

Public Assessment Report

Mutual Recognition Procedure

Budenofalk 2mg/Dose Rectal Foam

(budenoside)

Procedure No: UK/H/0334/001/MR

UK Licence No: PL 08637/0011

Dr Falk Pharma GmbH

LAY SUMMARY

Budenofalk 2mg/dose Rectal Foam (budesonide)

This is a summary of the Public Assessment Report (PAR) for Budenofalk 2mg/dose Rectal Foam (PL 08637/0011; UK/H/0334/002/DC). It explains how the application for Budenofalk 2mg/dose Rectal Foam 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 Budenofalk 2mg/dose Rectal Foam.

For practical information about using Budenofalk 2mg/dose Rectal Foam, patients should read the package leaflet or contact their doctor or pharmacist.

Budenofalk 2mg/dose Rectal Foam may be referred to as Budenofalk Rectal Foam in this report.

What is Budenofalk Rectal Foam and what is it used for?

Budenofalk Rectal Foam is used for the treatment of:

- inflammation of the rectum (back passage) and the lower part of the colon (sigmoid colon), known by doctors as ulcerative colitis.

How does Budenofalk Rectal Foam work?

Budenofalk Rectal Foam contains the active substance budesonide, a type of locally acting steroid with a high local anti-inflammatory effect used to treat inflammatory bowel disease. It is thought that the mode of action of budesonide is predominantly based on a local action in the gut.

How is Budenofalk Rectal Foam used?

Budenofalk Rectal Foam should always be used exactly as instructed by the doctor. The patient should check with the doctor or pharmacist, if he/she is not sure.

Budenofalk Rectal Foam may only be used rectally; it has to be inserted through the anus. It is not intended to be taken by mouth. Budenofalk Rectal Foam should not be swallowed.

Please read section 3 of the Patient Information Leaflet (available on the MHRA website) for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Budenofalk Rectal Foam can only be obtained with a prescription.

What benefits of Budenofalk Rectal Foam have been shown in studies?

The company provided its own data on efficacy and safety studies.

These studies have shown that Budenofalk Rectal Foam is effective in treating patients with distal ulcerative colitis and is well tolerated.

What are the possible side effects from Budenofalk Rectal Foam?

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If any of the following symptoms are experienced by the patient after using Budenofalk Rectal Foam, the patient should contact his/her doctor immediately:

- infection

- headache

The following side effects have been reported:

The most common side effects with Budenofalk Rectal Foam (that affect less than 1 in 10 patients) are:

- burning or pain in the rectum

For the full list of all side effects reported with Budenofalk Rectal Foam, see section 4 of the package leaflet.

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

Why is Budenofalk Rectal Foam approved?

It was concluded that, in accordance with EU requirements, Budenofalk Rectal Foam has been shown to be effective in the treatment of inflammation of the rectum (back passage) and the lower part of the colon (sigmoid colon), known by doctors as ulcerative colitis and the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Budenofalk Rectal Foam?

Safety information has been included in the Summary of Product Characteristics and the package leaflet for Budenofalk Rectal Foam, 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 as well.

Other information about Budenofalk Rectal Foam.

A national Marketing Authorisation for Budenofalk Rectal Foam (PL 08637/0011) was granted in the UK to Dr Falk Pharma GmbH on 15 June 2006.

Through a first-wave Mutual Recognition Procedure, Austria, Denmark, Spain, Finland, Greece, Ireland, Italy, Luxembourg, Romania and Sweden agreed to grant a Marketing Authorisation for the product on 23 January 2009.

The full PAR for Budenofalk Rectal Foam follows this summary.

For more information about treatment with Budenofalk Rectal Foam read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2015.

Budenofalk 2mg/dose Rectal Foam (budesonide)

PL 08637/0011

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 5
Pharmaceutical assessment	Page 6
Preclinical assessment	Page 15
Clinical assessment	Page 17
Overall conclusions and risk benefit assessment	Page 24
Summary of Product Characteristics	Page 25
Patient Information Leaflet	Page 26
Labelling	Page 27
Annex 1 – Table of contents of the PAR update for MRP and DCP	Page 29
Annex 1.1	Page 30

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a Marketing Authorisation for the medicinal product Budenofalk 2mg/dose Rectal Foam (PL 08637/0011) to Dr Falk Pharma GmbH on 15 June 2006. Subsequently, the product went through a first-wave Mutual Recognition Procedure involving the Concerned Member States (CMS), Austria, Denmark, Spain, Finland, Greece, Ireland, Italy, Luxembourg, Romania and Sweden; the procedure was completed on 23 January 2009.

The product is a Prescription Only Medicine.

The application was submitted as an abridged application according to Article 10.1 [formerly article 10.1(a)(iii), last paragraph] of Directive 2001/83/EC, as a line extension to Budenofalk 3mg Capsules (PL 08637/0002). The application represents a change in pharmaceutical form, strength and route of administration.

The product contains the active ingredient budesonide, which is a glucocorticosteroid, and is indicated for the treatment of active ulcerative colitis that is limited to the rectum and the sigmoid colon.

A clinical programme of Phase I, IIb and III trials has been presented in support of this application.

PHARMACEUTICAL ASSESSMENT

1. INTRODUCTION

This national standard abridged application is for a rectal foam containing 2mg budesonide per actuation (per 1.2 g product) presented as an emulsion in a pressurised container. The applicant has proposed that the product is indicated for the treatment of active ulcerative colitis that is limited to the rectum and sigmoid colon in adults.

This application has been made under Article 10.1 [formerly last paragraph of Article 10.1(a)(iii)] of Directive 2001/83/EC, as amended, as a line extension to Budenofalk 3mg Capsules (PL 08637/0002). The application represents a change in pharmaceutical form, strength and route of administration.

The applicant sought scientific advice in the UK in 1999 and in Germany in 2000.

2. COMMON TECHNICAL DOCUMENT SUMMARIES

2.1 INTRODUCTION

A brief but satisfactory introduction has been provided.

2.2 QUALITY OVERALL SUMMARY (QOS)

A satisfactory Quality Overall Summary has been provided.

3. ACTIVE SUBSTANCE

3.1 GENERAL INFORMATION

3.1.1 Nomenclature

rINN: Budesonide

Chemical names: C-22*S* (epimer A) and C-22*R* (epimer B) epimers of 16 α ,17-[(1*RS*)-butylidenebis(oxy)]-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione

3.1.2 Structure

C₂₅H₃₄O₆

MW: 430.5

3.1.3 General Properties

White to almost white crystalline powder, practically insoluble in water, freely soluble in methylene chloride and soluble in alcohol. Solutions of budesonide are less stable above pH 4.

3.2 MANUFACTURE

3.2.1 Manufacturer

A suitable site of manufacture has been provided.

3.2.2 Manufacturing process description and process controls

A copy of the current Certificate of Suitability has been provided. No requirements in addition to the requirements of the Ph Eur monograph for budesonide are stated on the certificate.

Details are covered by the Certificate of Suitability.

3.2.3 Control of materials

The Certificate of Suitability states that the active substance meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

Details are covered by the Certificate of Suitability.

3.2.4 Controls of Critical Steps and Intermediates

Details are covered by the Certificate of Suitability.

3.2.5 Process validation and/or valuation

Details are covered by the Certificate of Suitability.

3.3 CHARACTERISATION

3.3.1 Elucidation of structure and other characteristics

Details are covered by the Certificate of Suitability.

Budesonide has a single chiral carbon, but is produced as a mixture of the two epimers.

3.3.2 Impurities

Potential impurities originating from the synthetic route have been described:

3.4 CONTROL OF ACTIVE SUBSTANCE

3.4.1 Specification

The active substance is used as a micronised grade and is controlled according to the Ph Eur monograph for Budesonide as well as the Certificate of Suitability. In addition, particle size limits have been stated.

3.4.2 Analytical procedures / validation

The methods are those of the monograph supplemented with a laser diffraction method for particle size analysis.

3.4.3 Batch analyses

Satisfactory Certificates of Analysis have been provided for batches manufactured at the proposed site in 1996, 2002 and 2003.

3.4.4 Justification of specification

The applicant has provided a justification for the proposed specification.

3.5 REFERENCE STANDARDS OR MATERIALS

Reference standards for budesonide and the related substances are supplied by a named supplier. The budesonide standard has been characterised against EPCRS. Satisfactory Certificates of Analysis have been provided for the reference standards.

3.6 CONTAINER CLOSURE SYSTEM

Batches of active substance are stored in double polyethylene bags in fibre carton drums. A satisfactory specification and declaration on suitability for food contact have been provided for the polyethylene bags.

3.7 STABILITY

3.7.1 Stability summary and conclusions

Stability data have been provided for batches of active substance (including 2 micronised batches) manufactured at the proposed site between 1997 and 2001. The batches were stored in the same type of containers as proposed for the commercial packs to simulate the bulk containers.

Analytical methods were as used for routine batch release.

Stability data provided: long-term ICH conditions

Test parameters: appearance, identification, loss on drying, isomers R and S, assay, related substances.

Only minor changes in assay and related substances were seen after 5 years storage under long-term conditions. The active substance manufacturer has proposed a re-test period of 5 years based on the data provided. This is acceptable.

3.7.2 Post-approval stability protocol and stability commitment

A minimum of 10% of batches (at least one per year) are included in the stability programme and tested over 5 years.

4. MEDICINAL PRODUCT

4.1 DESCRIPTION AND COMPOSITION OF THE MEDICINAL PRODUCT

Table 1: Qualitative composition of ingredients

Ingredient	Reference Standard
Budesonide	Ph Eur
Propylene glycol	Ph Eur
Purified water	Ph Eur
Emulsifying wax	NF
Macrogol stearyl ether	Ph Eur
Cetyl alcohol	Ph Eur
Citric acid monohydrate	Ph Eur
Disodium edetate	Ph Eur
Sorbic acid	Ph Eur
Propane / butane 2.5 bar	NF

No Genetically Modified Organisms are included in the product.

4.2 PHARMACEUTICAL DEVELOPMENT

4.2.1 Components of the medicinal product

The function of each ingredient included in the product has been described. No results have been provided for excipient-active compatibility studies. However, no major instability problems have been seen in the stability programme.

4.2.2 Formulation development

A summary of the development studies has been provided. This is satisfactory and covers selection of the formulation, and details of the batches used in the pre-clinical and clinical studies. Data have also been provided to demonstrate the accuracy and precision of the metering device.

4.2.3 Physicochemical, biological and microbiological properties

The pressurised product has been shown to exhibit sufficient self-preserving power. A test for the efficacy of antimicrobial preservation has been performed in accordance with the Ph Eur method. The acceptance criteria were met.

Various studies on parameters that may affect the physical properties of the foam have been summarised.

4.2.5 Manufacturing process development

A satisfactory summary has been provided. Also see section 4.3.5.

4.2.6 Container and closure system

Details are provided in section 4.7 of this report.

4.3 MANUFACTURE

4.3.1 Manufacturer(s)

A copy of a GMP Certificate has been provided for the proposed manufacturing site. The manufacturing site was last inspected by the Regional Medicines Inspectorate of North-Western Switzerland on 6th May 2003. A Mutual Recognition Agreement is in place with Switzerland.

The product will be released at Dr. Falk Pharma GmbH, Leinenweberstr. 5, 79108 Freiburg, Germany. A copy of a GMP Certificate has been provided together with the Manufacturing Licence for the site.

4.3.2 Batch formula

A satisfactory formula has been provided for the manufacture of the proposed maximum batch size.

4.3.3 Description of manufacturing process and process controls

A flow chart of the manufacturing process has been provided.

4.3.4 Control of critical steps and intermediates

Satisfactory tests and acceptance criteria have been set for in-process testing. Risk analysis of control of the critical steps has been performed and the results presented.

4.3.5 Process validation and/or evaluation

Process validation studies have been reported for the manufacture of 5 batches of finished product. Levels of emulsifying agents from 50-100% of target levels have been studied. Results have been provided for the fatty phase, active substance phase and basic emulsion. Results have also been provided for the filling of the emulsion and propellants. Satisfactory results for homogeneity in the cans have been provided. Satisfactory certificates of analysis have been provided for 4 of the 5 batches (see section 4.5.3).

A commitment has been provided that the manufacturing process will be validated at full commercial batch size through the manufacture of at least three batches. A satisfactory validation protocol has been provided. The protocol includes a risk analysis and discussion on the critical manufacturing steps.

4.4 CONTROL OF EXCIPIENTS

4.4.1 Specifications

All ingredients comply with relevant Ph Eur monographs with the exception of Polawax, isobutane, N-propane and N-butane that are controlled to the NF monographs.

Satisfactory Certificates of Analysis have been provided for each ingredient.

4.4.2 Excipients of human or animal origin

The MAA form indicates that no materials of animal or human origin are contained in or used in the manufacturing process for the proposed product.

