IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Hydrocortisone 5 mg Tablet
Hydrocortisone
PA22865/003/003

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 Hydrocortisone 5mg Tablet, from Renata Pharmaceuticals (Ireland) Limited on 2nd February 2024 for Use as replacement therapy in primary, secondary or acute adrenocortical insufficiency and pre-operatively, during serious trauma or illness in patients with known adrenal insufficiency or doubtful adrenocortical reserve.

The marketing authorisation application for Hydrocortisone 5mg Tablets is being submitted as a hybrid application under Article 10.3 of Directive 2001/83/EC as amended.

The decentralised application concerns a line extension application for hydrocortisone tablets to previously authorised Hydrocortisone 10mg and 20mg Tablets by Renata Pharmaceuticals Ireland to add a new strength of the drug product Hydrocortisone 5mg Tablets

The bioequivalence study was performed on Hydrocortisone 20 mg Tablets Renata Pharmaceutical Limited and the reference product Hydrocortisone 20mg Tablets (Auden Mc Kenzie).

With Ireland as the Reference Member State in this Decentralized Procedure, Renata Pharmaceuticals (Ireland) Limited is applying for the Marketing Authorisations for Hydrocortisone 5 mg Tablets in IE only.

No Scientific advice was given as part of this submission.

The product will be subject to medical prescription which may not be renewed.

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	Hydrocortisone 5mg Tablet
Name(s) of the active substance(s) (INN)	Hydrocortisone
Pharmacotherapeutic classification (ATC code)	H02AB09
Pharmaceutical form and strength(s)	5mg Tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA22865/003/003
Marketing Authorisation Holder	Renata Pharmaceuticals (Ireland) Limited
MRP/DCP No.	IE/H/0831/003/DC
Reference Member State	IE
Concerned Member State	None

II. QUALITY ASPECTS

II.1. Introduction

This application is for Hydrocortisone 5mg Tablet.

II.2 Drug substance

The active substance is hydrocortisone, an established active substance described in the European and British 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

Hydrocortisone 5 mg tablets contain 5mg of the active substance hydrocortisone.

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)

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 tablets 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 Hydrocortisone 5mg Tablet.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This extension application is submitted in accordance with Article 10(3) of European Directive 2001/83/EC as a hybrid application. This application involves the addition of a new 5 mg strength to an existing MA, PA22865/003/001-002. This active substance is a generic formulation of Hydrocortone 10 mg Tablets (Teva B.V, NL) on the European market since 1978. No new preclinical data have been submitted. The overview provided based on literature review is thus appropriate. This is acceptable for this type of application.

III.5 Ecotoxicity/environmental risk assessment

The active ingredient, hydrocortisone is a well-established molecule which has been available within Europe for many years. Due to this, an overall increase in use would not be expected due to the introduction of a new 5 mg strength, and therefore no overall increase in the environmental risk associated with the use of this product is expected. Consequently, as it is not expected that there will be any significant change in the environmental risk associated with the authorisation of this generic product, further environmental studies are not considered necessary.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of hydrocortisone are well known. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As hydrocortisone is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The applicant has provided a justification that introduction of this new 5 mg strength would not result in an overall increase in use and therefore there would be no increase in environmental risk. This can be accepted. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Hydrocortisone 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 Hydrocortisone 20mg Tablets marketed by MAH Auden MacKenzie.

For this generic application, which concerns an oral immediate release dosage form the applicant has not submitted a new bioequivalence study. The clinical study which demonstrated bioequivalence between the originator 20 mg test and reference product, has been provided.

A single dose, randomised, open label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Hydrocortisone 20mg Tablet of Renata Limited was compared to the reference product Hydrocortisone 20mg Tablet of Auden McKenzie (Pharma Division) Ltd. Based on the pharmacokinetic parameters of active substance the reference tablet marketed by and test tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

With respect to the grant of a biowaiver for the hydrocortisone 5mg tablets, the bioequivalence guidelines general requirements were found to have been met.

The Hydrocortisone 5mg Tablets are manufactured by the same manufacturing process as the Hydrocortisone 20mg Tablets.

The qualitative composition of the 5 mg and 20 mg tablet strengths are the same.

Finally, the in vitro dissolution data for the Hydrocortisone 5 mg Tablets is comparable to that of the Hydrocortisone 20 mg Tablets, which in turn is comparable to the reference product.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Hydrocortisone is readily absorbed from the gastrointestinal tract and 90% or more of the drug is reversibly bound to protein.

The binding is accounted for by two protein fractions. One, corticosteroid-binding globulin is a glycoprotein; the other is albumin.

Hydrocortisone is metabolised in the liver and most body tissues to hydrogenated and degraded forms, such as tetrahydrocortisone and tetrahydrocortisol which are excreted in the urine, mainly conjugated as glucuronides, together with a very small proportion of unchanged hydrocortisone.

IV.3 Pharmacodynamics

Hydrocortisone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract.

Hydrocortisone is believed to be the principal corticosteroid secreted by the adrenal cortex. Naturally occurring glucocorticosteroids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. They are also used for their potent anti-inflammatory effects in disorders of many organ systems. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.'

IV.4 Clinical Efficacy

Hydrocortisone is a well-known active substance. No new clinical efficacy data has been submitted which is acceptable for a generic application.

IV.5 Clinical Safety

Hydrocortisone is a well-known active substance. No new clinical safety data has been submitted which is acceptable for a generic application.

A risk management plan was submitted, 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 Hydrocortisone 5mg tablets.

Safety specification

Important identified risks	None
Important potential risks	None
Missing information	None

Routine pharmacovigilance and risk minimisation activities are sufficient to identify, characterise, prevent or minimise risks relating to Hydrocortisone 5mg tablets.

Periodic Safety Update Reports (PSURs) shall 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

Hydrocortisone is a well-known active substance and has been widely marketed. As this is a generic application, no new efficacy or safety data have been submitted, which is acceptable. Efficacy and safety are expected to be similar to the reference product. The product information SmPC and patient leaflet are consistent with those of the reference product.

V. OVERALL CONCLUSIONS

Hydrocortisone 5mg Tablets is a new strength of the generic form of Hydrocortisone 20 mg Tablets (Auden McKenzie). Hydrocortisone 20mg Tablets is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents.

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 Hydorcortisone 5 mg Tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

01.02.2029