Public Assessment Report

Decentralised Procedure

Haloperidol 200micrograms/ml and 1mg/ml Oral Solution

(haloperidol)

Procedure number: UK/H/5717/001-002/DC

UK licence no: PL 39307/0024-0025

Syri Limited, t/a Thame Laboratories
LAY SUMMARY
Haloperidol 200micrograms/ml and 1mg/ml Oral Solution
(haloperidol)

This is a summary of the public assessment report (PAR) for Haloperidol 200micrograms/ml and 1mg/ml Oral Solution (PL 39307/0024-25; UK/H/5717/001-02/DC). It explains how Haloperidol 200micrograms/ml and 1mg/ml Oral Solution were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Haloperidol 200micrograms/ml and 1mg/ml Oral Solution.

The medicinal products may be referred to as Haloperidol Oral Solution in this lay summary for ease of reading.

For practical information about using Haloperidol Oral Solution, patients should read the package leaflets or contact their doctor or pharmacist.

What is Haloperidol Oral Solution and what is it used for?
Haloperidol Oral Solution is a ‘hybrid medicine’. This means it is similar to the reference medicine already authorised in the European Union (EU) called HALDOL TM 2 mg/ml Oral Liquid (Janssen-Cilag Limited) containing the same active substance but it differs in strength.

Haloperidol is used for illnesses that affect the way patients think, feel or behave. They may make patients:
- Feel confused
- See, hear or feel things that are not there (hallucinations)
- Believe things that are not true (delusions)
- Feel unusually suspicious (paranoia)
- Feel very excited, agitated, enthusiastic or hyperactive
- Feel very aggressive or violent.

Haloperidol is also used for Gilles de la Tourette syndrome and movements that can’t be controlled (tics) and hiccups that won’t go away.

How is Haloperidol Oral Solution used?
Haloperidol Oral Solution is taken by mouth. Patients must use the measuring syringe provided in the pack to deliver the required dose.

This medicine must be taken or given exactly as advised by the doctor. If unsure check with a doctor or pharmacist.

The dose will depend on:
- Age
- How serious symptoms are
- Whether a patient has other medical problems
- How a patient has reacted to similar medicines in the past.

The dose for children depends on their weight. Children will normally be given 0.025 to 0.05mg per kilogram body weight. Half the dose should be taken in the morning and the other half in the evening. The maximum dose children should take each day is 10mg.
The box containing 200micrograms/ml medicine will contain a 1ml dosing syringe, a 3 ml dosing syringe, and a syringe adaptor.

The 3ml oral syringe should be used when the dose volume to be administered is more than 1ml. A 1ml oral syringe is recommended when a dose volume of 1ml or less has to be given and when an additional volume of 0.1ml or more is required but less than 1 ml. If patients are unsure how to administer the medicine they should ask a pharmacist.

The box containing this medicine will contain a 1 ml dosing syringe, a 10 ml dosing syringe, and a syringe adaptor.

A 10ml oral syringe is recommended when a dose volume more than 1 ml has to be given. A 1ml oral syringe is recommended when a dose volume of 1ml or less has to be given and when an additional volume of 0.1ml or more is required but; less than 1 ml.

There are two different strengths available for this product: the 200micrograms/ml strength and 1mg/ml strength. Patients must check which of the two strengths has been prescribed for them. It should be noted that when using the 1ml syringe for a different strength, the volume will provide a different dose. For single dose of 0.5 mg or below (equivalent to 2.5ml or less of the 200micrograms/ml oral solution) the 200 micrograms/ml oral solution should be used. Any dosage greater than 0.5 mg (equivalent to more than 2.5ml of the 200micrograms/ml oral solution) should use the 1mg/ml oral solution.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription from a doctor.

**How does Haloperidol Oral Solution work?**

Haloperidol Oral Solution contains the active ingredient haloperidol, which belongs to a group of medicines called “neuroleptics”. They work by blocking dopamine D2 receptors in the dopaminergic pathways of the brain.

**What benefits of Haloperidol Oral Solution have been shown in studies?**

No additional studies were needed as this medicine is a hybrid medicine that is administered as an oral solution and contains the same active substance as the reference medicine, HALDOL TM 2 mg/ml Oral Liquid (Janssen-Cilag Limited).

**What are the possible side effects of Haloperidol Oral Solution?**

Like all medicines, Haloperidol Oral Solution can cause side effects, although not everybody gets them.

For information about side effects that may occur with taking Haloperidol Oral Solution, please refer to the package leaflets or the Summaries of Product Characteristics available on the MHRA website.

**Why is Haloperidol Oral Solution approved?**

The MHRA decided that this medicine’s benefits are greater than its risks and recommended that it be approved for use.
What measures are being taken to ensure the safe and effective use of Haloperidol Oral Solution?
A risk management plan has been developed to ensure that Haloperidol Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Haloperidol Oral Solution, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Haloperidol Oral Solution
The UK agreed to grant Marketing Authorisations for Haloperidol Oral Solution on 20 December 2016. Marketing Authorisations were granted in the UK on 05 January 2017. The Concerned Member State, Republic of Ireland, withdrew from the procedure prior to the grant of the Marketing Authorisation.

The full PAR for Haloperidol Oral Solution follows this summary.

This summary was last updated in February 2017.
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I Introduction

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Haloperidol 200micrograms/ml and 1mg/ml Oral Solution, are approvable.

These products are prescription-only medicines (legal status POM).

Haloperidol 200micrograms/ml is indicated for use in children when low doses of haloperidol need to be administered. The indications are:

- Childhood behavioural disorders, especially when associated with hyperactivity and aggression
- Gilles de la Tourette Syndrome
- Childhood schizophrenia.

Haloperidol 1mg/ml Oral Solution is used in adults and children. The indications are:

Adults:

- Schizophrenia: treatment of symptoms and prevention of relapse.
- Other psychoses: especially paranoid.
- Mania and hypomania
- Mental or behavioural problems such as aggression, hyperactivity and self-mutilation in the mentally retarded and in patients with organic brain damage.
- As an adjunct to short term management of moderate to severe psychomotor agitation, excitement, violent or dangerously impulsive behaviour.
- Intractable hiccup
- Gilles de la Tourette syndrome and severe tics.

Children:

- Childhood behavioural disorders, especially when associated with hyperactivity and aggression
- Gilles de la Tourette Syndrome
- Childhood schizophrenia

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). There was only one Concerned Member State (CMS), Republic of Ireland, which withdrew from the procedure prior to the grant of the Marketing Authorisation.

The applications for Haloperidol 200micrograms/ml and 1mg/ml Oral Solution were made under Article 10(3) of Directive 2001/83/EC, as amended, as so-called hybrid applications. The applicant has cross referred to HALDOL TM 2 mg/ml Oral Liquid (PL 00242/0035R) first authorised to Janssen-Cilag Limited on 07 June 1989.

Haloperidol acts as a central dopamine receptor antagonist. It also has some anticholinergic activity and binds to opiate receptors. It also acts at peripheral dopamine receptors.

No new non-clinical or clinical studies were conducted, which is acceptable given that these are hybrid applications, which are cross-referring to an oral solution. The product is an oral solution containing the same active substance as the currently authorised reference product. Thus, in accordance with the Guideline on the Investigation of Bioequivalence.
(CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the applicant was not required to submit bioequivalence studies for these applications.

A detailed Risk Management Plan has been submitted for these products and it is satisfactory.

The RMS has been assured that acceptable standards of GMP are in place for this product types at all sites responsible for the manufacture and assembly of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considered that the applications could be approved at the end of procedure (Day 210) on 20 December 2016. After a subsequent National phase, the UK granted a Marketing Authorisation (PL 39307/0024-0025) for these products on 05 January 2017.
II Quality aspects

II.1 Introduction
The finished product is an oral solution. Each ml of oral solution contains 200 micrograms or 1 mg of the active substance haloperidol.

Other ingredients consist of pharmaceutical excipients (S)-lactic acid, methyl parahydroxybenzoate (E218) and purified water.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients are sourced from animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

The finished products are supplied in amber (Type III) glass bottles containing 100ml and 200ml of the oral solution with a tamper evident, child resistant plastic cap consisting of a polypropylene, polyethylene and an expanded polyethylene (EPE) liner.

The 200micrograms/ml strength is supplied with a 1ml polypropylene oral syringe with 0.01ml graduation markings, a 3ml polypropylene oral syringe with 0.1ml graduation markings and a low density polyethylene (LDPE) syringe adaptor for the bottle.

The 1mg/ml strength is supplied with a 1ml polypropylene oral syringe with 0.01ml graduation markings, a 10ml polypropylene oral syringe with 0.5ml graduation markings and a low density polyethylene (LDPE) syringe adaptor for the bottle.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging are controlled to satisfactory standards and comply with relevant European Pharmacopoeia monograph and/or EU regulation requirements on plastic materials and articles intended to come in contact with food.

II.2 Drug Substance

Haloperidol

INN: Haloperidol
Chemical Name: 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one

Structure:

![Structure of Haloperidol](image)

Molecular formula: C_{21}H_{23}ClFNO_{2}
Molecular weight: 375.9 g/mol
Physical form: White or almost white powder.
Solubility: Haloperidol is practically insoluble in water, slightly soluble in ethanol (96%), in methanol and in methylene chloride.

Haloperidol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, haloperidol, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3 Medicinal Product
Pharmaceutical development
The objective of the pharmaceutical development programme was to obtain a stable oral solution containing haloperidol that could be considered as hybrid medicinal products of HALDOL TM 2 mg/ml Oral Liquid (Janssen-Cilag Limited).

Suitable pharmaceutical development data have been provided for these applications.

Comparative dissolution and impurity profiles have been provided for the proposed and reference products.

Manufacture of the products
Satisfactory batch formulae have been provided for the manufacture of the products, along with appropriate account of the manufacturing processes. The manufacturing processes have been validated at pilot-scale batch size and shown satisfactory results. The Marketing Authorisation holder has committed to performing process validation studies on consecutive full-scale production batches following grant of the marketing authorisations.

Product Specifications
The finished product specifications are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened bottle, with storage condition “Do not store above 25°C”. Once the bottle is opened, the product should be used within 30 days.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of Marketing Authorisations is recommended for these applications.

III Non-clinical aspects
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of haloperidol are well-known. As this is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.
The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since these products are intended for substitution of an originator product, their use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of these applications from a non-clinical point of view.

IV Clinical aspects
IV.1 Introduction
No new clinical data have been submitted and none are required for applications of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
No bioequivalence studies to compare the test and reference products have been conducted. The applicant has adequately justified the absence of bioequivalence studies in accordance with the CHMP Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr*#).

IV.3 Pharmacodynamics
No new pharmacodynamics data are required for these applications and none have been submitted.

IV.4 Clinical efficacy
No new clinical efficacy data are required for these applications and none have been submitted.

IV.5 Clinical safety
No new clinical safety data are required for these applications and none have been submitted.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Haloperidol 200micrograms/ml and 1mg/ml Oral Solution.
A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hypersensitivity to haloperidol or excipients</td>
<td>The risk of hypersensitivity to haloperidol or excipients of the drug product are described in the SPC Sections 4.3, 4.4 and 4.8, and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Cardiac arrhythmias (including QT – interval prolongation, torsade de pointes, ventricular arrhythmia)</td>
<td>The risks (1) of cardiac arrhythmias (including QT–interval prolongation, torsade de pointes, ventricular arrhythmia) associated with use of the drug product (2) associated with use of the drug product in patients with cardiac arrhythmias (including QT–interval prolongation, torsade de pointes, ventricular arrhythmia) and (3) associated with concomitant use of the drug product with drugs which prolong QT interval are described in the SPC Sections 4.3, 4.4, 4.5, 4.8, and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Hypotension</td>
<td>The risk of hypotension associated with use of the drug product is described in the SPC Section 4.8 and PIL Section 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>The risk of tardive dyskinesia associated with use of the drug product is described in the SPC Sections 4.4, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<tr>
<td>Extrapyramidal symptoms</td>
<td>The risk of extrapyramidal symptoms associated with use of the drug product is described in the SPC Sections 4.4, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome</td>
<td>The risk of NMS associated with the use of the drug product is described in the SPC Sections 4.4, 4.8 and PIL Section 4, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Central nervous system depression</td>
<td>The risk of CNS depression associated with use of the drug product are described in the SPC Sections 4.3, 4.4, 4.5, 4.7, 4.8 and PIL Sections 2, 4, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Concomitant use with lithium</td>
<td>The risks associated with concomitant use of the drug product with lithium are described in the SPC Section 4.5 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Concomitant use with CYP3A4 and CYP2D6 inhibitors</td>
<td>The risks associated with the concomitant use of the drug product with CYP3A4 and CYP2D6 inhibitors are described in the SPC Sections 4.4, 4.5 and PIL Section 2, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Seizures</td>
<td>The risk of seizures associated with use of the drug product is Sections 4.4, 4.5, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>The risk of hepatitis associated with use of the drug product is described in the SPC Sections 4.4,</td>
<td>None</td>
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<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<tr>
<td>Use in patients with hyperthyroidism</td>
<td>The risks associated with use of the drug product in patients with hyperthyroidism are described in the SPC Section 4.4 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
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</table>

**Important potential risk**

| Medication Error | The risks of medication error associated with use of the drug product are described in the SPC Sections 4.2, 6.6 and PIL Section 3 and appropriate advice is provided to the prescriber to minimise these risks. | None |
| Agranulocytosis and other blood dyscrasias | The risks of agranulocytosis and other blood dyscrasias associated with the use of the drug product are described in the SPC Section 4.8 and PIL Section 4 and appropriate advice is provided to the prescriber to minimise these risks. | None |
| Serious skin reactions (Steven Johnson syndrome, Toxic epidermal necrolysis) | The risks of serious skin reactions (Steven Johnson syndrome, Toxic epidermal necrolysis) associated with the use of the drug product are described in the SPC Section 4.8 and PIL Section 4 and appropriate advice is provided to the prescriber to minimise these risks. | None |
| Cerebrovascular adverse events | The risks of cerebrovascular adverse events associated with use of the drug product are described in the SPC Section 4.4 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks. | None |
| Increased mortality | The risk of increased mortality | None |
### IV.7 Discussion on the clinical aspects

The grant of Marketing Authorisations is recommended for these applications.

### V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet (PIL) was English.

The package leaflet meets the criteria for readability, as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

### VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with haloperidol is considered to have demonstrated the therapeutic value of the compound. The benefit risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The currently approved labelling is listed below:
Each ml of oral solution contains 1mg haloperidol.
This product also contains methyl parahydroxybenzoate (E218). Read the package leaflet for further information.

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN

PL 39307/0025  
POM

Administration:
For oral use.
Use as directed by your doctor.
Read the package leaflet before use.

Storage:
Do not store above 25°C.
Discard 30 days after first opening.
Discard date:______________
Haloperidol 1mg/ml Oral Solution

Each ml of oral solution contains 1mg haloperidol.

This product also contains methyl parahydroxybenzoate (E219).

Keep the package leaflet for further information.

Each pack contains the 100ml bottle of oral solution, adaptor and oral syringes

Thame Laboratories

Batch: EXP:

CR/UK/H/5717/01-2/DC
Haloperidol 1mg/ml Oral Solution

Each ml of oral solution contains 1mg haloperidol.

This product also contains methyl parahydroxybenzoate (E219).

For further information, please refer to the product leaflet.

Each pack contains the 200ml bottle of oral solution, adaptor and oral syringes.
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Steps taken after the initial procedure with an influence on the Public Assessment Report
(Type II variations, PSURs, commitments)

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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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</thead>
</table>