**IPAR**

**Public Assessment Report for a**
**Medicinal Product for Human Use**

Scientific Discussion

Fludrocortisone Acetate Renata 0.1 mg tablets
Fludrocortisone acetate
PA22865/007/001

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.

**CONTENTS**

## I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Fludrocortisone Acetate Renata 0.1 mg tablets., from Renata Pharmaceuticals (Ireland) Limited on the 15th December 2023 for:

With IE as RMS and Malta as CMS, this application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is a generic application.

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: | Fludrocortisone Acetate Renata 0.1 mg tablets |
| Name(s) of the active substance(s) (INN) | Fludrocortisone Acetate |
| Pharmacotherapeutic classification (ATC code) | H02AA02 |
| Pharmaceutical form and strength(s) | 0.1 mg tablet |
| Marketing Authorisation Number(s) in Ireland (PA) | PA22865/007/001 |
| Marketing Authorisation Holder | Renata Pharmaceuticals (Ireland) Limited |
| MRP/DCP No. | IE/H/1226/001/DC |
| Reference Member State | IE |
| Concerned Member State | MT |

## II. QUALITY ASPECTS

### II.1. Introduction

This application is for Fludrocortisone Acetate Renata 0.1 mg tablets

### II.2 Drug substance

The active substance is fludrocortisone acetate, 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

| Active Ingredient | Function | 0.1 mg tablet (mg/tablet) | Reference |
|---|---|---|---|
| fludrocortisone acetate (micronised) | Active substance | 0.100 | Ph. Eur. |

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.

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.

*Adventitious Agent Safety*

Scientific data have been provided for lactose monohydrate and compliance with the Note For Guidance on Minimising the Risk if Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been satisfactorily demonstrated

## 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 Fludrocortisone Acetate Renata 0.1 mg tablets.

# III. NON-CLINICAL ASPECTS

## III.1 Introduction

This active substance is a generic formulation of Fludrocortisone acetate 0.1 mg tablets (Mylan) on the European market since April 1978. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of fludrocortisone acetate are well known. As fludrocortisone acetate is a widely used, well-known active substance, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The overview provided based on literature review is thus appropriate.

## III.5 Ecotoxicity/environmental risk assessment

Since Fludrocortisone Acetate Renata 0.1 mg tablets is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

**III.6 Discussion on the non-clinical aspects**

The pharmacodynamic, pharmacokinetic and toxicological properties of fludrocortisone acetate are well known. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As fludrocortisone acetate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

**IV. CLINICAL ASPECTS**

**IV.1 Introduction**

Fludrocortisone acetate 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 Fludrocortisone acetate, Mylan IRE Healthcare Limited (PA2010/064/001).

The applicant has submitted one bioequivalence study in support of this application. The application form states that Fludrocortisone Acetate 0.1 mg Tablets (UK, PL 39699/0071) has been used in the BE study. Prior to the Brexit transition period, this product was a 'joint pack' product with IE product PA 1691/018/001 which is marketed as Fludrocortisone acetate, Mylan IRE Healthcare Limited (PA2010/064/001) since 2020.

There is only one dose level therefore a biowaiver is not required.

A Randomized, Open Label, Balanced, Two Treatment, Two Period,Two Sequence, Single Dose, Crossover Bioequivalence Study of Fludrocortisone Acetate 0.1 mg tablet of Renata Limited, with Florinef Acetaat tablet 0.1 mg (Fludrocortisone Acetate 0.1mg Tablets) Manufactured By Haupt Pharma Amareg GmbH, Donaustaufer StraBe 378 93055 Regensburg, Duitsland, in Normal, Healthy, Adult, Human Subjects Under Fasting Condition. This study demonstrated bioequivalence between both products.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference Fludrocortisone acetate, Mylan IRE Healthcare Limited (PA2010/064/001).

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

**IV.2 Pharmacokinetics**

Absorption
A potent mineralocorticoid with some glucocorticoid properties, well absorbed, metabolised slowly with a T½ of up to 30 hours. It has strong sodium retaining capacity.

Elimination
Fludrocortisone is highly protein bound and is eliminated by the kidneys, mostly as inactive metabolites. The pharmacodynamic half-life of fludrocortisone is approximately 18 to 36 hours. The duration of action is 1 to 2 days.

**IV.3 Pharmacodynamics**
Pharmacotherapeutic group: Mineralocorticoids, ATC code: H02AA02.

Corticosteroids are thought to act, at least in part, by controlling the rate of synthesis of proteins at the cellular level. The relationship between this activity and the metabolic effects is not yet totally clear.

The physiologic action of fludrocortisone acetate is similar to that of hydrocortisone but the glucocorticoid effect is 15 times as potent and the mineralocorticoid effect is 125 times greater. Sodium reabsorption in the renal distal tubules and in other tissues appears to account for the physiologic action characteristic of mineralocorticoids. Small doses of these drugs result in marked sodium retention and increased urinary excretion of potassium and hydrogen.

Blood pressure is also elevated apparently because of these effects on electrolytes. Larger doses inhibit endogenous adrenal cortical secretion, thymic activity, and pituitary corticotropin excretion; high doses also promote the deposition of liver glycogen, and unless protein intake is adequate, induce negative nitrogen balance.

**IV.4 Clinical Efficacy**
The efficacy of fludrocortisone acetate is well established.

**IV.5 Clinical Safety**
The safety of fludrocortisone acetate is well established and is captured in the SmPC.

**Risk Management Plan**

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 Fludrocortisone Acetate Renata 0.1 mg tablets.

Safety specification

The following safety concerns have been included in the Safety Specification RMP Part II.VIII by the Applicant:

| **Summary of safety concerns** | |
|---|---|
| **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.

Summary of the RMP

The submitted Risk Management Plan, version 0.1, dated 4th April 2022 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
At the request of the RMS;
Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

**Periodic Safety Update Report (PSUR)**

With regard to PSUR submission, the MAH should take the following into account:
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. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
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.

In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

### IV.6 Discussion on the clinical aspects

The safety and efficacy of fludrocortisone acetate is well established. The MAH submitted a single bioequivalence study using Fludrocortisone acetate 0.1 mg Tablets (UK, PL 39699/0071). Prior to the Brexit transition period, this product was a 'joint pack' product with IE product PA 1691/018/001 which is marketed as Fludrocortisone acetate, Mylan IRE Healthcare Limited (PA2010/064/001) since 2020.
Bioequivalence has been shown. The product information is aligned with Fludrocortisone acetate, Mylan IRE Healthcare Limited (PA2010/064/001).

## V. OVERALL CONCLUSIONS

Fludrocortisone Acetate Renata 0.1 mg tablets is a generic form of Fludrocortisone acetate 0.1 mg Tablets (UK, PL 39699/0071). Prior to the Brexit transition period, this product was a 'joint pack' product with IE product PA 1691/018/001 which is marketed as Fludrocortisone acetate, Mylan IRE Healthcare Limited (PA2010/064/001) since 2020. It 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 Fludrocortisone acetate, Mylan IRE Healthcare Limited (PA2010/064/001).

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 Fludrocortisone Acetate Renata 0.1 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

4th October 2028