HYDROCORTISONE 10 MG TABLETS

(Hydrocortisone)

PL 20072/0238

UKPAR

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LAY SUMMARY

The MHRA granted Waymade Plc (trading as Sovereign Medical) a Marketing Authorisation (licence) for the medicinal product Hydrocortisone 10 mg Tablets on 27 September 2012. This product is a prescription-only medicine (POM).

Hydrocortisone 10 mg Tablets contains the active ingredient hydrocortisone which belongs to a group of medicines called steroids. Their full name is corticosteroids. These are used to replace adrenal hormones in your body, which you may be lacking.

Corticosteroids occur naturally in the body and help to maintain health and well-being. Boosting your 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 your condition worse. You must take this medicine regularly to get maximum benefit from it.

This medicine is used:
- as replacement therapy for children with congenital adrenal hyperplasia which affects your body’s natural production of steroids
- in an emergency to treat severe asthma and allergic reactions in adults and children.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Hydrocortisone 10 mg Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

The licence underwent a change of ownership (CoA) to the Marketing Authorisation Holder (MAH) Amdipharm PLC on 09 May 2013 (PL 20072/0238).
HYDROCORTISONE 10 MG TABLETS
PL 20072/0238

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Waymade Plc, a Marketing Authorisation for the medicinal product Hydrocortisone 10 mg Tablets (PL 06464/2876) on 27 September 2012. This product is a prescription-only medicine (POM).

Hydrocortisone 10 mg Tablets are indicated for:

- replacement therapy in congenital adrenal hyperplasia in children.
- the emergency treatment of severe bronchial asthma, drug hypersensitivity reactions, serum sickness, angioneurotic oedema and anaphylaxis in adults and children.

This is an application for a known active substance submitted according to Article 8.3 of Directive 2001/83/EC as amended, as a line-extension to Hydrocortisone 20 mg Tablets (PL 06464/0701) which was first authorised to The Boots Company Plc in 1972 and subsequently underwent a change of ownership to the current Marketing Authorisation Holder (MAH), Waymade Plc on 07 January 1999.

Hydrocortisone is an adrenal corticosteroid having glucocorticoid and some mineralocorticoid properties. Hydrocortisone is the synthetic form of the endogenously produced cortisol and is used in glucocorticoid replacement therapy. Following oral administration, hydrocortisone is rapidly and well absorbed from the gastrointestinal tract and the absorption and bioavailability has been reported to be more than 95% for an oral 20 mg dose (tablets).

No new non-clinical data have been submitted, which is acceptable given that the product is a line-extension of an approved product licence containing a well-known active substance.

One bioequivalence study (single dose) was submitted to support this application, comparing the higher strength test product Hydrocortisone 20 mg Tablets (Waymade Plc) and the reference product Hydrocortisone 20 mg Tablets (Merck Sharp and Dohme, Portugal). As Merck Sharp and Dohme are not currently marketing Hydrocortisone 20 mg Tablets in the UK, the reference product was obtained from the Portuguese market. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the product is a line-extension of an approved product licence containing a well-known active substance.

No new or unexpected safety concerns were raised during the assessment of this application and it was, therefore, judged that the benefits of taking Hydrocortisone 10 mg Tablets outweigh the risks; hence a Marketing Authorisation has been granted.

The licence underwent a change of ownership (CoA) to the Marketing Authorisation Holder (MAH) Amdipharm PLC on 09 May 2013 (PL 20072/0238).
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Hydrocortisone.
Chemical name: 11β,17,21-Trihydroxypregn-4-ene-3,20-dione

Structure:

\[
\text{Molecular formula: } C_{21}H_{30}O_5
\]
\[
\text{Molecular weight: } 362.5
\]

Appearance: Hydrocortisone is a white or almost white, crystalline powder.

Solubility: Hydrocortisone is practically insoluble in water, sparingly soluble in acetone and in ethanol (96 per cent), slightly soluble in methylene chloride.

Hydrocortisone is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance hydrocortisone are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

MEDICINAL PRODUCT
Other ingredients
Other ingredients consist of pharmaceutical excipients, lactose monohydrate, pregelatinised starch and calcium stearate.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of this product.
Pharmaceutical development
The aim of the development programme was to formulate safe, efficacious, tablets containing 10 mg hydrocortisone (per tablet).

Suitable pharmaceutical development data have been provided for this application.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

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

Finished product specification
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The finished product is packaged in the following presentations:

- amber glass bottles with high density polyethylene (HDPE)/polypropylene cap containing 100 tablets
- polyvinyl chloride (PVC)/aluminium foil blister packs containing 30 tablets

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability
Stability studies were performed in accordance with current guidelines on batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months for the amber bottles and 18 months for the PVC/aluminium foil blister packs, with the storage conditions ‘Do not store above 25°C.’

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory.
A package leaflet has previously been submitted to the MHRA for Hydrocortisone 20 mg Tablets (PL 06464/0701), along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains. As the proposed PIL for Hydrocortisone 10 mg Tablets (PL 06464/2876) is similar in layout and content to the approved PIL for Hydrocortisone 20 mg Tablets (PL 06464/0701), additional readability testing is not deemed necessary.

**MAA Form**
The MAA form is satisfactory.

**Expert Report (Quality Overall Summary)**
A quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
It is recommended that a marketing authorisation is granted for this application.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
The pharmacological, pharmacokinetic and toxicological properties of hydrocortisone are well-known. As this product is a line-extension of an approved product licence containing a well-known active substance, no further data have been submitted and none are required. An overview based on a literature review is, thus, appropriate.

NON-CLINICAL EXPERT REPORT
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
Since this line-extension application for Hydrocortisone 10 mg Tablets is a different strength of a well-established active substance, in the same form as the approved product Hydrocortisone 20 mg tablets, it is not likely to change the total market of hydrocortisone and will not lead to an increased exposure to the environment. An environmental risk assessment (ERA) is therefore not deemed necessary.

CONCLUSION
It is recommended that a marketing authorisation is granted for this application.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of hydrocortisone is well-known. With the exception of the bioequivalence study, no pharmacokinetic or pharmacodynamic data were submitted for this line-extension application, and none were required for an application of this type.

The following bioequivalence study was submitted:

An open label, randomised, two-treatment, two-sequence, single dose, crossover study to compare the pharmacokinetics of the test product Hydrocortisone 20 mg Tablets (Waymade Plc) versus the reference product Hydrocortisone 20 mg Tablets (Merck Sharp and Dohme, Portugal) in healthy adult volunteers under fasted conditions.

All volunteers were administered dexamethasone 2 mg (0.5 mg x 4 tablets) 9 hours prior to dosing of the study drug in order to suppress endogenous hydrocortisone production.

On the day of dosing, all volunteers received a single oral dose of either the test or the reference product administered with 240 ml of water under fasted conditions. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 16 hours post dose. The washout period between treatment periods was at least 4 days.

The pharmacokinetic results for hydrocortisone, for the test product versus the reference product are presented below (geometric least squares mean with ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>(In-transformed) Geometric Least Squares Mean</th>
<th>90% Confidence Interval (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product-B</td>
<td>Reference Product-A</td>
</tr>
<tr>
<td>C_{max} (ng / mL)</td>
<td>276.640</td>
<td>273.184</td>
</tr>
<tr>
<td>AUC_{0-t} (ng h / mL)</td>
<td>1011.442</td>
<td>1001.095</td>
</tr>
<tr>
<td>AUC_{0-} (ng h / mL)</td>
<td>1029.183</td>
<td>1019.683</td>
</tr>
</tbody>
</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
90% CI* 90% Geometric Confidence Interval using log-transformed data
Reference Product A= Hydrocortisone 20 mg Tablets (Merck Sharp and Dohme, Portugal)
Test product B= Hydrocortisone 20 mg Tablets (Waymade Plc)
The 90% confidence intervals for AUC and $C_{\text{max}}$ for test versus reference product for hydrocortisone are within predefined acceptance criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 rev 1/, Corr**). Thus, the data show that the 20 mg test product is bioequivalent to the 20 mg reference product.

As the 10 mg and 20 mg strengths of the product meet the criteria specified in the current guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98rev 1/Cor **), the results and conclusions of the bioequivalence study on the 20 mg strength can be extrapolated to the 10 mg strength.

**Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for this application.

**Efficacy**
No new efficacy data were submitted and none were required for this application.

**Safety**
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labels are acceptable. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

**Clinical Expert Report**
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for this product.

**Conclusion**
There are no objections to the approval of this product from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Hydrocortisone 10 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for an application of this type.

Bioequivalence has been demonstrated between the applicant’s Hydrocortisone 20 mg Tablets and its respective reference product Hydrocortisone 20 mg Tablets (Merck Sharp and Dohme, Portugal). As the 10 mg and 20 mg strengths of the product meets the biowaiver criteria specified in the current guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98rev 1/Corr**), the results and conclusions of the bioequivalence study on the 20 mg strength can be extrapolated to the 10 mg strength tablet.

SAFETY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of hydrocortisone is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s test product and its respective reference product. 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.
HYDROCORTISONE 10 MG TABLETS

PL 20072/0238

STEPS TAKEN FOR ASSESMENT

1 The MHRA received the marketing authorisation application on 13 June 2011.

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 17 June 2011.

3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 29 September 2011, 05 April 2012, 10 July 2012, 04 August 2012 and 20 August 2012 and the clinical dossier on 29 September 2011 and 05 April 2012.

4 The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 24 November 2011, 24 April 2012, 12 July 2012, 06 August 2012 and 29 August 2012 and clinical dossier on 24 November 2011 and 24 April 2012.

5 The application was determined on 27 September 2012.
HYDROCORTISONE 10 MG TABLETS

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STEPS TAKEN AFTER ASSESSMENT

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 April 2013</td>
<td>Change of Ownership (CoA)</td>
<td>CoA from PL 06464/2876 to PL 20072/0238</td>
<td>Approved 09 May 2013.</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

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.
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.
Hydrocortisone 10 mg Tablets

Each tablet contains 10 mg hydrocortisone. Also contains lactose monohydrate.

See leaflet for further information.

For oral use. Take as directed by your doctor.

Keep out of the reach and sight of children.

Do not store above 25°C.

Hydrocortisone
10 mg tablets

30 Tablets

MHRA PAR – Hydrocortisone 10 mg Tablets (PL 20072/0238)
BLISTER: