IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Droperidol 0.5 mg/ml solution for injection
Droperidol
PA22835/005/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Droperidol 0.5 mg/ml Solution for Injection, from Sintetica GmbH on 17th July 2023 for prevention and treatment of post-operative nausea and vomiting (PONV) in adults including that caused by morphine and derivatives and, as second line, in children (2 to 11 years) and adolescents (12 to 18 years)

With Ireland as the Reference Member State, a marketing authorisation is applied for in IE, DK, FI, IS, NO, SE, RO and IT under procedure IE/H/1217/001/DC. This decentralised application is submitted as a generic application according to Article 10(1) of Directive 2001/83/EC. The active substance, droperidol, is not considered a new active substance.

The reference product is Xomolix 0.5mg/ml Solution for Injection (MAH: Kyowa Kirin Holdings B.V) authorised in Ireland since 16 September 2011.

Nationally this is a prescription only medicine which may not be renewed (category A).

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Droperidol 0.5 mg/ml Solution for Injection
Name(s) of the active substance(s) (INN)	Droperidol
Pharmacotherapeutic classification (ATC code)	N05AD08
Pharmaceutical form and strength(s)	0.5 mg/ml Solution for Injection
Marketing Authorisation Number(s) in Ireland (PA)	PA22835/005/001
Marketing Authorisation Holder	Sintetica GmbH
MRP/DCP No.	IE/H/1217/001/DC
Reference Member State	IE
Concerned Member State	DK FI IS IT NO RO SE

II. QUALITY ASPECTS

This application is for Droperidol 0.5 mg/ml Solution for Injection.

II.2 Drug substance

The active substance is droperidol, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The finished product is a solution for injection containing 0.5 mg/ml of droperidol.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Droperidol 0.5 mg/ml solution for injection.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the European/Irish market for 12 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

III.5 Ecotoxicity/environmental risk assessment

Since droperidol is intended for generic substitution, an increase in environmental exposure is not anticipated. Environmental risk assessment studies are not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Droperidol are well known. As Droperidol is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Droperidol is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during this decentralised procedure is in accordance with that accepted for the reference product, Xomolix 0.5mg/ml Solution for Injection marketed by MAH: Kyowa Kirin Holdings B.V)

This is a generic application; therefore, additional clinical studies are not required as bioequivalence has been established. Furthermore, as this is parenteral administration (administered intravenously) bioequivalence studies are not required in accordance with the EMA guideline on the investigation of bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr).

The submitted clinical efficacy and safety overviews are based on the reference product data and on recent clinical data available in literature which further corroborate the positive risk-benefit balance of droperidol intended for intravenous use.

IV.2 Pharmacokinetics

The action of a single intravenous dose of droperidol commences 2-3 minutes following administration. The tranquillising and sedative effects tend to persist for 2 to 4 hours, although alertness may be affected for up to 12 hours.

Distribution: Following intravenous administration, plasma concentrations fall rapidly during the first 15 minutes; this is metabolismindependent, redistribution of the drug. Plasma protein binding amounts to 85-90%. The distribution volume is approximately 1.5 l/kg.

Biotransformation: Droperidol is extensively metabolised in the liver, and undergoes oxidation, dealkylation, demethylation and hydroxylation by cytochrome P450 isoenzymes 1A2 and 3A4, and to a lesser extent by 2C19. The metabolites are devoid of neuroleptic activity.
Elimination: Elimination occurs mainly through metabolism; 75% is excreted via the kidneys. Only 1% of the active substance is excreted unchanged with urine, and 11% with faeces. Plasma clearance is 0.8 (0.4 - 1.8) l/min. The elimination half-life (t ½ß) is 134 ± 13 min.

Drug Interactions: A study combining ondansetron (4 mg) and droperidol (1 mg) showed that when administered together there was no pharmacokinetic interaction between the two drugs

IV.3 Pharmacodynamics
Pharmacotherapeutic group: Butyrophenone derivatives, ATC code: N05AD08.

Mechanism of action:
Droperidol is a butyrophenone neuroleptic. Its pharmacologic profile is characterised mainly by dopamine-blocking and weak α1-adrenolytic effects. Droperidol is devoid of anticholinergic and antihistaminic activity. Droperidol's inhibitory action on dopaminergic receptors in the chemoreceptor trigger zone in the area postrema, gives it a
potent antiemetic effect, especially useful for the prevention and treatment of postoperative nausea and vomiting and/or induced by opioid analgesics.

IV.4 Clinical Efficacy

This is a generic application, therefore additional clinical studies are not required as bioequivalence has been established. Furthermore, as this is parenteral administration (administered intravenously) bioequivalence studies are not required in accordance with the EMA guideline on the investigation of bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). The clinical efficacy overview is based on the reference product data and on recent clinical data available in literature. Information provided in this clinical overview is bridged with the SmPC of the reference product and available literature data on droperidol used in the prevention and treatment of PONV.

IV.5 Clinical Safety

The clinical safety overview is based on the reference product data and on recent clinical data available in literature. Information provided in the clinical overview is bridged with the SmPC of the reference product and available safety literature data on droperidol used in the prevention and treatment of PONV.

QT prolongation during treatment with droperidol has been identified as a risk in particular in cases of:

- Use of a high dose of droperidol
- QT interval prolonged at baseline
- Use of concomitant QT prolonging drugs
- Administration to patients suffering from cardiac disease, including patients with coronary artery disease.

These risk categories have been fully identified in the Summary of Product Characteristics. As a prevention measure, droperidol remains contraindicated in patients with suspected prolongation of the QT interval or with congenital long QT syndrome.

All contraindications to use, warnings and potential interactions are outlined in the Product Information. (PI)

The most frequently reported adverse events during clinical experience are incidents of drowsiness and sedation. In addition, less frequent reports of hypotension, cardiac arrhythmias, neuroleptic malignant syndrome (NMS) and symptoms associated with NMS, plus movement disorders, such as dyskinesias, plus incidents of anxiety or agitation have occurred. For further details and full list of potential adverse reactions please review the PI.

The MAH has submitted a risk management plan, 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 Droperidol 0.5 mg Solution for Injection. Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the MAH which is endorsed.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the MAH which is endorsed.

For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

IV.6 Discussion on the clinical aspects

This is a generic application, the application dossier has been submitted in accordance with the Directive 2001/83/EC, as amended as a generic 10.1 application.

The reference product is well established in the EU being authorised since 2011. Droperidol has demonstrated efficacy and has a well-established documented safety profile.

This is a generic application, therefore additional clinical studies are not required as bioequivalence has been established. Furthermore, as this is parenteral administration (administered intravenously) bioequivalence studies are not required in accordance with the EMA guideline on the investigation of bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr).

The product information is in line with that of the reference product.

V. OVERALL CONCLUSIONS

Droperidol 0.5 mg/ml Solution for Injection, from Sintetica GmbH is a generic form of The Xomolix 0.5mg/ml Solution for Injection (MAH: Kyowa Kirin Holdings B.V) authorised in Ireland since 16 September 2011.

Xomolix 0.5mg/ml Solution for Injection is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Droperidol 0.5 mg/ml Solution for Injection, from Sintetica GmbH demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

06.06.2028