COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fludrace 31.25 micrograms, tablets (fludrocortisone acetate)

NL License RVG: 125017

Date: 23 February 2023

This module reflects the scientific discussion for the approval of Fludrace 31.25 micrograms, tablets. The marketing authorisation was granted on 12 July 2022. 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
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
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation Fludrace 31.25 micrograms, tablets, from ACE Pharmaceuticals B.V.

The product is indicated as a supplement for primary adrenocortical insufficiency (Addison's disease) and in congenital adrenocortical hyperplasia (adrenogenital syndrome) accompanied by saline loss, as complement treatment with a glucocorticoid. Fludrace is indicated for use in adults and children aged 2 to 18 years.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a line extension to the current marketing authorisation of Fludrace 62.5 micrograms, tablets (RVG 50721), registered since 1992 in the Netherlands by ACE Pharmaceuticals B.V.

The 31.25 micrograms formulations were being supplied to patients via pharmacy preparations before this market authorisation was requested. With this new formulation, the MAH aims to facilitate dosing for children aged 2 to 18 years.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC. The dossier includes a complete quality module. Regarding the non-clinical and clinical modules, only data relevant for the extension are included. For the non-clinical and clinical data of fludrocortisone, reference is made to the existing marketing authorisations of Fludrace 62.5 micrograms, tablets.

II. QUALITY ASPECTS

II.1 Introduction

Fludrace (31.25 micrograms) is a white round tablet scored on one side and debossed with “3” on the other side. The score line is only intended to break the tablet to make it easier to swallow and not to divide the tablet into equal doses.

Each tablet contains as active substance 31.25 micrograms fludrocortisone acetate.

The tablets are packed in a high-density polyethylene (HDPE) bottle with a polypropylene lid containing desiccant.

The excipients are: lactose monohydrate, maize starch and magnesium stearate. These excipients are commonly used excipients for this pharmaceutical form and manufacturing process and they comply with their European Pharmacopoeia (Ph.Eur.) monographs.

II.2 Drug Substance

The active substance is fludrocortisone acetate, an established active substance described in the Ph.Eur. It is a white or almost white, crystalline powder, practically insoluble in water, sparingly soluble in ethanol and slightly soluble in ether.

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 European Pharmacopoeia.

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 meets the requirements of the CEP and the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with these specifications have been provided for one batch.

Stability of drug substance

The active substance is stable for 5 years 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 current line extension is based on a new formulation compared to the original strength of 62.5 micrograms. The current tablet strength of 31.25 micrograms has the same weight and size as the original strength, the smaller amount of drug substance is compensated by lactose monohydrate.

The two strengths can be distinguished by their inscription. The product is developed for administration in adults and children in the age of 2 to 18 years. The minimum age for children of 2 years is based on a study for another product (levamisole tablets) sponsored by the MAH, investigating the use of different tablet sizes in children aged 2 years and older, with tablets of the same size as Fludrace. The ability to swallow tablets is dependent on their size, but also on the type of coating and palatability, but it was sufficiently supported that at least part of the patients could swallow the tablets from the age of 2 years.

Manufacturing process

The tablets are produced by direct compression. The active substance is mixed with the excipients to obtain a homogenous distribution in the final blend. The final blend is compressed in tablets and the tablets are packed in HDPE containers. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients

The excipients comply with Ph. Eur. requirements. 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 is based on the monograph for in the Ph.Eur. and includes tests for appearance, identity, average mass, uniformity of mass, dimensions, resistance to crushing, disintegration, dissolution, related substances, assay, uniformity of dosage units, water activity and microbiology. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided on three production scaled batches. The batches were stored at 25°C/60% RH (9-18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in HPDE containers. Photostability studies have been performed as part of the forced degradation studies and showed that the product is photostable.

Based on the provided stability data, a shelf-life of 2 years could be granted, and no temperature restrictions are required in the storage conditions. The product should be stored in the original packaging to protect against moisture.

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

Certificates of suitability issued by the EDQM have been provided for lactose 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 MEB considers that Fludrace 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)

The Fludrace 31.25 micrograms tablets are a line extension of Fludrace 62.5 micrograms tablets. The 31.25 micrograms formulations are currently supplied to patients via pharmacy preparations. Therefore, this market authorisation 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 line extension formulation of Fludrace 62.5 micrograms tablets which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature on fludrocortisone. Fludrocortisone is a widely used, well-known active substance. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB 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 overview justifies why there was no need to generate additional clinical data, except for the efficacy study discussed below which supports indicated use in children of 2 years and older. The line extension was based on a biowaiver of additional strengths of the 62.5 micrograms tablets. The MEB found that no further clinical studies were required.

IV.2 Pharmacokinetics

Biowaiver

The Fludrace 31.25 micrograms tablets are a line extension of Fludrace 62.5 micrograms tablets. The line extension is based upon a biowaiver for additional strengths. The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The two products are manufactured by the same process, are proportional in quantitative compositions and similar in quality. The dissolution was investigated according to the EMA Bioequivalence guideline and the data confirm that the two dissolution profiles are similar. The tablets dissolve very rapidly (i.e. >85% within 15 minutes) at three pH levels. The biowaiver was sufficiently supported and could be granted.

IV.3 Pharmacodynamics, clinical efficacy, clinical safety

For this authorisation, reference was made to the clinical studies and experience with Fludrace 62.5 micrograms tablets, which justified that no new studies were required.

IV.4 Risk Management Plan

The MAH has referred to the risk management plan (RMP) of Fludrace 62.5 micrograms tablets for this line extension. The therapeutic indications are the same for both products, therefore no updated RMP was necessary. The MEB found that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience in pharmacodynamics, clinical efficacy and clinical safety of Fludrace 62.5 micrograms tablets, on which the line extension is based. A biowaiver of strengths was granted. No clinical studies were deemed necessary. Risk management was adequately addressed.

V. USER CONSULTATION

Because the new 31.25 micrograms strength has been added to the existing package leaflet (PL) for Fludrace 62.5 micrograms tablets, no new user testing was necessary.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fludrace 31.25 micrograms, tablets has a proven chemical-pharmaceutical quality and is an approvable line extension of Fludrace 62.5 micrograms, tablets, which is a well-known medicinal product with an established favourable efficacy and safety profile. The new formulation is considered to be an approvable addition to the original product. The new

formulation can facilitate dosing for children aged 2 to 18 years, previously needing pharmacy preparations.

A biowaiver was granted, in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The MEB has therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 12 July 2022.

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
Type II: B.I.a.1.b	Submission of the new ASMF of the same AIM	No	28-4-2020	Approved	N/A