4.5 CONTROL OF MEDICINAL PRODUCT

4.5.1 Specification

The proposed specification has been provided and is satisfactory.

The specification includes the requirements of the Ph Eur monograph for Rectal Preparations and the category Rectal Foams. The Ph Eur requirements of the monograph Medicated Foams (except that no specific limit is included for relative foam density) and Pressurised Pharmaceutical Preparations are met.

4.5.2 Analytical procedures / Validation of analytical procedures

The in-house methods for assay of budesonide and disodium edetate, and related substances have been suitably validated.

4.5.3 Batch analyses

Batch analysis data have been provided for 5 batches of product manufactured between February 1997 and May 2003. All batches were manufactured at the proposed commercial manufacturing site and packed in cans containing 1.35ml metering heads. The oldest batch fails with respect to budesonide and sorbic acid assay. All other batches comply with the proposed specification, although results were not provided for all specification parameters.

4.5.4 Characterisation of impurities

Synthesis impurities and degradation products have been characterised using an HPLC method.

Analytical reports have been provided that summarise the studies performed that resulted in identification of the named impurities.

Acute and subacute toxicity studies and mutagenicity studies have been reported. The suitability of these studies has been considered by the pre-clinical assessor, with respect to a named degradation product, for which levels have been seen to increase throughout shelf-life, potentially to a level that requires toxicological qualification.

4.5.5 Justification of specifications

A justification for the release and shelf-life limits has been provided. This is satisfactory.

4.6 REFERENCE STANDARDS OR MATERIALS

Satisfactory details of the suppliers and certificates of analysis have been provided for budesonide, sorbic acid and for related substances.

4.7 CONTAINER-CLOSURE SYSTEM

The product is presented in an aluminium container with a metering valve system. The Ph Eur requirements of the monograph Pressurised Pharmaceutical Preparations are met. Drawings have been provided. The container is internally coated with protective lacquers and resins. Compatibility results following visual examination have been provided for several lacquers. No colouration or damage was seen after 6 months at room temperature or under accelerated conditions. The canister is provided with 14 PVC applicators (with polyethylene protective caps) coated with white soft paraffin (Ph Eur) and liquid paraffin (Ph Eur), together with bags for disposal of the used applicators. A plastic safety tab prevents accidental actuation of the canister. The PVC applicators are prepared from PVC that complies with the Ph Eur 'Materials based on plasticised PVC for containers for human blood and blood components'.

To support the proposed lacquers the applicant has provided copies of product/technical data sheets, Material Safety Data Sheets according to Directive 91/155/EEC, TSE declarations and declarations on suitability for food use (mostly in accordance with 2002/72/EC).

Compatibility trials have been conducted between the emulsion and the valves. No evidence of incompatibility was seen at 25°C. The results of studies into potential extractables have been reported. Details of the contact materials and an indication of the contact times have been provided. A general statement has been provided that the materials are approved for food contact, and are used in other pressurised containers for pharmaceutical use (including at least 3 other rectal foam products). It is stated that leaching tests were not performed due to the relative low surface area coming into contact with the emulsion. Migration studies were performed but only with those materials continuously in contact with the suspension.

Suitability of packaging contact materials with respect to food contact:

With respect to contact materials, the components of the metering valve system comply with relevant EU directives.

The product must be vigorously shaken prior to use and the dome depressed fully in the upside down position.

Adequate testing will be performed on receipt of consignments of the packaging components. Specifications and drawings have been provided for batches of packaging components.

4.8 STABILITY

4.8.1 Stability summary and conclusion

Stability data were provided for several batches of product. All batches were manufactured at the proposed commercial site between February 1997 and May 2003 and packed in the proposed commercial packs. All batches were stored in cans sealed with a metering head. Can lacquers were varied.

The analytical methods used were as described for routine batch release. An HPLC method was developed with results generated from October 2003. Results have been provided for one batch stored for 33 months and for two batches stored for 12 months. All three batches indicated at least 95% of the nominal content.

Stability data provided: 25°C/60% (2x30*, 1x24, 1x12*, 1x6* months), 30°C/60% (1x12*, 2x6* months), 40°C/75% (1x9, 1x6 months)

* 1 batch at each time point for the 25°C/60% samples and all 30°C/60% samples stored inverted

Test parameters: appearance, filling weight, weight/puff, number of puffs, foam volume, duration of expansion, pH, purity, assay of budesonide (per can and per puff), sorbic acid and disodium edetate, microbial quality and examination of can interior*.

* porosity check according to DIN 55436/3

A number of out-of-specification results were seen across the stability studies. At 25°C/60%, failures occurred within the proposed shelf life period in weight per puff values, in desonide values, in budesonide assay and in disodium edetate per can. At 30°C/60%, failures occurred in foam volume, in filling weight and in disodium edetate assay. At 40°C/75%, failures in desonide and sorbic acid levels occurred after 6 months and in assay values after 9 months storage. The early failures in weight per puff were due to incomplete filling of the meter head. With experience of handling the canisters these initial problems have been reduced. This is not seen as a key failure in a quality attribute of the stored product. Recent results are satisfactory. Desonide is a key starting material in the synthesis of the active substance and not a degradation product. Where levels of up to 0.6% occur in the stability batches this is due to levels near to the 0.5% limit at time of manufacture. Failures represent a measure of the analytical variation around the inherent level in the batches. Recent batches of active substance have lower levels of desonide such that commercial batches should comply. Again, this is not seen as a quality issue for the product. The other fluctuations in assay values are not reflected in overall trends.

The applicant has proposed a shelf-life of 2 years for product carrying the storage recommendations 'Do not store above 25°C. Do not refrigerate or freeze'. An in-use shelf life of 4 weeks is proposed, supported by the results of an in-use stability study over 4 weeks at 25°C/60% (testing for appearance, purity, assay of budesonide and sorbic acid, and microbial purity).

It is reasonable that the product is to be stored at or below 25°C, but not refrigerated or frozen and a shelf life of 24 months is acceptable.

4.8.2 Post-approval stability protocol and stability commitment

A commitment has been provided that a further two production batches will be placed on store and that the ongoing studies will be continued to the proposed shelf life.

4.9 BIOAVAILABILITY

A clinical programme of Phase I, IIb and III trials has been presented in support of this application. It has been stated that the proposed commercial formulation was used in all phases of the clinical programme. Satisfactory batch data have been provided for all batches of test product used in the clinical studies. However, it is noted that a batch used in the Phase IIb dose-finding study was outside the lower release specification limit for budesonide assay and sorbic acid content, but within the shelf life limits.

Absorption of budesonide is rapid and essentially terminated after 3 hours following rectal administration as an enema. Systemic bioavailability is higher after rectal administration compared to oral administration due to avoidance of first pass metabolism.

Test product: Budenofalk 2mg Rectal Foam

Table 4: Pharmacokinetic results after a single dose and multiple dose study with the test product in 18 healthy subjects.

Test parameter	Test Product Mean \pm SD Day 1	Test Product Mean \pm SD Day 5
AUC _{0-12h} or AUC _{ss} (ng.h/ml)	4.59 \pm 2.94	4.30 \pm 2.58
AUC _{0-∞} or AUC _{ss} (ng.h/ml)	5.36 \pm 3.60	4.30 \pm 2.58
C _{max} (ng/ml)	0.84 \pm 0.55	0.90 \pm 0.49
t _{max} (h)	2.14 \pm 1.28	1.81 \pm 0.88
t _{1/2} (h)	4.05 \pm 1.28	-

No evidence of potential for accumulation is seen.

Serum samples were analysed using a validated method.

5. MAA FORM

The MAA form is satisfactory.

6. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is satisfactory.

7. LABELLING

The labelling is satisfactory.

8. PATIENT INFORMATION LEAFLET

The leaflet is satisfactory.

9. STATEMENT ABOUT THE AUTHOR OF THE OVERALL QUALITY SUMMARY

The Expert for the report on Quality is a pharmacist and is appropriately qualified.

10. CONCLUSIONS

A Marketing Authorisation may be granted

PRECLINICAL ASSESSMENT

Background

Comments below are in response to a request from Pharmaceutical Assessor in relation to the toxicological characterisation of a degradation product (hereafter 'the impurity'), in the above product, for which a submission for a UK licence has been made. In the initial documentation supplied by the company, the impurity limits in the finished product specification at the two-year end of shelf-life were at a concentration that requires toxicological qualification. The submission relates to introduction of a rectal foam containing budesonide for relief of symptoms of ulcerative colitis.

Regulatory Guidance

Reference is made to ICH Q3B on Impurities in New Medicinal Products: it is acknowledged that budesonide is not a new active substance, and to this extent, the guideline is not directly applicable. Nevertheless, the scientific approach to toxicological qualification of an impurity in a new medicinal product is detailed in this guideline and the principles apply in this instance.

GLP Status

Safety studies submitted are compliant with GLP.

Summary of applicant's studies

The applicant has conducted the following studies:

- Ames test (bacterial reverse mutation assay) with the impurity.
- single dose toxicity in the mouse by the intravenous route with budesonide
- single dose toxicity in the mouse by the intravenous route with the impurity
- 2 and 4 week toxicity in the dog by the rectal route with finished drug product (3 studies in total).

Consideration of adequacy of the applicant's studies to qualify the impurity

Ulcerative colitis is a condition which is likely to be associated with repeated, intermittent use of medication which may stretch over decades. The necessary assessment is (see Attachment 3, ICH Q3B):

- general toxicity assessment with repeated dose daily administration in one species by the clinical route of administration (minimum duration of 4 weeks. Given the likelihood of multiple frequent use of product by some patients, 2 weeks is judged insufficient);
- mutation assay in bacteria and chromosomal aberration (clastogenicity) assay in mammalian cells;
- local tolerance assessment.

Whereas the company have completed adequate assessments of single dose toxicity and local tolerance, and the Ames test is valid, the company's studies do not provide necessary information on the impurity in two respects, namely:

- (1) the potential clastogenicity in mammalian cells and
- (2) repeated-dose general toxicity using excess exposure to the impurity.

Conclusions

These points were put to the company, who agreed to reduce the limit for the impurity to a level which does not require toxicological qualification, and therefore no further studies are necessary. As such, there are no pre-clinical issues that prevent authorisation of this product.

CLINICAL ASSESSMENT

1. Introduction

Budenofalk rectal foam contains the steroid budesonide in a foam preparation for topical application to the rectum and sigmoid colon in patients with active distal ulcerative colitis.

2. Background

This application is for a product with different pharmaceutical form, strength and route of administration from the company's original product Budenofalk 3mg capsules (PL 086370002)

3. Indications

The foam is intended for the treatment of active ulcerative colitis that is limited to the rectum and sigmoid colon.

4. Dose and Dosage schedule

One actuation of 2mg budesonide daily in adults over the age of 18years.
No experience in children.

5. Toxicology

No formal data are presented and none are required for this application.

6. Clinical Pharmacology

As is stated in the Clinical Pharmacology summary, Budesonide, a non-halogenated glucocorticosteroid (16*a*, 17*a* -butylidendioxy-11 β , 21-dihydroxy- 1, 4-pregnadien -3,20 -dion) structurally related to hydroxyprednisolone, belongs to the corticosteroids with the highest receptor affinity. It shows a high ratio of topical to systemic activity, explained by a high hepatic first-pass metabolism. Budesonide has anti-inflammatory, anti-allergic, anti-exudative and anti-oedematous properties. The pharmacological action of budesonide is attributed to inhibition of mediator release from mast cells. Additionally, a stabilisation of bio-membranes has been demonstrated.

The 16*a*, 17*a*-acetal group of budesonide facilitates enhanced topical anti-inflammatory activity, greater affinity for the glucocorticoid receptor, and stability in extra-hepatic tissues. Budesonide undergoes extensive hepatic first-pass metabolism (approximately 90%) via oxidative and reductive pathways, resulting in metabolites with little to no biologic activity. The two main metabolites, 6 β -hydroxy budesonide and 16*a*-hydroxy prednisolone show considerably less glucocorticoid activity than the parent drug. Main pharmacological properties of budesonide as compared to prednisolone are depicted in the following table:

Comparison of main pharmacological properties of the glucocorticoid prednisolone and budesonide

	Prednisolone	Budesonide
Relative activity for glucocorticoid receptor	13	195
Relative topical anti-inflammatory	1	1000
Clearance (l/min)	0.23	1.20
Systemic availability (%)	80	9

First developed for treatment of bronchial asthma and allergic rhinitis, budesonide has also been introduced for the treatment of IBD. Delayed-release budesonide preparations for oral administration and budesonide enemas for rectal administration have been developed and proved to be an effective therapy for Crohn's disease and distal ulcerative colitis, respectively, with fewer corticosteroid-typical side effects, in particular HPA axis suppression.

The rapid hepatic breakdown of budesonide in a non-cirrhotic liver reduces systemic bioavailability and the potential for corticosteroid-related side effects.

