Public Assessment Report

Decentralised Procedure

Fludrocortisone Acetate 0.1 mg Tablets

(Fludrocortisone acetate)

Procedure No: UK/H/6019/001/DC

UK Licence Number: PL 17299/0001

Tiofarma B.V.
LAY SUMMARY

Fludrocortisone Acetate 0.1 mg Tablets

(fludrocortisone acetate, tablets, 0.1mg)

This is a summary of the Public Assessment Report (PAR) for Fludrocortisone Acetate 0.1 mg Tablets (PL 17299/0001; UK/H/6019/001/DC). It explains how Fludrocortisone Acetate 0.1 mg Tablets was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Fludrocortisone Acetate 0.1 mg Tablets.

The product will be referred to as Fludrocortisone Acetate Tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Fludrocortisone Acetate Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Fludrocortisone Acetate Tablets and what are they used for?

Fludrocortisone Acetate Tablets are a ‘generic medicine’. This means that Fludrocortisone Acetate Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Florinef Tablets 0.1 mg (E.R. Squibb & Sons Limited).

Fludrocortisone Acetate Tablets belong to a group of medicines called steroids. Their full name is corticosteroids. These corticosteroids occur naturally in the body, and help to maintain health and well-being.

Fludrocortisone Acetate Tablets are used to replace the hormones that are normally produced by glands attached to a patient’s kidneys. These hormones will not be produced by a person’s body if they suffer from a condition called Addison’s disease.

Fludrocortisone Acetate Tablets are also used to treat a condition called ‘salt losing adrenogenital syndrome’ which is a different form of hormone imbalance.

How do Fludrocortisone Acetate Tablets work?

This medicine contains the active ingredient, fludrocortisone acetate.

Boosting a patient’s body with extra corticosteroid (such as fludrocortisone acetate) is an effective way to treat various illnesses involving inflammation (swelling) in the body. Fludrocortisone Acetate Tablets reduce this inflammation, which could otherwise go on making the patient’s condition worse. The patient must take this medicine regularly to get maximum benefit from it.

How are Fludrocortisone Acetate Tablets used?

The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

This medicine is for oral use.
Adults and the Elderly:
To treat Addison’s Disease, the usual daily dose range is 0.05 mg (half a tablet) to 0.3 mg (3 tablets) to be taken once a day. Patients on long term treatment may require the addition of a different type of steroid tablet during times of illness or stress.

To treat Adrenal hyperplasia, the usual daily dose range is 0.1 mg (one tablet) to 0.2 mg (2 tablets).

Children
The dose is adjusted according to size and weight but is always kept as low as possible.

The patient must make sure that they take the full course as prescribed by their doctor. The patient must not suddenly stop taking Fludrocortisone Acetate Tablets as this may make them ill.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Fludrocortisone Acetate Tablets have been shown in studies?
Because Fludrocortisone Acetate Tablets are a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine Florinef Tablets 0.1 mg (E.R. Squibb & Sons Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Fludrocortisone Acetate Tablets?
Because Fludrocortisone Acetate Tablets is a generic medicine and is bioequivalent to the reference medicine Florinef Tablets 0.1 mg (E.R. Squibb & Sons Limited), its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Fludrocortisone Acetate Tablets, see section 4 of the package leaflet available on the MHRA website.

Why was Fludrocortisone Acetate Tablets approved?
It was concluded that, in accordance with EU requirements, Fludrocortisone Acetate Tablets have been shown to have comparable quality and to be bioequivalent to Florinef Tablets 0.1 mg (E.R. Squibb & Sons Limited). Therefore, the MHRA decided that, as for Florinef Tablets 0.1 mg (E.R. Squibb & Sons Limited); the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Fludrocortisone Acetate Tablets?
A risk management plan (RMP) has been developed to ensure that Fludrocortisone Acetate Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Fludrocortisone Acetate Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.
Other information about Fludrocortisone Acetate Tablets

The Marketing Authorisation for Fludrocortisone Acetate Tablets was granted in the UK on 09 November 2015.

The full PAR for Fludrocortisone Acetate Tablets follows this summary.

For more information about treatment with Fludrocortisone Acetate Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in December 2015.
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I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Fludrocortisone Acetate Tablets (PL 17299/0001; UK/H/6019/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated for partial replacement therapy for primary and secondary adrenocortical insufficiency in Addison's disease and for the treatment of salt-losing adrenogenital syndrome.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Malta as Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Florinef Tablets 0.1 mg (PL 00034/5027R), which was authorised to E.R. Squibb & Sons Limited on 16 November 1988.

Qualitatively, the physiological action of fludrocortisone acetate is similar to hydrocortisone. In very small doses, fludrocortisone maintains life in adrenalectomised animals, enhances the deposition of liver glycogen and produces thymic involution, eosinopenia, retention of sodium and increased urinary excretion of potassium.

