Decentralised Procedure

RMS Day 210 Assessment Report

OVERVIEW

Budenofalk
9 mg gastro-resistant granules
(Budesonide)

UK/H/2778/001/DC

Applicant: Dr. Falk Pharma GmbH

Reference Member State	UK
Start of the procedure:	30 October 2009
Date of this report:	10 December 2010 (Day 211)

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product(s) in the RMS	Budenofalk Uno 9 mg Gastro-resistant Granules
INN (or common name) of the active substance(s):	Budesonide
Pharmaco-therapeutic group (ATC Code):	A07EA
Pharmaceutical form(s) and strength(s):	9 mg Gastro-resistant Granules
Reference Number(s) for the Decentralised Procedure	UK/H/2778/001/DC
Reference Member State:	UK
Member States concerned:	AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, HU, IE, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI and SK.
Applicant (name and address)	Dr Falk Pharma GmbH; Leinenweberstrasse 5, D-79108 Freiburg, Germany
Names and addresses of manufacturer(s) of dosage form	Losan Pharma GmbH; Otto-Hahn Strasse 13, Neuenburg, D-79395, Germany Riemser Speciality Production GmbH; Gartenstrasse 6/ Vorholzweg 16, Laupheim, D-88471, Germany
Names and addresses of manufacturer(s) responsible for batch release in the EEA	Dr Falk Pharma GmbH; Leinenweberstrasse 5, D-79108 Freiburg, Germany
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I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the questions raised by RMS and CMSs on quality, safety and efficacy, the RMS considers that the application for Budenofalk Uno 9 mg gastro-resistant granules in the treatment of acute collagenous colitis, could be approvable provided that satisfactory response is given to the outstanding SmPC issues (Section VI).

II. EXECUTIVE SUMMARY

II.1 Problem statement

The product under consideration is Budenofalk Uno 9 mg gastro-resistant granules for the treatment of acute collagenous colitis. This is an article 8(3) application with United Kingdom as the RMS. The first EU marketing authorisation of budesonide capsules (Budenofalk 3mg) (as referred to in this application) was granted in 1998.

With UK as the Reference Member State in this Decentralised Procedure, Dr Falk Pharma GmbH, Germany is applying for the Marketing Authorisations for Budenofalk Uno 9mg gastro-resistant granules in AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, HU, IE, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI and SK.

II.2 About the product

This decentralised application is for sachet of gastro-resistant granules containing 9mg of the glucocorticoid budesonide, under the name Budenofalk Uno 9 mg gastro-resistant granules with UK as the Reference Member State. The proposed product is a sachet of 9 mg gastro-resistant granules of budesonide as active substance. Its composition is based on an existing product, Budenofalk 3 mg capsules (PL 08637/0002) marketed by the applicant, Dr. Falk Pharma GmbH in UK since 4 January 1999 (outgoing MR since 9 April 2001).

Budesonide is classified in the "corticosteroids acting locally" group of the Anatomical Therapeutic Chemical (ATC) classification system, ATC code A07EA06. It is characterised by its high affinity to the glucocorticoid receptor and high presystemic and hepatic metabolism which results in potent local anti-inflammatory activity. Budesonide, is a mixture of the C-22S (epimer A) and the C-22R (epimer B) epimers of 16,α17α butylidenedioxy-11β,21-dihydroxypregna-1,4-diene-3,20-dione. It is stated to be poorly absorbed *in vivo* and undergoes extensive first-pass metabolism. Budenofalk is formulated to deliver the budesonide to the lower part of the GI-tract, where it has a local anti-inflammatory effect. Oral preparations of budesonide, which is a topically acting glucocorticoid steroid are used to treat inflammatory bowel disease.

II.3 General comments on the submitted dossier

The present application is submitted under article 8(3) of directive 2001/83/EC, as amended (known active substance) through decentralised procedure. The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory framework.

Satisfactory overall summaries of the dossier have been submitted regarding the quality, non-clinical and clinical parts have been submitted.

No Risk Management Plan other than documentation of pharmacovigilance system has been provided. For generics this is generally acceptable if the innovator product is not subject to specific risk management measures, which is not the case for budesonide.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

GMP
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product, except for the API manufacturing site. A replacement QP declaration is required to ensure acceptable standards of GMP are in place.

GLP
No new non-clinical studies were submitted in support of this application. Reference is made to published data in the Non-Clinical Overview but the GLP status of these cannot be verified.

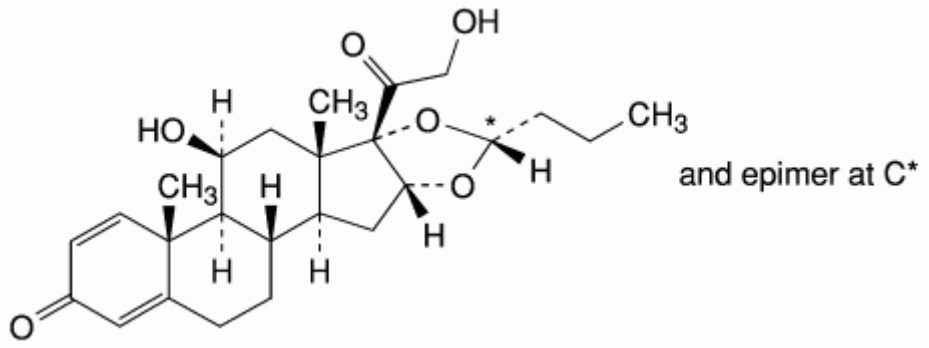
GCP
No issues regarding GCP aspects have been identified during the review of this dossier.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The drug substance, budesonide, contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of a mixture of the C-22S (epimer A) and the C-22R (epimer B) epimers of 16α,17-[(1RS)-butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione, calculated with reference to the dried substance and has the following structure:



Budesonide is a white or almost white, crystalline powder, practically insoluble in water, freely soluble in methylene chloride and sparingly soluble in alcohol. The micronized version of the drug substance is manufactured by SICOR Società Italiana Corticosteroidi S.R.L. is subject to the Ph. Eur. Certificate of Suitability R1-CEP 1997-067-Rev 05.

The drug substance specification includes tests for appearance, solubility, identification, related substances, residual solvents, loss on drying, particle size and assay.

The API is packed in double polyethylene bags within fibre drums. When stored in the proposed packaging, a re-test period of 36 months is acceptable.

Drug Product

The drug product is formulated as gastro-resistant granules which are white to off-white with a lemon smell and flavour. The product is based on the previously authorised Budenofalk 3 mg Capsule product. The granules have the same qualitative and quantitative composition as the capsules with the addition of flavour blend to improve palatability. Comparative dissolution studies have identified that the proposed product has a similar dissolution profile to the capsules.

The drug product is manufactured by Losan Pharma GmbH (Germany) and Riesmer Specialty Production GmbH (Germany) [manufacture of bulk granules only]. Batch release is undertaken by Dr Falk Pharma GmbH (Germany) only. The manufacturing process is well characterised and the critical steps and in-process controls identified. Validation of the manufacturing process will be undertaken on the first three production scale batches.

The excipients are well known and widely used in the pharmaceutical industry. The drug product specification and the methods used to control the drug product appear appropriate.

The product is packaged within sachets of polyester (PETP)/ aluminium (Alu)/ polyethylene (LDPE) and foil. It is proposed that the product is stable for 36 months within this packaging material.

III.2 Non clinical aspects

The pharmacological, pharmacokinetic and toxicological properties of budesonide are well known. As budesonide is a well known active substance, no further studies are required and the applicant has provided none. An overview based on a literature review is, thus, appropriate.

No non-clinical studies have been conducted; a review of the published data has been presented. The non-clinical overview has been written by Bernhard Tewes PhD, of Dr Falk Pharma GmbH, Germany and with suitable experience in pharmacology, pharmacokinetics and toxicology. The overview cites over 60 references up to 2008 in the published literature and is dated September 2009. The non-clinical overview discusses the information from cited literature for the active drug substance, budesonide. The overview is acceptable.

All the impurities and residual solvents are controlled at acceptable ICH and Pharm Eur limits. The Applicant argued that as the product is the same as that already approved and that it is likely that its use to treat collagenous colitis will increase overall use of the active substance. No change in the environmental risk assessment of budesonide is anticipated.

There are no major objections from a non-clinical point of view, to the grant of a marketing authorisation of Budenofalk Uno 9 mg gastro-resistant granules.

III.3 Clinical aspects

To support the application, the applicant has submitted 5 studies based on publications; as report 9 clinical pharmacology studies and 2 In-vitro dissolution studies.

Both oral preparations of Budenofalk (capsules and sachets) contain Eudragit-coated gastro-resistant granules which release budesonide at pH ≥6.4. The granules in the sachets and capsules are identical. The clinical studies with oral Budenofalk that are presented in this application were carried out with the existing capsule formulation.

The applicant has provided as evidence 3 Phase III Clinical Studies in patients with active collagenous colitis. These comprise 1 controlled clinical trial with Budenofalk, Dr Falk Pharma GmbH and 2 controlled clinical trials performed with Entocort, AstraZeneca. Therefore, the 2 studies performed with Entocort, AstraZeneca are not considered pivotal phase III studies, but as supportive data only.

The applicant has provided sufficient data, with primary analysis, as presented, shows a statistically significant difference on responder rates.

There were no safety concerns arising from the studies submitted and Cumulative data on the safety of Budenofalk® confirm and support the good safety profile noted thus far. The current product information adequately reflects the present knowledge and experience with Budenofalk®.

Pharmacovigilance system

The RMS considers that 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.

Risk Management Plan
Not applicable

Periodic Safety Update Report (PSUR)

The applicant has not requested a different PSUR cycle upon approval. The RMS considers the submission of 6-monthly PSURs not necessary and recommends PSUR submissions to be aligned with the EU Harmonised Birthday and related Data Lock Points as published on the HMA website: **agreed EU HBD (1992-04-30), next DLPs: 2010-04-30, 2013-04-30**

IV. BENEFIT RISK ASSESSMENT

The applicant has now provided an adequate review of both published data and clinical study data to demonstrate a positive risk/benefit outcome. Therefore, approval is recommended for Budenofalk Uno 9 mg gastro-resistant granules for the treatment of acute collagenous colitis.

V. PROPOSED LIST OF OUTSTANDING ISSUES

V.1 Quality aspects

Potential serious risks to public health
None.

Points for clarification
None

V.2 Non-clinical aspects

Potential serious risks to public health
None

Points for clarification
None

V.3 Clinical aspects

Potential serious risks to public health
None

Points for clarification
None

VI. PROPOSED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

Legal Status
POM

Follow-up measures
N/A

Specific obligations
N/A

VI.1 Summary of Product Characteristics (SPC)

None

VI.2 Package Leaflet (PL)

VI.2.1 Package Leaflet

None

VI.2.2 Assessment of User Testing

None.

VI.3 Labelling

None.

VI.4 Module 1

None.