Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Haloperidol 5mg/ml solution for Injection (haloperidol)

UK Licence No: PL 30684/0267

Dawa Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

Haloperidol 5mg/ml solution for Injection
(haloperidol)

This is a summary of the Public Assessment Report (PAR) for Haloperidol 5mg/ml solution for Injection (PL 30684/0267). It explains how the application for Haloperidol 5mg/ml solution for Injection was assessed and its authorisation recommended as well as the conditions of use. It is not intended to provide practical advice on how to use Haloperidol 5mg/ml solution for Injection.

For practical information about using Haloperidol 5mg/ml solution for Injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Haloperidol 5mg/ml solution for Injection and what is it used for?
Haloperidol 5mg/ml solution for Injection is a 'generic medicine'. This means that Haloperidol 5mg/ml solution for Injection is similar to a 'reference medicine' already authorised in the European Union (EU) called Haldol Injection.

Haloperidol 5mg/ml solution for Injection is used in adults for illnesses affecting the way people think, feel or behave. These include mental health problems (such as schizophrenia and bipolar disorder) and behavioural problems. Haloperidol 5 mg/ml solution for injection is also used in adults to help control movements in Huntington's disease and to prevent or treat nausea and vomiting (feeling and being sick) after surgery. Haloperidol 5 mg/ml solution for injection may be used on its own or with other medicines and is sometimes used when other medicines or treatments have not worked, caused unacceptable side effects, or cannot be taken by mouth.

How does Haloperidol 5mg/ml solution for Injection work?
This medicine contains the active ingredient haloperidol, which belongs to a group of medicines called antipsychotics. It helps to control and reduce symptoms by blocking the actions of dopamine (a chemical messenger) in the brain.

How is Haloperidol 5mg/ml solution for Injection used?
This medicine can only be obtained with a prescription.

A doctor will decide how much Haloperidol 5 mg/ml solution for injection the patient needs and for how long. It may be some time before the patient feels the full effect of the medicine. A doctor will normally give a low dose to start with, and then will adjust the dose to suit the patient. The dose of Haloperidol 5 mg/ml solution for injection will depend on the patient's age, the condition they are being treated for, whether they have kidney or liver problems and any other medicines they are taking.
In adults, the starting dose will normally be between 1 and 5 mg. Patients may be given extra doses, normally 1 to 4 hours apart. Patients will not be given more than a total of 20 mg each day.
Elderly people will normally start on half the lowest adult dose. The dose will then be adjusted until the doctor finds the dose that suits the patient best. Elderly people will not be given more than a total of 5 mg each day unless a doctor decides a higher dose is needed.
Haloperidol 5 mg/ml solution for injection is given by a doctor or nurse. It is for intramuscular use, and is given as an injection into a muscle.

What benefits of Haloperidol 5mg/ml solution for Injection have been shown in studies?
The company provided data from the published literature on haloperidol. No additional studies were needed as Haloperidol 5mg/ml solution for Injection is a generic medicine that is given as an injection and contains the same active substance, in the same concentration, as the reference medicine, Haldol Injection.

What are the possible side effects of Haloperidol 5mg/ml solution for Injection?
As Haloperidol 5mg/ml solution for Injection is a generic medicine, its possible side effects are taken as being the same as those of the reference medicine, Haldol Injection.

For the full list of all side effects reported with Haloperidol 5mg/ml solution for Injection, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why was Haloperidol 5mg/ml solution for Injection approved?
It was concluded that, in accordance with EU requirements, Haloperidol 5mg/ml solution for Injection has been shown to have comparable quality and to be comparable to Haldol Injection. Therefore, the MHRA decided that, as for Haldol Injection, the benefits outweigh the identified risks and recommended that Haloperidol 5mg/ml solution for Injection can be approved for use.

What measures are being taken to ensure the safe and effective use of Haloperidol 5mg/ml solution for Injection?
A risk management plan (RMP) has been developed to ensure that Haloperidol 5mg/ml solution for Injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Haloperidol 5mg/ml solution for Injection 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 5mg/ml solution for Injection
A Marketing Authorisation was granted in the UK on 27 September 2018.