Two bioequivalence studies (conducted under fasting conditions) were submitted to support this application. The applicant has stated that the bioequivalence studies were conducted in accordance with the clinical research guidelines established by the basic principles defined in the ICH-GCP guidelines, ICMR guidelines for Biomedical Research on Human Subjects, Schedule Y (amended version) of CDSCO (Central Drugs Standard Control Organization), “Guideline on the investigation of bioequivalence”, CPMP/EWP/QWP/1401/98 Rev. 1/Corr, London 20 January 2010 and the principles enunciated in the “Declaration of Helsinki” (Recommendations guiding physicians in biomedical research involving human subjects, WMA General Assembly, Republic of South Africa, 1996) and ethical conditions laid down in the EU Directive 2001/20/EC or its equivalent.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 110) on 13 October 2015. After a subsequent national phase, a licence was granted in the UK on 09 November 2015.
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 0.1 mg of fludrocortisone acetate, as the active ingredient. Other ingredients consist of the pharmaceutical excipients sodium starch glycolate, lactose monohydrate, talc and magnesium stearate.

Fludrocortisone Acetate Tablets are packaged in PVC/PVdC/aluminium blisters in pack sizes of 100 tablets. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN:    Fludrocortisone acetate
Structure:

![Fludrocortisone Acetate Structure](image)

Molecular formula:  C$_{23}$H$_{31}$FO$_6$
Molecular weight:  422.5
Description:  White to almost white crystalline powder
Solubility  Practically insoluble in water, sparingly soluble in ethanol and chloroform, slightly soluble in ether.

Fludrocortisone acetate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specification.

Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
II.3. Medicinal Product

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious tablets containing 0.1 mg of fludrocortisone acetate per tablet, that are a generic version of the reference product Florinef Tablets 0.1 mg (E.R. Squibb & Sons Limited). A satisfactory account of the pharmaceutical development has been provided.

Comparative in-vitro dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months with the storage condition, ‘Store below 30 ºC. Store in the original package in order to protect from light.’

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.
III  NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of fludrocortisone acetate are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Fludrocortisone Acetate Tablets are intended for generic substitution, this 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
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV  CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of fludrocortisone acetate is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of fludrocortisone acetate.

Based on the data provided, Fludrocortisone Acetate Tablets can be considered bioequivalent to Florinef Tablets 0.1 mg (E.R. Squibb & Sons Limited).

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence studies (one pilot and one pivotal study):

PILOT STUDY
A single blind, balanced, randomised, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the applicant’s test product Fludrocortisone Acetate 0.1 mg Tablets (Tiofarma B.V.) versus the reference product, Florinef Tablets 0.1 mg (E.R. Squibb & Sons Limited), in healthy adult subjects under fasting conditions.
This pilot study was designed and conducted in accordance with a standard bioequivalence study. However, the sample size of subjects was arbitrarily chosen and the purpose of this study was to accurately ascertain the intrasubject CV and to determine an acceptable sample size for the bioequivalence study.

The subjects were administered a single dose (0.1 mg) of either the test or the reference product under fasting conditions. Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 14 days.

The pharmacokinetic results are presented below:

**Table: Summary of pharmacokinetic parameters for test and reference product for fludrocortisone (geometric least squares mean, ratios and 90% confidence interval):**

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Geometric Least Squares Mean*</th>
<th>Ln-transformed</th>
<th>90% Confidence Interval</th>
<th>Intra-subject CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product (T)</td>
<td>Reference Product (R)</td>
<td>T/R (%)</td>
<td>Lower</td>
</tr>
<tr>
<td>Cmax (pg/mL)</td>
<td>1013.16</td>
<td>1131.2336</td>
<td>89.56</td>
<td>78.65</td>
</tr>
<tr>
<td>AUC0-4 (pg h/mL)</td>
<td>2717.30</td>
<td>3044.6773</td>
<td>89.25</td>
<td>85.50</td>
</tr>
</tbody>
</table>

AUC0-4 = area under the plasma concentration-time curve from zero to t hours  
Cmax = maximum plasma concentration

The pilot study failed to demonstrate bioequivalence between the test product Fludrocortisone Acetate 0.1 mg Tablets (Tiofarma B.V.) and the reference product Florinef Tablets 0.1 mg (E.R. Squibb & Sons Limited), as the 90% CI of the log transformed Cmax was not within 80-125. In addition to the smaller than required sample size that was achieved in this study, it is also noted that there was a difference in the assay content between test (98.8%) and the reference (104.5%) of more than 5% which could have possibly contributed to the failure to demonstrate bioequivalence in this pilot study. However, this study determined the intrasubject CV as 23.5%, based on which a sample size was planned for the pivotal bioequivalence study.

Further based on the results of the study, the wash-out period was reduced from 15 days to 9 days and a more intensive plasma sampling schedule was undertaken around the anticipated Cmax in the pivotal study. These changes are appropriate and acceptable.

**PIVOTAL STUDY**

A single-blind, balanced, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the applicant's test product Fludrocortisone Acetate 0.1 mg Tablets (Tiofarma B.V.) versus the reference product, Florinef Tablets 0.1 mg (E.R. Squibb & Sons Limited), in healthy adult subjects under fasting conditions.

Subjects were administered a single dose (0.1 mg) of either the test or the reference product under fasting conditions. Blood samples were collected for plasma levels before dosing and up to and including 36 hours after each administration. The washout period between the treatment phases was 9 days. The pharmacokinetic results are presented below:
Table: Summary of pharmacokinetic parameters for test and reference product for fludrocortisone (geometric least squares mean, ratios and 90% confidence interval):

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Ln-transformed</th>
<th>90% Confidence Interval</th>
<th>Intra subject CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric Least Squares Mean*</td>
<td>Test Product (T)</td>
<td>Reference Product (R)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>1138.7028</td>
<td>1181.5287</td>
<td>96.38</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (pg h/mL)</td>
<td>2759.0021</td>
<td>3010.3006</td>
<td>91.65</td>
</tr>
</tbody>
</table>

**Conclusion**
The 90% confidence intervals of the test/reference ratio for AUC and C<sub>max</sub> values for fludrocortisone lie within the acceptable limits of 80.00% to 125.00%, for the pivotal study, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Florinef Tablets 0.1 mg (E.R. Squibb & Sons Limited).

### IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

### IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

### IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

### IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

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*AUC<sub>0-t</sub>* area under the plasma concentration-time curve from zero to t hours

*C<sub>max</sub>* maximum plasma concentration
Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Hypothalamic pituitary adrenal suppression</th>
</tr>
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<tbody>
<tr>
<td>Treatment in patient with local or systemic viral infection,</td>
<td>Treatment in patient with local or systemic viral infection, systemic fungal infections or in active infections not controlled by antibiotics, septicaemia, tuberculosis</td>
</tr>
<tr>
<td>systemic fungal infections or in active infections not</td>
<td></td>
</tr>
<tr>
<td>controlled by antibiotics, septicaemia, tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Treatment in patients with infections like chickenpox, shingles</td>
<td>Use in patients with congestive heart failure and hypertension</td>
</tr>
<tr>
<td>shingles and measles</td>
<td>Myasthenia gravis, steroid myopathy, tendon rupture</td>
</tr>
<tr>
<td>Use in patients with congestive heart failure and hypertension</td>
<td>Use in patients with peptic ulcer and those receiving NSAIDs</td>
</tr>
<tr>
<td>Myasthenia gravis, steroid myopathy, tendon rupture</td>
<td>Use in patients with liver failure.</td>
</tr>
<tr>
<td>Use in patients with peptic ulcer and those receiving NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Use in patients with liver failure.</td>
<td></td>
</tr>
<tr>
<td>Rare instances of anaphylactoid reactions</td>
<td></td>
</tr>
<tr>
<td>In patients with epilepsy</td>
<td></td>
</tr>
<tr>
<td>Latent diabetes mellitus and aggravation of existing diabetes</td>
<td>Use in patients with glaucoma or family history of glaucoma</td>
</tr>
<tr>
<td>Use in patients with glaucoma or family history of glaucoma</td>
<td>Use in patients with thrombophlebitis</td>
</tr>
<tr>
<td>Use in patients with thrombophlebitis</td>
<td>Patients with lactose intolerance</td>
</tr>
<tr>
<td>Patients with lactose intolerance</td>
<td>Severe psychiatric disturbance</td>
</tr>
<tr>
<td>Severe psychiatric disturbance</td>
<td>Use in patients with metastatic cancer</td>
</tr>
<tr>
<td>Use in patients with metastatic cancer</td>
<td>Use in patients with renal failure</td>
</tr>
<tr>
<td>Use in patients with renal failure</td>
<td>Growth retardation in children</td>
</tr>
<tr>
<td>Growth retardation in children</td>
<td><strong>Drug interactions</strong></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
<th>Use in pregnancy</th>
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<tr>
<td>Use during lactation</td>
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</table>

<table>
<thead>
<tr>
<th>Important missing information</th>
<th>Effect on fertility</th>
</tr>
</thead>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

**IV.7 Discussion on the clinical aspects**

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s test product Fludrocortisone Acetate Tablets versus the reference product, Florinef Tablets 0.1 mg (E.R. Squibb & Sons Limited).

The grant of a marketing authorisation is recommended for this application.

**V User consultation**

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

**VI Overall conclusion, benefit/risk assessment and recommendation**

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with fludrocortisone acetate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Fludrocortisone Acetate Tablets is presented below: