Public Assessment Report

Decentralised Procedure

Hydrocortisone 10 mg and 20 mg Tablets

(Hydrocortisone)

Procedure No: UK/H/5777/001-2/DC

UK Licence Number: PL 20046/0302-0303

Focus Pharmaceuticals Limited
This is a summary of the Public Assessment Report (PAR) for Hydrocortisone 10 mg and 20 mg Tablets (PL 20046/0302-0303; UK/H/5777/001-02/DC). It explains how Hydrocortisone 10 mg and 20 mg Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Hydrocortisone 10 mg and 20 mg Tablets.

The products will be collectively referred to as Hydrocortisone Tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Hydrocortisone Tablets, patients should read the package leaflets or contact their doctor or pharmacist.

**What are Hydrocortisone Tablets and what are they used for?**

Hydrocortisone Tablets are ‘generic medicines’. This means that Hydrocortisone Tablets are similar to ‘reference medicines’ already authorised in the European Union (EU) called Hydrocortisone 10 mg and 20 mg Tablets (Auden Mckenzie (Pharma Division) Limited).

Hydrocortisone Tablets are indicated:
- For use as replacement therapy in congenital adrenal hyperplasia in children.
- Pre-operatively, and during serious trauma or illness in children with known adrenal insufficiency or doubtful adrenocortical reserve.

**How do Hydrocortisone Tablets work?**

The active ingredient, hydrocortisone belongs 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. Boosting the body with extra corticosteroid (such as hydrocortisone) is an effective way to treat various illnesses involving inflammation in the body. Hydrocortisone reduces 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 Hydrocortisone 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 must check with their doctor or pharmacist if they are not sure. The amount of medicine the patient has to take each day will depend on their illness.

The patient should always carry a Steroid Treatment Card. The patient must make sure their doctor or pharmacist gives them this and has filled out the details including the dose and how long the patient will have the treatment.

The number of tablets to be taken will be on the label of the patient’s medicine. If the patient is unsure about the dose they should take, they must talk to their doctor or pharmacist.

The usual dose in children is 0.4 to 0.8 mg/kg given as two or three doses per day. Children will be prescribed the lowest possible dose. A doctor will keep an eye on their growth and development.

Please read section 3 of the package leaflets 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 Hydrocortisone Tablets have been shown in studies?**
Because Hydrocortisone Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Hydrocortisone 10 mg and 20 mg Tablets (Auden Mckenzie (Pharma Division) 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 Hydrocortisone Tablets?**
Because Hydrocortisone Tablets are generic medicines and are bioequivalent to the reference medicines Hydrocortisone 10 mg and 20 mg Tablets (Auden Mckenzie (Pharma Division) Limited), their benefits and possible side effects are taken as being the same as the reference medicines.

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

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

**Why was Hydrocortisone Tablets approved?**
It was concluded that, in accordance with EU requirements, Hydrocortisone Tablets has been shown to have comparable quality and to be bioequivalent to Hydrocortisone 10 mg and 20 mg Tablets (Auden Mckenzie (Pharma Division) Limited). Therefore, the MHRA decided that, as for Hydrocortisone 10 mg and 20 mg Tablets (Auden Mckenzie (Pharma Division) 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 Hydrocortisone Tablets?**
A risk management plan (RMP) has been developed to ensure that Hydrocortisone Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPC) and the package leaflets for Hydrocortisone 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 Hydrocortisone Tablets**
The Republic of Ireland and the UK agreed to grant Marketing Authorisations for Hydrocortisone Tablets on 13 September 2016. Marketing Authorisations were granted in the UK on 10 October 2016.

Hydrocortisone 10 mg and 20 mg Tablets were originally granted to Lamda Laboratories SA (PL 43945/0001-0002) on 10 October 2016. Following a change of ownership on 20 October 2016, these products are currently licensed to Focus Pharmaceuticals Limited (PL 20046/0302-0303).

The full PAR for Hydrocortisone Tablets follows this summary.

For more information about treatment with Hydrocortisone Tablets, read the package leaflets, or contact your doctor or pharmacist.

