control of anxiety, insomnia, nausea and vomiting in the Alcohol Withdrawal Syndrome, haloperidol may be given intramuscularly in doses of 2- 5mg every 4 to 6 hours for up to 24 hours.

Children: Parenteral administration of haloperidol is not recommended for children. Oral treatment should succeed parenteral administration as soon as practicable.

4.3 Contraindications

Use in lactation in women breast-feeding infants.

Use in comatose states.

Use in patients with Parkinson's disease and/or where there is a lesion of the basal ganglia.

CNS depression due to alcohol or other depressant drugs.

Use in patients hypersensitive to haloperidol decanoate and other butyrophenones, or any of the excipients.

Clinically significant cardiac disorders (e.g. recent acute myocardial infarction, uncompensated heart failure, bradycardia or second or third degree heart block, arrhythmias treated with class IA and III anti arrhythmic medicinal products).

QTc interval prolongation.

History of ventricular arrhythmia or Torsades de pointes.

Uncorrected hypokalaemia.

Other QT prolonging drugs.

4.4 Special warnings and precautions for use

Rare cases of sudden death have been reported in psychiatric patients receiving antipsychotic drugs, including Haloperidol Injection.

Cardiovascular Effects:

Cardiac effects such as QT-prolongation and /or ventricular arrhythmias have been reported rarely. They may occur more frequently with high doses and in predisposed patients (see section 4.9).

The risk/benefit of Haloperidol Injection 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 (ECG's and potassium levels), particularly during initial phase of treatment.

Haloperidol Injection should be used with caution in patients known to be slow metabolisers of CYP2D6, and during use of cytochrome P450 inhibitors.

Baseline ECG prior to treatment in all patients, (~~see section 4.3~~) 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 patient basis. Whilst on therapy, reduce dose if QT is prolonged and discontinue if QTc is >500ms.

Avoid concomitant neuroleptics.

The risk of QT prolongation and/or ventricular arrhythmias may be increased with parenteral use, particularly intravenous administration. ECG monitoring should be performed for QT interval prolongation and for serious cardiac dysrhythmias if haloperidol is administered intravenously. Haloperidol Injection must not be administered intravenously.

Tachycardia and hypotension have been reported in occasional patients.

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. Less commonly hypertension has also 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 Injection BP 5mg/1ml and preventive measures undertaken.

Increased Mortality in Elderly people with Dementia

Elderly patients with dementia-related psychosis treated with antipsychotic drugs (conventional and atypical) are at an increased risk of death.

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.

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 including the two mentioned above 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.

Haloperidol Injection BP 5mg/1ml is not licensed for the treatment of dementia related behavioural disturbances.

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.

This medicinal product contains negligible amount of sodium i.e. 'essentially sodium-free'.

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 and elevated plasma CPK levels. Hyperthermia is often an early sign of this syndrome 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.

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. 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 this time, the full syndrome may not develop.

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).

Hepatobiliary 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.

Additional considerations:

It is recommended that patients being considered for this drug be initially put on oral haloperidol to exclude the possibility of an unexpected adverse sensitivity to it.

As with all antipsychotic agents, Haloperidol Injection 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.

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

It should only be used with great caution in patients with pheochromocytoma.

4.5 Interaction with other medicinal products and other forms of interactions

Use of haloperidol with concomitant QT prolonging drugs may result in additional QT prolongation and is not recommended (see section 4.3-Contraindications).

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 characterized 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 have been observed when haloperidol was given with a combination of the metabolic inhibitors ketoconazole (400mg/day) and paroxetine (20mg/day). It may be necessary to reduce the haloperidol dosage.

Use of drugs that cause electrolyte imbalance may increase the risk of ventricular arrhythmias during concomitant use of haloperidol (see Section 4.4- Special warnings and precautions for use).

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 significant reduction of haloperidol plasma levels. Therefore during combination treatment the Haloperidol dose or dosage interval should be adjusted, when needed. 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 been reported.

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

Haloperidol may impair the antiparkinsonian 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 the following symptoms were reported during the concomitant use of lithium and Haloperidol: encephalopathy, extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, brain stem disorder, acute brain syndrome and coma. Most of these symptoms were reversible. It remains unclear whether this represents a distinct clinical entity. Signs of encephalopathy-like syndrome include confusion, disorientation, headache, disturbances of balance and drowsiness. One report showing symptomless EEG abnormalities on the combination suggested that EEG monitoring might be advisable.

Nonetheless, it is advised that in patients who are treated concomitantly with lithium and Haloperidol, the Haloperidol should be given in the lowest effective dosage and lithium levels should be monitored and therapy should be stopped immediately if such

symptoms occur.

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

Concurrent use with anti-convulsants may require an increase in their dosage.

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

4.6 Pregnancy and lactation

Pregnancy

The safety of haloperidol in pregnancy has not been established and it should not be used during pregnancy unless considered essential by the physician. There is some evidence of harmful effects in some but not all animal studies. There are reports of two cases of limb malformations observed following maternal use of haloperidol along with other drugs which have suspected teratogenic potential. Causal relationship was not established.

Reversible extra-pyramidal symptoms have been observed in neonates exposed to haloperidol in utero during the last trimester of pregnancy.

Lactation:

Haloperidol 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. The user should not drive or operate machinery unless the drug has been shown not to interfere with his physical or mental ability.

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 Class	Organ	Adverse Drug Reactions
--------------	-------	------------------------

		Frequency Category				
		Very Common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 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; Muscle Contractions Involuntary; Sedation;	Neuroleptic malignant syndrome; Motor dysfunction; 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; Pruritus; Hyperhidrosis		Leukocytoclastic Vasculitis; Dermatitis Exfoliative
Musculoskeletal and Connective Tissue Disorders			Torticollis; Muscle rigidity; Muscle Spasms; Musculoskeletal stiffness	Trismus; Muscle Twitching	
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.

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 with a depot injection is unlikely when administered correctly. However the following are theoretical manifestations that might occur:

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

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:

There is no specific antidote to haloperidol, and treatment of overdose is primarily supportive. For comatose patients a patent airway should be established and maintained with mechanically assisted ventilation if necessary.

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

Hypotension and circulatory collapse should be treated by the use of intravenous fluids, plasma or concentrated albumin and vasopressor agents such as dopamine or noradrenaline. Adrenaline should not be used.

Severe extrapyramidal manifestations should be treated with antiparkinsonian medications and 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

Pharmacotherapeutic group: Butyrophenone Derivatives

ATC Code: N05A D01

Haloperidol Decanoate is an ester of haloperidol and decanoic acid and is, as such, a depot neuroleptic belonging to the butyrophenone group. After intramuscular injection, Haloperidol Decanoate is gradually released from muscle tissue and hydrolysed slowly into free haloperidol which enters the systemic circulation. Haloperidol Decanoate has no antihistaminergic or anticholinergic activity. As a direct consequence of the central dopamine blocking effect, Haloperidol Decanoate has an incisive activity on delusions and hallucinations and an activity on the basal ganglia.

5.2 Pharmacokinetic properties

Haloperidol is absorbed from the gastrointestinal tract, metabolised in the liver and excreted via urine and bile, with evidence of enterohepatic recycling. The drug is widely distributed and crosses the blood-brain barrier. It is extensively bound to plasma proteins. Haloperidol has a mean plasma half-life of 7 - 20 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

Lactic acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: 3 years.
The product should be used immediately after opening.

6.4 Special precautions for storage

Do not store above 25°C.
Keep ampoules in outer carton.

6.5 Nature and contents of container

1 ml, clear glass one-point-cut (OPC) ampoules, glass type I Ph. Eur. borosilicate glass packed in cardboard cartons to contain 10 x 1 ml ampoules.

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

For single use only. Discard any remaining solution after use.
Do not use if the solution is cloudy, discoloured or if there are any particles present.

7. MARKETING AUTHORISATION HOLDER

Antigen Pharmaceuticals Ltd.
Chandler House
Castle Street
Roscrea
Co. Tipperary

8. MARKETING AUTHORISATION NUMBER

PA 73/101/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 12 October 1988

10. DATE OF REVISION OF THE TEXT

October 2010