Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Haloperidol 1.5 mg Tablets
Haloperidol 5 mg Tablets
Haloperidol 10 mg Tablets

(haloperidol)

PL 44041/0147 - 0149

Noumed Life Sciences Limited

LAY SUMMARY

Haloperidol 1.5 mg, 5mg and 10 mg Tablets (haloperidol)

This is a summary of the Public Assessment Report (PAR) for Haloperidol 1.5 mg, 5 mg and 10 mg Tablets. It explains how these products 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 these products.

These products will be referred to as Haloperidol Tablets in this lay summary for ease of reading.

For practical information about using Haloperidol Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Haloperidol Tablets and what are they used for?

Haloperidol 5 mg and 10 mg Tablets:

These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) called Aloperidin 5 mg and 10 mg Tablets.

Haloperidol 1.5 mg Tablets

This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the European Union (EU) called Aloperidin 5 mg Tablets, albeit with certain differences. In this case, Haloperidol 1.5 mg Tablets are for a change in strength.

Haloperidol Tablets are used in adults, adolescents and children for illnesses affecting the way they think, feel or behave. These include mental health problems (such as schizophrenia and bipolar disorder) and behavioural problems.

These illnesses may make the patient:

- Feel confused (delirium)
- See, hear, feel or smell things that are not there (hallucinations)
- Believe things that are not true (delusions)
- Feel unusually suspicious (paranoia)
- Feel very excited, agitated, enthusiastic, impulsive or hyperactive
- Feel very aggressive, hostile or violent.

In adolescents and children, Haloperidol Tablets are used to treat schizophrenia in patients aged 13 to 17 years, and to treat behavioural problems in patients aged 6 to 17 years.

Haloperidol Tablets are also used:

- In adolescents and children aged 10 to 17 years and in adults for movements or sounds who can’t control (tics), for example in severe Tourette’s syndrome
- In adults to help control movements in Huntington’s disease.

Haloperidol Tablets are sometimes used when other medicines or treatments have not worked or caused unacceptable side effects.

How do Haloperidol Tablets work?
These medicines contain the active ingredient haloperidol which belongs to a group of medicines called 'antipsychotics'. It works by helping to restore the balance of certain natural substances in the brain (neurotransmitters).

How are Haloperidol Tablets used?
The pharmaceutical form of these medicines is a tablet and the route of administration is oral (via the mouth).

How much should the patient take
The patient's doctor will tell them how many tablets to take and for how long. Their doctor will also tell them whether to take this medicine one or more times a day. It may be some time before the patient feels the full effect of the medicine. The patient's doctor will normally give them a low dose to start, and then adjust the dose to suit them. It is very important the patient takes the correct amount.

The dose of haloperidol will depend on:
- The patient's age
- What condition the patient is being treated for
- Whether the patient has problems with their kidneys or liver
- Other medicines the patient is taking.

Adults
- The dose will normally be between 0.5 mg and 10 mg each day.
- The patient's doctor may adjust this to find the dose that suits them best.
- The highest dose adults should take depends on the condition they are being treated for and varies between 5 mg and 20 mg each day.

Elderly people
- Elderly people will normally start on 0.5 mg each day or half the lowest adult dose.
- The number of tablets the patient takes will then be adjusted until the doctor finds the dose that suits them best.
- The highest dose elderly people should take is 5 mg each day unless their doctor decides a higher dose is needed.

Children and adolescents 6 to 17 years of age
- The dose will normally be between 0.5 mg and 3 mg each day.
- Adolescents up to 17 years of age being treated for schizophrenia or behavioural problems may have a higher dose, up to 5 mg each day.

Taking Haloperidol Tablets
- Swallow the tablets with some water.
- 1.5 mg & 5 mg tablets: The score line is only there to help you break the tablet if you have difficulty swallowing it whole.
- 10 mg tablets: The tablet can be divided into equal doses.

