IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Hydromorphone-HCl Krugmann 1.3 mg capsules, hard
HYDROMORPHONE HYDROCHLORIDE
PA1688/022/001

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 Hydromorphone-HCl Krugmann 1.3mg & 2.6mg Capsule hard from Mundipharma Pharmaceuticals Limited on 17th September 2021 for the treatment of severe pain.
This application for a marketing authorisation was submitted in accordance with Article 10c of Directive 2001/83/EC and is referred to as an 'informed consent' application. This means that the Marketing Authorisation Holder for Palladone 1.3mg and 2.6mg capsules, an authorised medicinal product in Europe, has permitted the applicant to refer to their dossier to obtain an authorisation for hydromorphone.. Hydromorphone has the same qualitative and quantitative composition in terms of actives substances and the same pharmaceutical form as Palladone 1.3mg and 2.6mg capsules.

IE was the Reference Member State for this decentralised procedure, with DE as CMS.

Hydromorphone is a prescription only medicine.

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

Name of the product	Hydromorphone-HCl Krugmann 1.3mg & 2.6mg Capsule hard
Name(s) of the active substance(s) (INN)	HYDROMORPHONE HYDROCHLORIDE
Pharmacotherapeutic classification (ATC code)	N02AA03
Pharmaceutical form and strength(s)	1.3mg & 2.6mg Capsule hard
Marketing Authorisation Number(s) in Ireland (PA)	PA1688/022/001-002
Marketing Authorisation Holder	Mundipharma Pharmaceuticals Limited
MRP/DCP No.	IE/H/1093/001-002/DC
Reference Member State	IE
Concerned Member State	DE

II. QUALITY ASPECTS

This application is for Hydromorphone-HCl Krugmann 1.3mg & 2.6 Capsule hard

II.2 Drug substance

The active substance is Hydromorphone Hydrochloride, an established 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

Composition of the medicinal product
Hydromorphone-HCl Krugmann 1.3mg capsules contain hydromorphone hydrochloride 1.30 mg equivalent to 1.16 mg hydromorphone.
Hydromorphone-HCl Krugmann 2.6mg capsules contain hydromorphone hydrochloride 2.60 mg equivalent to 2.32 mg hydromorphone.

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 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. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for Capsules, 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 Hydromorphone-HCl Krugmann 1.3mg & 2.6 Capsules.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Pallodone 1.3 mg and 2.6 mg Capsules on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

The company have performed an environmental risk assessment, the results of which are described in the following table.

Summary of main study results

Substance (INN/Invented Name): hydromorophone hydrochloride					
CAS-number (if available): 466-99-9					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	< -1.14 and 0.707 within pH range 4.0-9.0			Potential PBT (N)
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	0.12	mg/L			> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 150.4			
Ready Biodegradability Test	OECD 301	N/A			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ =9- 11 d $DT_{50,\ sediment}$ = 25-37 d $DT_{50,\ whole\ system}$ = >10% % shifting to sediment =			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	≥ 93	mg/L	Highest conc tested
Daphnia sp. Reproduction Test	OECD 211	NOEC	9.5	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	5.4	mg/L	Fathead minnow; NOEC used for risk assessment (PNEC)
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	7.8	mg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	238	mg/kg	Chironomids

Conclusions on studies:

Hydromorphone hydrochloride is not a PBT substance. Considering the above data, hydromorophone hydrochloride is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of hydromorphone hydrochloride are well known. As hydromorphone hydrochloride is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable for this type of application. Based on the results of the environmental risk assessment, hydromorphone hydrochloride is not expected to pose a risk to the environment. Nonclinical sections of the SmPC are in line with the originator which is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Palladone.

Hydromorphone is a well-known active substance with established efficacy and tolerability. This medicinal product is the same as Palladone on the European market.

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IV.2 Pharmacokinetics

Hydromorphone is absorbed from the gastrointestinal tract and undergoes pre-systemic elimination resulting in a mean oral bioavailability of about 32% (range 17-62%). In vitro studies have demonstrated limited (approximately 8%) binding of hydromorphone to serum proteins, which was independent of total hydromorphone concentration up to the highest concentration examined (80 ng.ml-1). This plasma level exceeds the maximum anticipated in normal clinical practice. Unlike morphine, hydromorphone is not metabolised to an active 6-glucuronide. Instead, it is extensively metabolised to hydromorphone-3-glucuronide. After a single oral dose to opioid naive individuals, hydromorphone is excreted primarily in urine as hydromorphone-3-glucuronide, with unconjugated hydromorphone, dihydroisomorphine and dihydromorphine accounting for 5.6%, 1.0% and 0.1% of the dose, respectively.

Hydromorphone should be used with caution in patients with renal or hepatic impairment, especially as the pharmacological activity of hydromorphone-3-glucuronide is not fully established, although the data provided by the applicant would indicate that it has low, if any, activity.

A terminal elimination phase associated with a half-life of around 17 hours has been identified for hydromorphone, which follows the shorter half-life of around four hours. This longer half-life determines the extent of linear accumulation to steady state and explains the difference between the plasma concentrations associated with a single dose in healthy volunteers and those recorded in patients following multiple dosing. A similar terminal phase has been reported for morphine.

IV.3 Pharmacodynamics

Hydromorphone is a semi-synthetic congener of morphine, differing structurally from morphine by the substitution of oxygen for the 6-hydroxyl group and the hydrogenation of the 7-8 double bond of the morphine molecule. Like morphine, hydromorphone is a 1 selective full opioid agonist; their pharmacological actions do not differ significantly. Hydromorphone and related opioids produce their major effects on the central nervous and gastrointestinal systems. The effects are diverse and include analgesia, drowsiness, changes in mood, respiratory depression, decreased gastrointestinal motility, nausea, vomiting and alterations of the endocrine and autonomic nervous systems.

IV.4 Clinical Efficacy

The efficacy and safety of hydromorphone in this indication are well established, and are illustrated in both original assessment reports and in the known bibliography. There have been no significant adverse event reports outside of those which would be expected for this class of medicinal product.

Hydromorphone is a strong opioid analgesic which is generally considered as second-line therapy in patients whose severe pain cannot be controlled using morphine.

IV.5 Clinical Safety

As above

Risk Management Plan

Safety specification

Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

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

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Periodic Safety Update Reports (PSURs) should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

Overall, the clinical efficacy and sfety characteristics of the product are acceptable and in line with the reference product.

V. OVERALL CONCLUSIONS

Hydromorphone-HCl 1.3mg and 2.6mg capsules are the same as Palladone 1.3mg and 2.6mg capsules . Palladone 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.

Based on the nature of the application and the information provided both by the applicant and what is already known about the product, the RMS considers that the benefit risk profile of this product is positive.

The HPRA, on the basis of the data submitted considered that Hydromorphone-HCl was the same as the reference product and therefore granted a marketing authorisation.

VI. REVISION DATE

19.03.2026

VII. UPDATES

Thissection reflects the significant changes following finalisation of the initialprocedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE