Medicines Evaluation Board

Public Assessment Report

Scientific discussion

Fludrocortisonacetaat RIA 0.1 mg tablets (fludrocortisone acetate)

NL/H/5850/001/DC

Date: 3 August 2026

This module reflects the scientific discussion for the approval of Fludrocortisonacetaat RIA 0.1 mg tablets. The procedure was finalised on 26 February 2025. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Fludrocortisonacetaat RIA 0.1 mg tablets, from RIA Generics Limited.

The product is indicated for support of glucocorticoid therapy in Addison disease and in congenital adrenal syndrome with salt loss, if an additional mineralocorticoid effect appears to be necessary.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Florinef Acetaat, tablets 0.1 mg, which has been registered in the Netherlands via national procedure (RVG 07897) since 29 April 1980.

The concerned member states (CMS) involved in this procedure were Poland and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Fludrocortisonacetaat RIA is a white, round shaped tablet and plain on both sides. Each tablet contains as active substance 0.1 mg of fludrocortisone acetate.

The excipients are: lactose monohydrate, sodium starch glycolate (type A), talc (E533) and magnesium stearate (E470b).

The tablets are packed in polyvinyl chloride (PVC)/polyvinylidene chloride (PVDC)/Aluminium blister packs or in a white opaque high-density polyethylene (HDPE) bottle with child-resistant closure.

II.2 Drug Substance

The active substance is fludrocortisone acetate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Fludrocortisone acetate is a white to almost white crystalline powder and is practically insoluble in water, sparingly soluble in ethanol and chloroform, slightly soluble in ether. The MAH provided information that indicates no polymorphic forms exist for the active substance.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is in line with the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The choices of packaging and manufacturing process are adequately justified based on the dosage form. The development of the quality control (QC) dissolution method has been adequately justified and the discriminatory power of the method was shown. The pharmaceutical development of the product has been adequately performed. The MAH included information on the formulation optimisation of the drug substance particle size and for lactose monohydrate and magnesium stearate.

Manufacturing process
The manufacturing process involves the sifting of all tablet's excipients and the active substance. This is followed by blending all components, with the exclusion of one excipient. After blending, the sifted excipient is added for lubrication. After lubrication tablets are formed by compression. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with Ph. Eur. requirements. The functionality related characteristics for each of the excipients are laid down in the dossier or are justified as not relevant for the performance of the drug product. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, dissolution, assay, related substances, water content and microbiological limits. Release and shelf-life requirements are identical, except for related substances. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scaled batches from the production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three production scaled batches stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months) for

blisters and at 25°C/60% RH (18 months) and 40°C/75% RH (6 months) for bottle packs. The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for at least 18 months for the blisters and the bottles. Based on the provided data at accelerated conditions for bottles, compliance with the dissolution limit during shelf-life has been sufficiently demonstrated. For the photostability study the MAH has included sufficient data on the initial impurity values of the batches used for the photostability data. The drug product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage condition is 'Do not store above 30°C'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for excipient lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Fludrocortisonacetaat RIA has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

At the time of submission of this application, before 1st of September 2024, the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) was not yet applicable. At the time of approval the conclusion for this medicinal product was: since Fludrocortisonacetaat RIA is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Florinef Acetaat which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Fludrocortisone acetate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The

member states agreed that no further clinical studies are required, besides the bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Fludrocortisonacetaat RIA 0.1 mg tablets (RIA Generics Limited, Ireland) was compared with the pharmacokinetic profile of the reference product Florinef Acetaat, tablets 0.1 mg (Viatris Healthcare B.V., the Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The dissolution data obtained with media of pH 1.2 and pH 4.5 are from a quality point of view considered to be acceptable as complementary to the bioequivalence study. The dissolution profiles obtained with media of pH 6.8 cannot be considered as similar. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence study GR-22-004

Design

A single-dose, randomised, open label, balanced, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 46 healthy male subjects, aged 20-44 years. Each subject received a single dose (0.1 mg) of one of the two fludrocortisone

Blood samples were collected pre-dose and at 0.16, 0.33, 0.5, 0.66, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14 and 24 hours after administration of the products.

The design of the study is acceptable.

Fludrocortisone acetate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of fludrocortisone acetate. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

All 46 included subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of fludrocortisone acetate, 0.1 mg under fasted conditions.

Treatment N=46	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	3729 ± 926	3883 ± 960	1202 ± 286	0.66 (0.33-2.00)
Reference	3683 ± 971	3846 ± 1011	1325 ± 404	0.66 (0.33-2.00)
***Ratio (90% CI)**	101.29 (99.44 -103.17)	101.02 (99.30 - 102.78)	92.31 (85.61 – 99.53)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 80 – 125. Based on the submitted bioequivalence study Fludrocortisonacetaat RIA is considered bioequivalent with Florinef Acetaat.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Fludrocortisonacetaat RIA. At the time of approval, the most recent version of the RMP was version 0.1 dated 16 August 2023.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Florinef Acetaat. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the approved PL of Florinef Acetaat (RVG 07897) and to the full user test conducted on the PL of Sertraline 50 mg and 100 mg film-coated tablets (NL/H/3452/001-002/DC; RVG 117160-3). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fludrocortisonacetaat RIA 0.1 mg tablets have a proven chemical-pharmaceutical quality and are a generic form of Florinef Acetaat, tablets 0.1 mg. Florinef Acetaat is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Fludrocortisonacetaat RIA with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 February 2025.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5850/IA/001/G	Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place. Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) - All other.	No	30-3-2026	Approved	N/A