The full PAR for Haloperidol 5mg/ml solution for Injection follows this summary. For more information about treatment with Haloperidol 5mg/ml solution for Injection, patients should read the package leaflet, or contact their doctor or pharmacist.

This summary was last updated in October 2018.

SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Dawa Limited a Marketing Authorisations for the medicinal product Haloperidol 5mg/ml solution for Injection (PL 30684/0267) on 27 September 2018.

This product is a prescription-only medicine (legal classification POM).

The application was made according to Article 10(1) of Directive 2001/83/EC, as amended. The reference product is Haldol Injection (PL 00242/0036R), which was granted a Marketing Authorisation to Janssen-Cilag Limited, in the UK, on 23 November 1988.

Haloperidol 5mg/ml solution for Injection is indicated in adult patients for:

- Rapid control of severe acute psychomotor agitation associated with psychotic disorder or manic episodes of bipolar I disorder when oral therapy is not appropriate.
- Acute treatment of delirium when non-pharmacological treatments have failed.
- Treatment of mild to moderate chorea in Huntington's disease, when other medicinal products are ineffective or not tolerated, and oral therapy is not appropriate.
- Single or combination prophylaxis in patients at moderate to high risk of postoperative nausea and vomiting, when other medicinal products are ineffective or not tolerated.
- Combination treatment of postoperative nausea and vomiting when other medicinal products are ineffective or not tolerated.

This product contains the active substance haloperidol, which is an antipsychotic belonging to the butyrophenones group. It is a potent central dopamine type 2 receptor antagonist, and at recommended doses, has low alpha-1 antiadrenergic activity and no antihistaminergic or anticholinergic activity. Haloperidol suppresses delusions and hallucinations as a direct consequence of blocking dopaminergic signalling in the mesolimbic pathway. The central dopamine blocking effect has activity on the basal ganglia (nigrostriatal bundles). Haloperidol causes efficient psychomotor sedation, which explains the favourable effect on mania and other agitation syndromes. The antidopaminergic effect on the chemoreceptor-trigger zone of the area postrema explains the activity against nausea and vomiting.

No new clinical or non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Haloperidol 5mg/ml solution for Injection is an aqueous solution at the time of administration and in line with the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), bioequivalence studies were not required.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of the product.

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

II QUALITY ASPECTS

II.1 Introduction

Haloperidol 5mg/ml solution for Injection is a colourless solution. Each ml of solution contains 5 mg of Haloperidol.

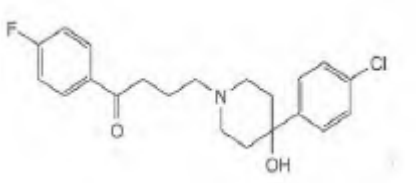
Other ingredients consist of the pharmaceutical excipients, namely lactic acid (pH modifier) and water for injections.

The finished product is packaged in 1ml clear One Point Cut (OPC) glass ampoules, glass type 1 Ph.Eur. borosilicate glass, packed in cardboard cartons in pack sizes of 5 x 1ml ampoules or 10 x 1ml ampoules.

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

II.2 Drug substance

rINN: Haloperidol
Ph. Eur name: Haloperidol
Chemical name: 4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one
Structure:



Molecular formula: $C_{21}H_{23}ClFNO_2$
Molecular weight: 375.9
Appearance: White or almost white powder

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

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a stable product that could be considered a generic medicinal product of Haldol Injection (Janssen-Cilag Limited).

A satisfactory account of the pharmaceutical development has been provided.

All the excipients comply with their respective European Pharmacopoeia monographs. None of the excipients are sourced from animal or human origin. This product does not contain or consist of genetically modified organisms (GMO).

Manufacturing Process

A Satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. Process validation has been carried out on three production scale batches. The results are satisfactory.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have

been adequately validated. Batch data have been provided and comply with the release specification. 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 finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 3 years for the unopened vial, with the special storage conditions of "Do not store above 25°C and Keep the ampoule in the outer carton in order to protect from light".

The product should be used immediately after opening.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for Haloperidol 5mg/ml solution for Injection.

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of haloperidol are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology

No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology

No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)

As this product is intended for generic substitution of products that are already marketed, no increase in environmental exposure to haloperidol is anticipated. Thus, the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for Haloperidol 5mg/ml solution for Injection.

IV. CLINICAL ASPECTS

IV.1 Introduction

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of haloperidol. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

A bioequivalence study was not submitted as the product meets the biowaiver criteria regarding parenteral solutions specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The test product is an aqueous solution at the time of administration and contains an active substance in the same concentration as the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy

No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical Safety

No new data on safety have been submitted and none are required for applications of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected

of occurring either in the Community or in a third country.

The MAH 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 5mg/ml solution for Injection.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Identified risk: Use in patients with Psychiatric disorders	**Text in SmPC Section 4.4 Special warnings and precautions for use** Cases of sudden death have been reported in psychiatric patients receiving antipsychotic drugs, including haloperidol.	None
Identified risk: Use in patients with Nervous system disorders	**Text in SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction** 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. **Text in SmPC Section 5.1Pharmacodynamic properties** Within the autonomic nervous system, haloperidol displays weak anticholinergic activities. Orthostatic hypotension that is mediated by a combination of central actions and peripheral alpha-adrenergic blockade, occurs less frequently during treatment with haloperidol in comparison with other antipsychotic therapy. Haloperidol binds to opiate receptors. **Text in SmPC 4.4 Special warnings and precautions for use:** 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 reinstituted, when the dosage is increased or when a switch is made to a different antipsychotic drug. Treatment should be discontinued as soon as possible.	None
Identified risk: Use in patients with Eye disorders (visual disturbance)	**Text in SmPC Section 4.7 Effects on ability to drive and use machines** Haloperidol may cause blurred vision. Patients should be advised not to undertake activities such as to drive or operate machinery during treatment.	None
Identified risk: Use in patients with Vascular disorders	**Text in SmPC Section 5.1Pharmacodynamic properties** Haloperidol is a central dopamine antagonist. It also	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	has some anticholinergic properties and is an opiatereceptor antagonist, and acts at peripheral dopamine receptors.	
Identified risk: Use in patients with Skin and subcutaneous tissue disorders (Rash, photosensitivity)	**Text in PIL section 4 Possible side effects:** Swelling of the face or throat. Hives (also known as nettle rash or urticaria), severe irritation, reddening or blistering of your skin. These may be signs of a severe allergic reaction. This only happens in a small number of people.	None
Identified risk: Use in patients with Cardiac disorders (Ventricular Fibrillation, Torsade de pointes, Ventricular Tachycardia, Extrasystoles, Electrocardiogram QT prolonged)	**Text in SmPC Section 4.3 Contraindications** In common with other neuroleptics, haloperidol has the potential to cause rare prolongation of the QT interval. Use of haloperidol is therefore contra-indicated in patients with clinically significant cardiac disorders (e.g. recent acute myocardial infarction, uncompensated heart failure, arrhythmias treated with class IA and III anti-arrhythmic medicinal products), QTc interval prolongation, history of ventricular arrhythmia or Torsades de pointes, clinically significant bradycardia, second or third degree heart block and uncorrected hypokalaemia. Known hypersensitivity to amantadine or any of the excipients may occur. **Text in SmPC Section 4.4 Special warnings and precautions for use** The risk-benefit of haloperidol treatment should be fully assessed before treatment is commenced and patients with risk factors for ventricular arrhythmias such as cardiac disease; family history of sudden death and/or QT prolongation; uncorrected electrolyte disturbances; subarachnoid haemorrhage; starvation; alcohol abuse should be monitored carefully (ECGs and potassium levels), particularly during the initial phase of treatment, to obtain steady plasma levels.	None