This summary was last updated in November 2016.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Hydrocortisone 10 mg and 20 mg Tablets (PL 20046/0302-0303; UK/H/5777/001-2/DC), are approvable. These products are prescription only medicines (POM), indicated for:

- For use as replacement therapy in congenital adrenal hyperplasia in children.
- Pre-operatively, and during serious trauma or illness in children with known adrenal insufficiency or doubtful adrenocortical reserve.

The applications were submitted using the Decentralised Procedures (DCP), with the UK as Reference Member State (RMS), and The Republic of Ireland as Concerned Member State (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Hydrocortisone 10 mg and 20 mg Tablets which were originally authorised to Merck, Sharp & Dohme Ltd on 23 February 1989 (PL 00025/5053R and 5054R) and underwent change of ownership procedures to Auden McKenzie (Pharma Division) Ltd on 03 June 2008 (PL 17507/0097-0098) and to S.N.S Pharmaceuticals Limited (PL 16876/0002-0030) on 27 December 2013 and to the current Marketing Authorisation Holder, Auden McKenzie (Pharma Division) Limited (PL 17507/0246 & 0248), on 23 January 2015.

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.

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

With the exception of one bioequivalence study, no new clinical data were provided with these applications. A bioequivalence study was submitted to support these applications, comparing the applicant’s test product Hydrocortisone 20 mg tablets with the reference product Hydrocortisone 20 mg tablets (Auden McKenzie (Pharma Division) UK) in healthy adult subjects, under fasting conditions. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

A summary of the pharmacovigilance system and a detailed risk management plan have been provided with this application and these are satisfactory.

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 applications could be approved at the end of procedure on 13 September 2016. After a subsequent national phase, licences were granted in the UK on 10 October 2016.
Hydrocortisone 10 mg and 20 mg Tablets were originally granted to Lamda Laboratories SA (PL 43945/0001-0002) on 10 October 2016. Following a change of ownership on 20 October 2016, these products are currently licensed to Focus Pharmaceuticals Limited (PL 20046/0302-0303).
II QUALITY ASPECTS

II.1 Introduction

Each tablet contains 10 mg or 20 mg hydrocortisone, as the active ingredient. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, maize starch and magnesium stearate.

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.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Hydrocortisone 10 mg and 20 mg Tablets are packaged in polyvinylchloride (PVC)/polyvinylidenechloride (PVDC) blisters lidded with aluminium foil containing 30 tablets. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance

INN: Hydrocortisone
Chemical name: 11β, 17α, 21-trihydroxypregn-4-ene-3, 20-dione
Structure:

```
        H      H
     O     CH3
  O          H     
 /\   \  /\   /\  
 CH3   CH3 CH3   CH3
```

Molecular formula: C21H30O5
Molecular weight: 362.5 g/mol
Description: White to almost white, crystalline powder.
Solubility: Practically insoluble in water, sparingly soluble in acetone and in ethanol (96%); slightly soluble in dichloromethane and very slightly soluble in ether.

Hydrocortisone 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.

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.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analyses data are provided that comply with the proposed specification.
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 10 mg or 20 mg hydrocortisone per tablet, that are generic versions of the reference products Hydrocortisone 10 mg and 20 mg Tablets (Auden Mckenzie (Pharma Division) 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.

Manufacture of the products
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated at pilot scale batch size and have shown satisfactory results. The process validation protocol to be followed for full-scale production batches has been provided and is satisfactory.

Finished Product Specifications
The finished product specifications proposed are acceptable. The 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 Products
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 30 months with the storage conditions ‘Do not store above 25°C’ and ‘Store in the original package in order to protect from light’.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of hydrocortisone 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 Hydrocortisone Tablets are intended for generic substitution, their use 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 applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of hydrocortisone is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

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 hydrocortisone.

Based on the data provided, Hydrocortisone Tablets can be considered bioequivalent to Hydrocortisone 20 mg Tablets (Auden Mckenzie (Pharma Division) Limited).

IV.2 Pharmacokinetics
In support of these applications, the applicant submitted the following bioequivalence study:

STUDY
An open-label, balanced, randomised, two-treatment, two-period crossover oral bioequivalence study of the applicant’s test product Hydrocortisone 20 mg Tablets versus the reference product Hydrocortisone 20 mg Tablets (Auden Mckenzie (Pharma Division) Limited) in healthy, adult, subjects under fasting conditions. The subjects were administered a single dose (20 mg) of either the test or the reference product under fasting conditions. A single dose of 4 mg dose of dexamethasone was administered at least 10 hours prior to investigational product administration to suppress endogenous cortisol secretion.

Blood samples were collected for plasma levels before dosing and up to and including 12 hours after each administration. The washout period between the treatment phases was 9 days. The pharmacokinetic results are presented below:
Table: Summary of comparative bioequivalence data and 90% Confidence Interval (CI) for hydrocortisone:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (A)</th>
<th>Reference (B)</th>
<th>% Ratio</th>
<th>90% Confidence Interval for A/B</th>
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<td>( \text{AUC}_{0-t} )</td>
<td>1130.86</td>
<td>1130.37</td>
<td>100.0426</td>
<td>97.5108 to 102.6401</td>
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<tr>
<td>( C_{\text{max}} )</td>
<td>343.26</td>
<td>314.97</td>
<td>108.9811</td>
<td>102.6162 to 115.7408</td>
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</table>

Conclusion
The 90% confidence intervals of the test/reference ratio for \( \text{AUC}_{0-t} \) and \( C_{\text{max}} \) values for hydrocortisone for the 20 mg strength lie within the acceptable limits of 80.00% to 125.00%, 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 Hydrocortisone 20 mg Tablets (Auden Mckenzie (Pharma Division) Limited).

As the 10 mg and 20 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 20 mg tablet strength can be extrapolated to the 10 mg strength tablet.

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

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

IV.5 Clinical safety
No new safety data were submitted and none are required.

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 Hydrocortisone Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:
**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 study, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s test product Hydrocortisone 20 mg Tablets and the reference product Hydrocortisone 20mg Tablets (Auden Mckenzie (Pharma Division) Limited).

The grant of Marketing Authorisations is recommended for these applications.

**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 products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with hydrocortisone 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 Hydrocortisone Tablets is presented below:
Hydrocortisone 20 mg Tablets

Each tablet contains 20mg hydrocortisone.
It also contains lactose,
For oral use,
Use only as directed by a doctor.
Read the package leaflet before use,
Do not store above 25°C.
Store in the original package in order to protect from light.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

PL 20046/0303
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Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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<tr>
<td>To update sections 1, 2, 4.2, 4.3, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2, 6.2, 6.6 of the SmPCs and corresponding sections of the PIL in-line with the QRD template and excipients guideline.</td>
<td>UK/H/5777/001-002/IB/001</td>
<td>SmPC and PIL</td>
<td>22/03/2017</td>
<td>21/04/2017</td>
<td>Approved on 19/04/2017</td>
<td>Yes-see Annex 1</td>
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Our Reference: PL 20046/0302-0002
PL 20046/0303-0002

Product: Hydrocortisone 10 mg Tablets
Hydrocortisone 20 mg Tablets

Marketing Authorisation Holder: Focus Pharmaceuticals Limited

Active Ingredient(s): Hydrocortisone

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/5777/001-002/IB/001

Reason:
To update sections 1, 2, 4.2, 4.3, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2, 6.2, 6.6 of the SmPCs and corresponding sections of the patient information leaflet (PIL) in-line with the QRD template and excipients guideline.

Supporting Evidence
Revised SmPC fragments and PIL.

Evaluation
The proposed changes to the SmPCs and PIL are in-line with the QRD template and excipients guideline. The updated SmPC fragments and PIL have been incorporated into the Marketing Authorisation.

Conclusion
The proposed changes to the SmPCs and PIL are acceptable.

In accordance with Directive 2010/84/EU, the current approved UK versions of the SmPCs and package leaflet for this product is available on the MHRA website.

Decision - Approved on 19 April 2017.