For further information on how Haloperidol Tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Haloperidol Tablets have been shown in studies?
Because Haloperidol Tablets are generic / hybrid medicines, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent / therapeutically equivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Haloperidol Tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Haloperidol Tablets are generic / hybrid medicines and are bioequivalent / therapeutically equivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

Why were Haloperidol Tablets approved?
It was concluded that, Haloperidol Tablets have been shown to be comparable to and to be bioequivalent / therapeutically equivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Haloperidol Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Haloperidol Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the PIL, 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 and reviewed continuously.

Other information about Haloperidol Tablets
Marketing Authorisations for Haloperidol Tablets were granted in the United Kingdom (UK) on 18 October 2021.

The full PAR for Haloperidol Tablets follows this summary.

This summary was last updated in December 2021.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Haloperidol 1.5 mg, 5 mg and 10 mg Tablets (PL 44041/0147 - 0149) could be approved.

The products are approved for the following indications:
Adult patients aged 18 years and above

- Treatment of schizophrenia and schizoaffective disorder.
- Acute treatment of delirium when non-pharmacological treatments have failed.
- Treatment of moderate to severe manic episodes associated with bipolar I disorder.
- Treatment of acute psychomotor agitation associated with psychotic disorder or manic episodes of bipolar I disorder.
- Treatment of persistent aggression and psychotic symptoms in patients with moderate to severe Alzheimer's dementia and vascular dementia when non- pharmacological treatments have failed and when there is a risk of harm to self or others.
- Treatment of tic disorders, including Tourette's syndrome, in patients with severe impairment after educational, psychological and other pharmacological treatments have failed.
- Treatment of mild to moderate chorea in Huntington's disease, when other medicinal products are ineffective or not tolerated.

Paediatric patients
Treatment of:

- Schizophrenia in adolescents aged 13 to 17 years when other pharmacological treatments have failed or are not tolerated.
- Persistent, severe aggression in children and adolescents aged 6 to 17 years with autism or pervasive developmental disorders, when other treatments have failed or are not tolerated.
- Tic disorders including Tourette's syndrome, in children and adolescents aged 10 to 17 years with severe impairment after educational, psychological and other pharmacological treatments have failed.

Haloperidol is an antipsychotic belonging to the butyrophenones group. It is a potent central dopamine type D2 receptor antagonist, and at recommended doses, has low alpha-1 antiadrenergic activity and no antihistaminergic or anticholinergic activity.

These applications were approved under Regulation 51B and 52B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) and Article 10(3) of Directive 2001/83/EC, as amended), as a generic / hybrid medicines of suitable originator medicinal products, Aloperidin 5 mg and 10 mg Tablets that have been licensed within the EU for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for a generic / hybrid medicinal products of suitable reference products.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic / hybrid medicinal products of suitable reference products. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

National marketing authorisations were granted in the United Kingdom (UK) on 18 October 2021.

II QUALITY ASPECTS

II.1 Introduction

Each tablet contains 1.5 mg, 5 mg or 10 mg of haloperidol.

In addition to haloperidol, these products also contain the excipients calcium hydrogen phosphate (E341), maize starch and magnesium stearate (E572). Haloperidol 5 mg and 10 mg Tablets also contain iron oxide yellow (E172).

The finished products are packaged in PVC-Alu blister packs containing 28, 50, 56, 84 or 100 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

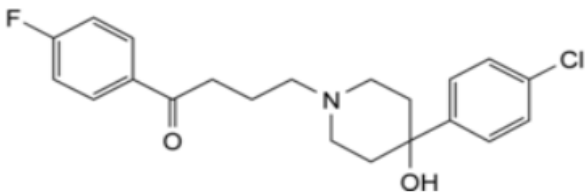
rINN: **Haloperidol**

Chemical Name: 4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one

Molecular Formula: $C_{21}H_{23}ClFNO_2$

Chemical Structure:

(Ph. Eur. monograph 0616)



Molecular Weight: 375.9

Appearance: White or almost white powder.

Solubility: 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 are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

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

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final products.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life 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 any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 30 months, with the storage conditions 'Store in the original package to protect from light', is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of haloperidol are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic / hybrid versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of haloperidol is well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence study:

STUDY
This study was an open label, balanced, randomised, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study comparing the test product Haloperidol 5 mg Tablets versus the reference product Aloperidin 5 mg Tablets in normal, healthy, adult, human subjects under fasted conditions.

Following an overnight fast of at least 10 hours, subjects were administered a single oral dose (5 mg) of either the test or reference product. Blood samples were taken pre-dose and up to 120 hours post dose, with a washout period of 18 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:
Table: Bioequivalence evaluation for haloperidol

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	100.3	96.74 - 103.90	5.5
C_{max}	101.9	91.59 - 113.29	16.5

[1] Estimated from the Residual Mean Squares.

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 5 mg product strength can be extrapolated to the other strengths.

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

IV.4 Clinical efficacy
No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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.

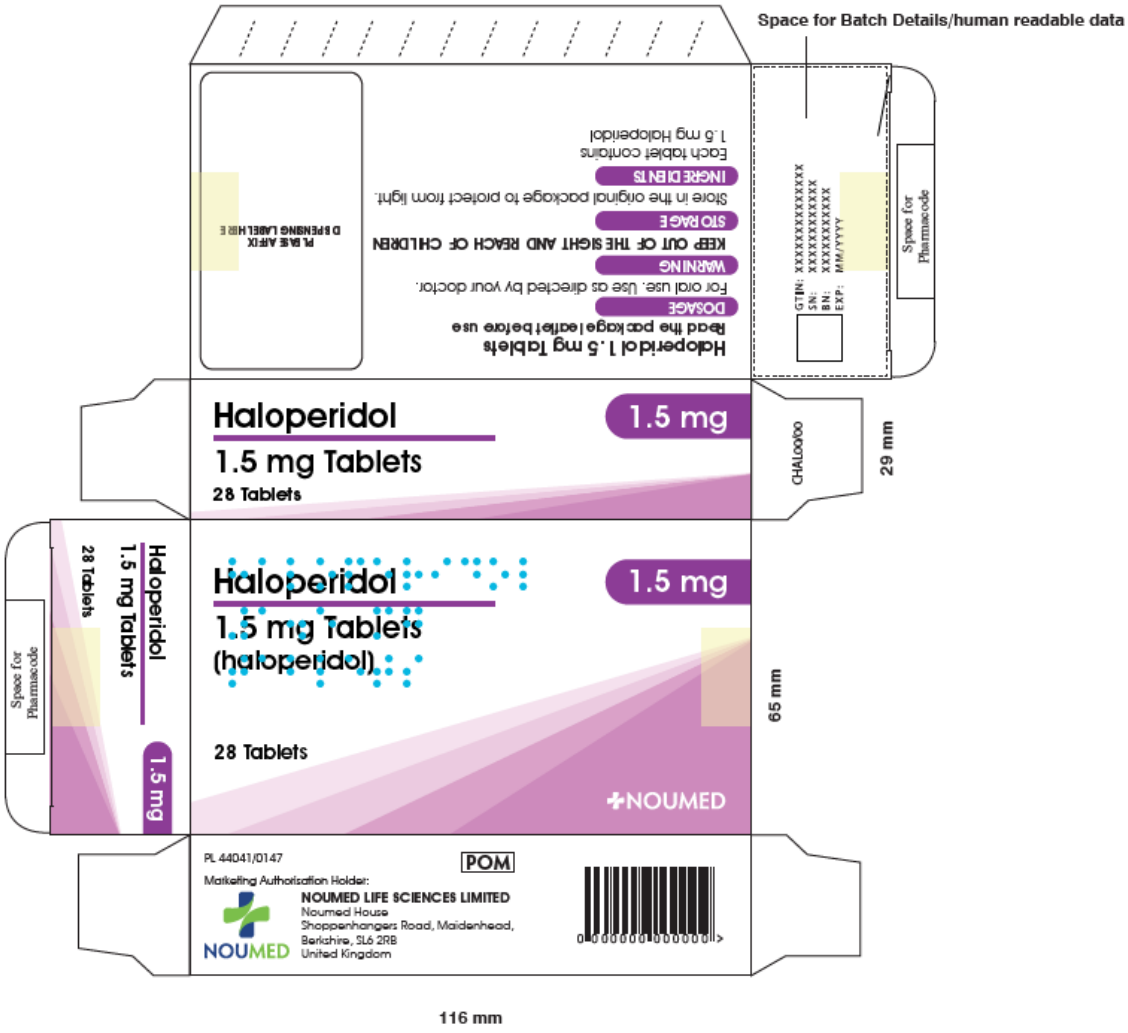
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

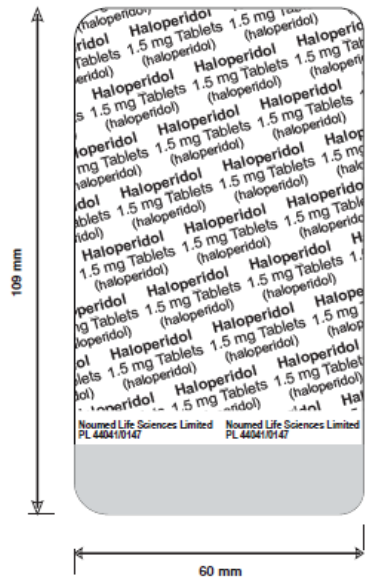
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with haloperidol is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

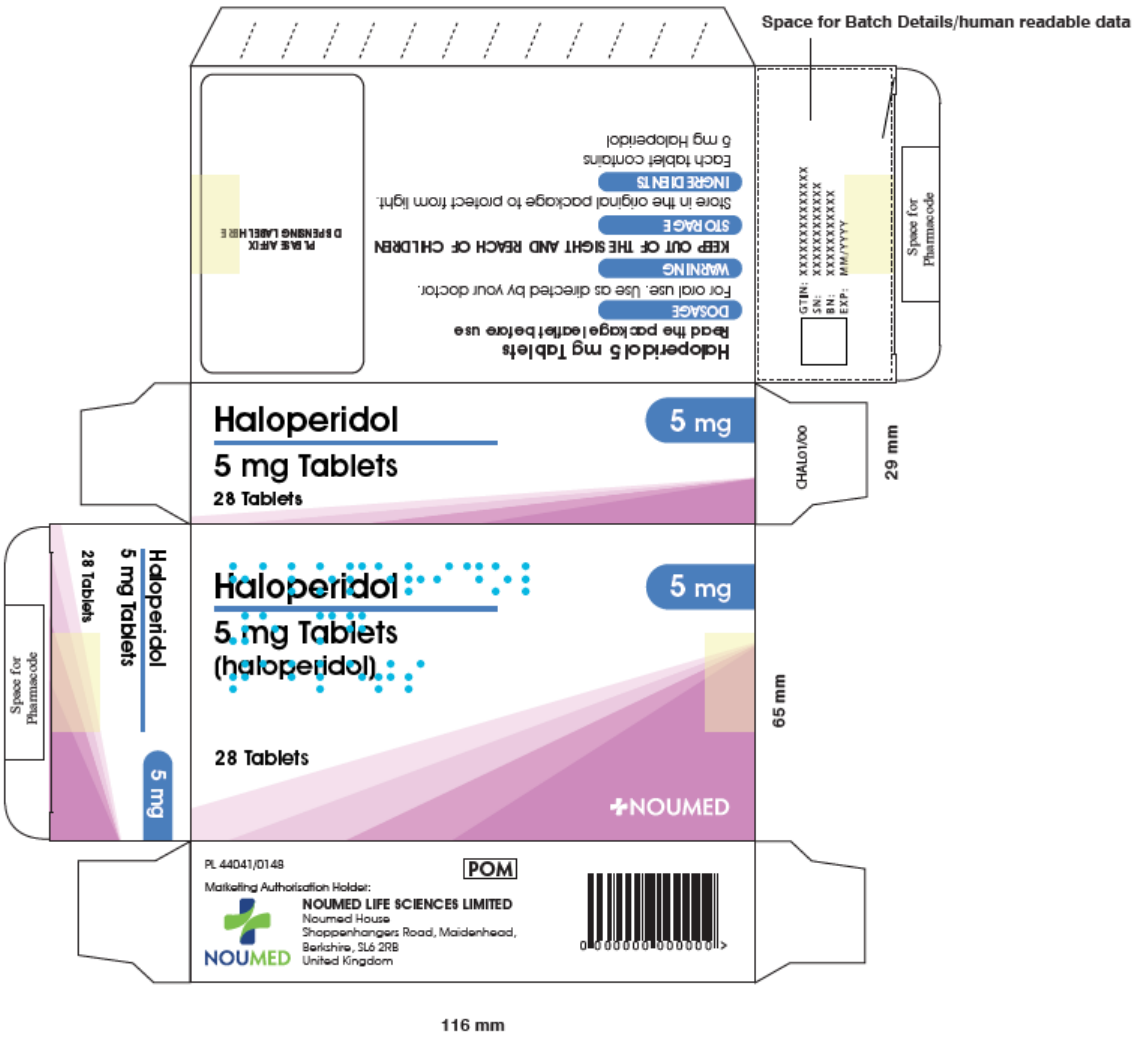
The Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

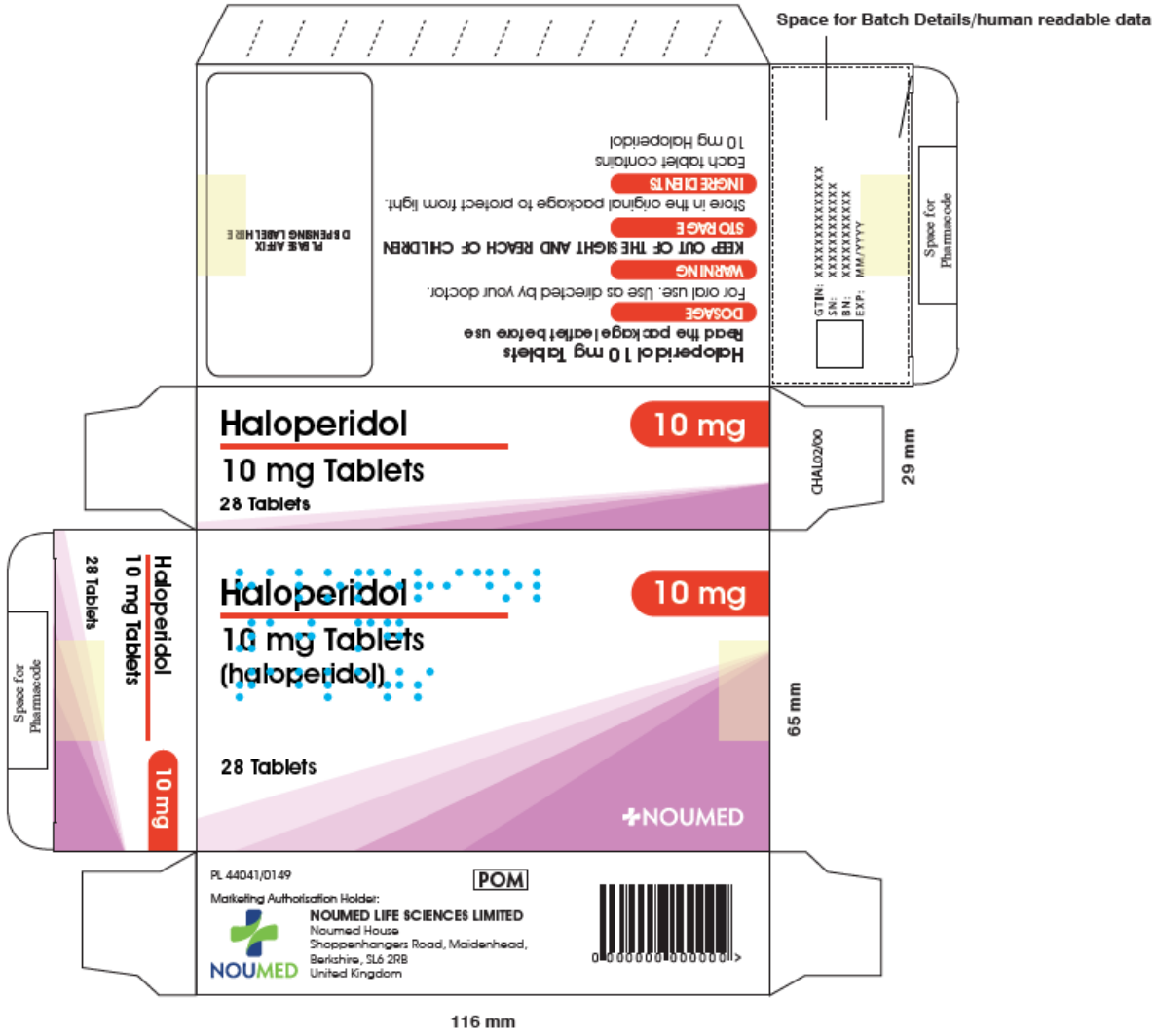
In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.


Space for Batch Details/human readable data
GTIN: XXXXXXXXXXXXX
SN: XXXXXXXXXXX
BN: XXXXXXXXXX
EXP: MM/YYYY
Space for Pharmacode
Haloperidol 1.5 mg Tablets
Read the package leaflet before use
DOSAGE
For oral use. Use as directed by your doctor.
WARNING
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN
STORAGE
Store in the original package to protect from light.
INGREDIENTS
Each tablet contains
1.5 mg Haloperidol
PLEASE AFFIX DISPENSING LABEL HERE
Haloperidol
1.5 mg Tablets
28 Tablets
1.5 mg
CHALOO/00
29 mm
Haloperidol
1.5 mg Tablets
(haloperidol)
28 Tablets
65 mm
NOUMED
PL 44041/0147
POM
Marketing Authorisation Holder:
NOUMED LIFE SCIENCES LIMITED
Noumed House
Shoppenhangers Road, Maidenhead,
Berkshire, SL6 2RB
United Kingdom
NOUMED
116 mm


Haloperidol 1.5 mg Tablets (haloperidol)
Noumed Life Sciences Limited PL 44041/0147
109 mm
60 mm


Space for Batch Details/human readable data
Haloperidol 5 mg Tablets
Read the package leaflet before use
DOSAGE
For oral use. Use as directed by your doctor.
WARNING
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN
STORAGE
Store in the original package to protect from light.
INGREDIENTS
Each tablet contains
5 mg Haloperidol
PLEASE AFFIX DISPENSING LABEL HERE
GTIN: XXXXXXXXXXXXX
SN: XXXXXXXXXX
BN: XXXXXXXXXX
EXP: MM/YYYY
Space for Pharmacode
Haloperidol
5 mg Tablets
28 Tablets
5 mg
CHALO1/00
29 mm
Haloperidol
5 mg Tablets
(haloperidol)
28 Tablets
5 mg
NOUMED
65 mm
PL 44041/0148
POM
Marketing Authorisation Holder:
NOUMED LIFE SCIENCES LIMITED
Noumed House
Shoppenhangers Road, Maidenhead,
Berkshire, SL6 2RB
United Kingdom
NOUMED
116 mm
109 mm
60 mm


Space for Batch Details/human readable data
Haloperidol 10 mg Tablets
Read the package leaflet before use
DOSAGE
For oral use. Use as directed by your doctor.
WARNING
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN
STORAGE
Store in the original package to protect from light.
INGREDIENTS
Each tablet contains
10 mg Haloperidol
GTIN: XXXXXXXXXXXXX
SN: XXXXXXXXXXXX
BN: XXXXXXXXXX
EXP: MM/YYYY
Space for Pharmacode
PLEASE AFFIX DISPENSING LABEL HERE
Haloperidol
10 mg Tablets
28 Tablets
10 mg
CHAL02/00
29 mm
Haloperidol
10 mg Tablets
(haloperidol)
28 Tablets
10 mg
65 mm
PL 44041/0149
POM
Marketing Authorisation Holder:
NOUMED LIFE SCIENCES LIMITED
Noumed House
Shoppenhangers Road, Maidenhead,
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109 mm

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**