Identified risk: Use in patients with Gastrointestinal disorders	**Text in SmPC 4.4 Special warnings and precautions for use:** Acute withdrawal symptoms including nausea, vomiting and insomnia have been very rarely described after abrupt cessation of high doses of antipsychotic drugs. Relapse may also occur and gradual withdrawal is advisable. **Text in SmPC 4.8 Undesirable effects:** Haloperidol is also indicated for Constipation, Dry	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	mouth, Salivary hypersecretion, Nausea.	
Identified risk: Use in patients with Hepatobiliary disorders (diaphoresis)	**Text in SmPC 4.4 Special warnings and precautions for use:** 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.	None
Identified risk: Use in patients with Renal and Urinary disorders	**Text in SmPC 4.4 Special warnings and precautions for use:** Caution is advised in patients with renal failure and pheochromocytoma.	None
Identified risk: Use in patients with Reproductive System Disorders (Menorrhagia, Menstrual Disorder, Sexual Dysfunction, Erectile dysfunction)	**Text in SmPC 4.8 Undesirable effects:** Symptoms like Erectile dysfunction, Menstrual Disorder, Sexual Dysfunction may cause.	None
Identified risk: Use in patients with Respiratory, thoracic and mediastinal Disorders (Dyspnoea, Bronchospasm)	**Text in SmPC 4.8 Undesirable effects:** Respiratory problems may cause with symptoms like dyspnoea and bronchospasm.Symptoms like difficulty in breathing, bronchospasm may have reported in the people.	None
Potential risk: Use in patients with Metabolic and Nutritional Disorders (Hypoglycemia)	**Text in SmPC 4.8 Undesirable effects:** This effect shown in less than 1 in 100 taking this medication. It is uncommon within the people. Symptoms like Hypoglycemia may cause. **Text in SmPC Section 4.4 Special warnings and precautions for use:** Very rare cases of hypoglycaemia and of Syndrome of Inappropriate ADH Secretion have been reported due to hormonal ffects.	None
Potential risk: Use in patients with Hepatobiliary Disorders (Acute Hepatic Failure, Cholestasis)	**Text in SmPC Section 4.8 Undesirable effects:** Symptoms like acute hepatic failure, cholestatis, heart disorders may be cause.	None
Potential risk: Use in patients with	**Text in SmPC Section 4.4 Special warnings and precautions for use:**	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Reproductive System Disorder (Gynaecomastia, Priapism)	Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligo- or amenorrhoea.	
Potential risk: Use in patients with Respiratory, thoracic and mediastinal Disorders (Laryngeal Oedema, Laryngospasm)	**Text in SmPC Section 4.8 Undesirable effects:** Symptoms like Laryngeal Oedema, Laryngospasm may be cause.	None
Missing risk: Use in patients with Overdose	**Text in SmPC 4.9 Overdose:** In general, the manifestations of haloperidol overdosage are an extension of its pharmacological actions, the most prominent of which would be severe extrapyramidal symptoms, hypotension and psychic indifference with a transition to sleep. The risk of ventricular arrhythmias possibly associated with QT-prolongation should be considered. The patient may appear comatose with respiratory depression and hypotension which could be severe enough to produce a shock-like state. Paradoxically hypertension rather than hypotension may occur. Convulsions may also occur.	None

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Haloperidol 5mg/ml solution for Injection.

V. USER CONSULTATION

The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

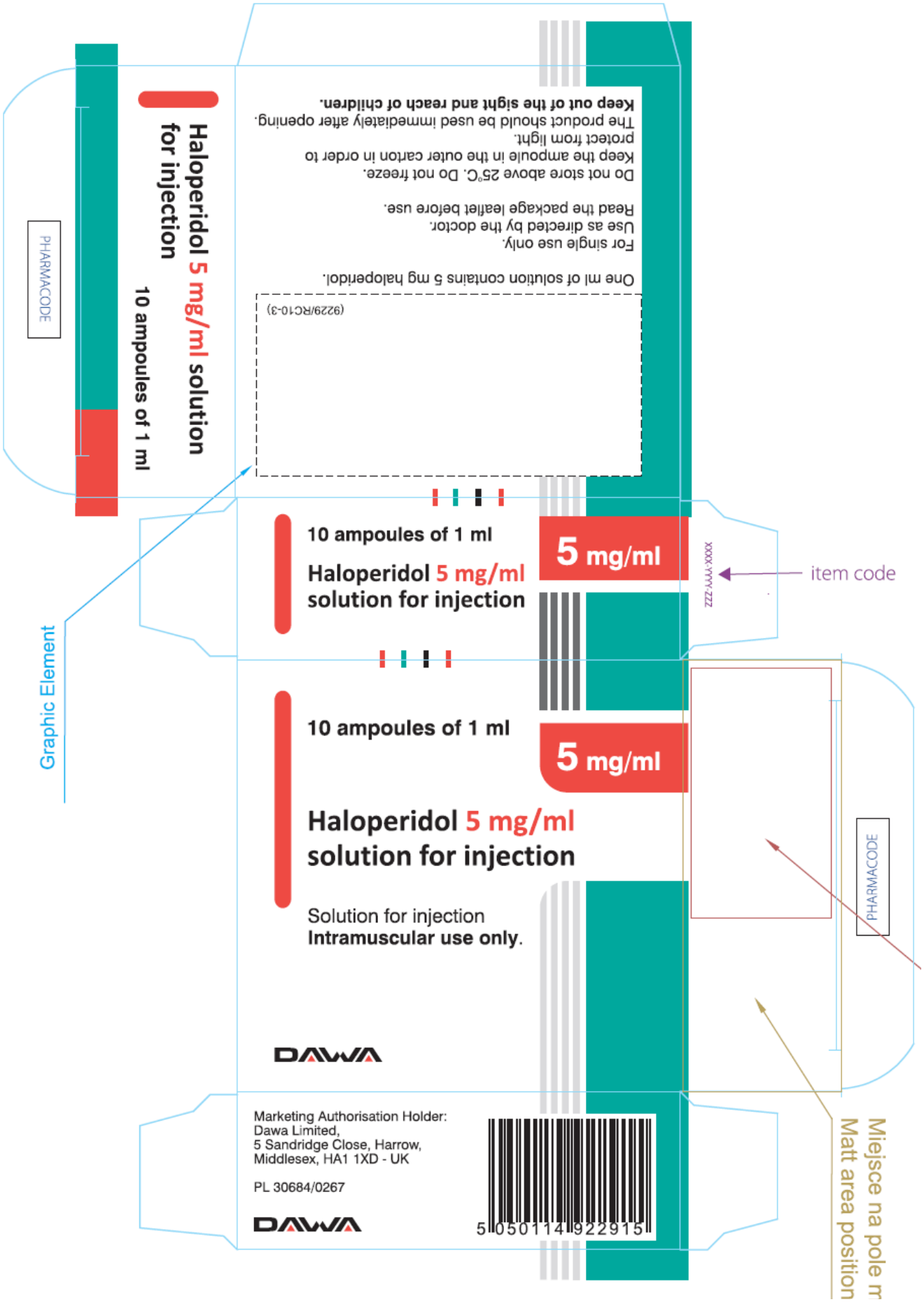
VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

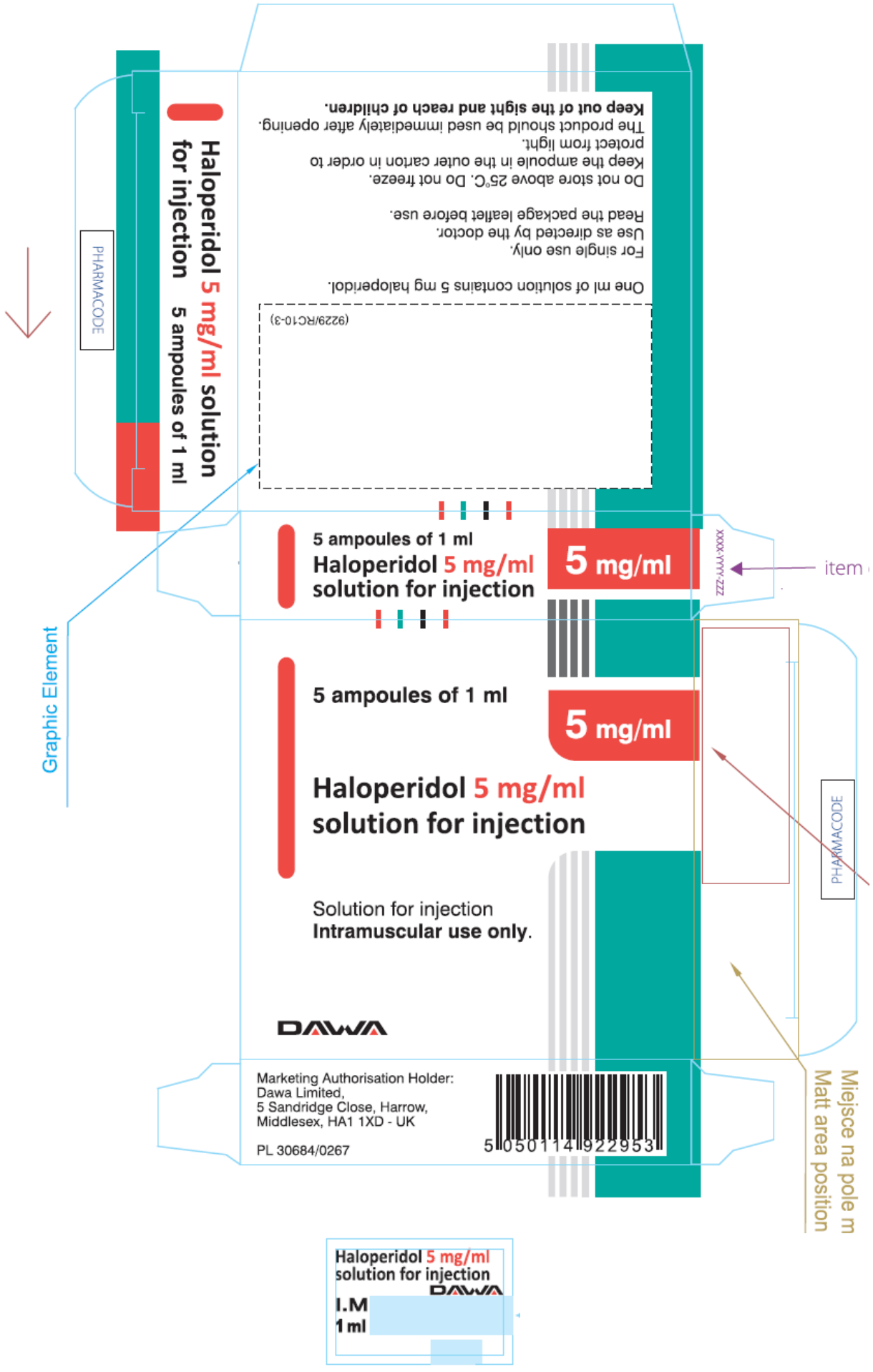
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant's product and the reference product are interchangeable. Extensive clinical experience with haloperidol is considered to have demonstrated 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 Labels

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

The approved labelling for Haloperidol 5mg/ml solution for Injection is presented below:


Haloperidol 5 mg/ml solution for injection
10 ampoules of 1 ml
PHARMACODE
(9229/RC10-3)
One ml of solution contains 5 mg haloperidol.
For single use only.
Use as directed by the doctor.
Read the package leaflet before use.
Do not store above 25°C. Do not freeze.
Keep the ampoule in the outer carton in order to protect from light.
The product should be used immediately after opening.
Keep out of the sight and reach of children.
10 ampoules of 1 ml
Haloperidol 5 mg/ml solution for injection
5 mg/ml
xxxx-yyyy-zzz
item code
Graphic Element
10 ampoules of 1 ml
5 mg/ml
Haloperidol 5 mg/ml solution for injection
Solution for injection
Intramuscular use only.
PHARMACODE
DAWA
Marketing Authorisation Holder:
Dawa Limited,
5 Sandridge Close, Harrow,
Middlesex, HA1 1XD - UK
PL 30684/0267
DAWA
5 050114 922915
Miejsce na pole m
Matt area position


Haloperidol 5 mg/ml solution for injection
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(9229/RC10-3)
5 ampoules of 1 ml
Haloperidol 5 mg/ml solution for injection
5 mg/ml
XXXX-YYYY-ZZZ
item
Graphic Element
5 ampoules of 1 ml
5 mg/ml
Haloperidol 5 mg/ml solution for injection
Solution for injection
Intramuscular use only.
DAWA
Marketing Authorisation Holder:
Dawa Limited,
5 Sandridge Close, Harrow,
Middlesex, HA1 1XD - UK
PL 30684/0267
5 050114 922953
PHARMACODE
Miejsce na pole m
Matt area position
Haloperidol 5 mg/ml solution for injection
DAWA
I.M
1 ml

Annex 1 Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)