Budesonide also shows a relatively high water solubility that allows for adequate intraluminal dissolution, whereas its lipid-soluble properties facilitate effective mucosal uptake and high local concentrations in intestinal tissue.

Budesonide (Budenofalk) foam has been developed as a line extension to the approved and marketed formulation budesonide (Budenofalk) 3-mg, pH-controlled release capsules.

Whereas the latter is intended to enable an effective topical treatment of Crohn's disease, budesonide (Budenofalk) foam should complement topical IBD therapy for the treatment of active distal ulcerative colitis (UC) that requires rectal administration for optimal topical availability of the drug. Topical corticosteroid and also budesonide formulations for rectal administration in the treatment of active distal UC have been already approved and are available on the market. These comprise foam (e.g. containing hydrocortisone) and enema formulations (e.g. budesonide).

As the pharmacological properties of glucocorticoids in general and oral as well as rectal budesonide, the last one administered rectally as enema, have been extensively investigated in the past, the clinical pharmacology (pharmacodynamics/pharmacokinetics) (PD/PK) development programme of budesonide (Budenofalk) foam, which represent a line extension, is restricted to the following studies:

- A Phase I clinical trial to investigate the single- and multiple-dose serum pharmacokinetics of budesonide administered rectally as a foam formulation as well as its systemic pharmacodynamic suppressive effects on the HPA axis and immunocompetent blood cells in healthy volunteers (BUF-7/BIO)
- A Phase I clinical trial to investigate the colonic spreading and single-dose serum pharmacokinetics of budesonide after single rectal administration as foam formulation in patients with active ulcerative colitis (BUF-4/BIO)

Beside *in-vivo* pharmacokinetic properties, certain pharmacodynamic aspects relevant to safety and tolerability of the newly developed budesonide (Budenofalk) foam formulation, namely its potential of HPA axis suppression and immunosuppressive effects as determined by alterations of immunocompetent blood cells, have also been addressed in the clinical Phase I study BUF-7/BIO. A clinical Phase IIb and the clinical Phase III trials in patients with active distal UC further contribute to safety-relevant pharmacological aspects, which are also outlined below:

- In the clinical Phase IIb trial BUF-5/UCA as well as in the phase III trials BUF-6/UCA and BUF-9/UCA, a potential alteration of the HPA axis was evaluated by means of serum cortisol determination.
- In the clinical Phase III trial BUF-6/UCA, measurement of osteocalcin and bone-specific alkaline phosphatase (bAP) was included to monitor potential systemic effects of treatment on bone metabolism.

An overview of the clinical trials on budesonide 2mg (Budenofalk) foam addressing these pharmacodynamic aspects is given below:

Study	Design Duration	Treatment	Subjects	Main Objectives
Clinical Pharmacology studies				
BUF-7/BIO Phase I	Non-ctrl, sc, op, single does, multiple dose	BUD foam 2 mg b.i.d.	n=18 HV	Single-dose pharmacokinetics Steady-state pharmacokinetics Systemic pharmacodynamics effects (lymphocytes/granulocyte blood count serum cortisol level)
Clinical Safety and Efficacy Studies				
BUF-5/UCA Phase IIb	Placebo-ctr, mc, ra, db, par	BUD foam 2 mg b.i.d. 2 mg o.d. Placebo	n=223 [#] UCP	Safety and efficacy, inter alia: <ul style="list-style-type: none"> • Potential alterations of HPA axis
BUF-6/UCA Phase III	Active-ctrl, mc, ra, op, par	BUD foam 2mg o.d. hCORT foam 100 mg o.d	n=251 [#] UCP	Safety and efficacy, inter alia: <ul style="list-style-type: none"> • Potential alterations of HPA axis • Potential alterations of bone metabolism
BUF-9/UCA Phase III	Active-ctrl, mc, ra, op, par	BUD foam 2 mg o.d. BUD enema 2mg o.d.	n=541 [#] UCP	Safety and efficacy, inter alia: <ul style="list-style-type: none"> • Potential alterations of HPA axis

[#] randomised; ctrl: controlled; sc: single-centre; mc: multicentre; op: open-label; ra: randomised; db: double-blind; dd: double-dummy; par: parallel (group); BUD: budesonide; hCORT; hydrocortisone acetate; HV: healthy volunteers; UC: active distal ulcerative colitis; P: Patients; b.i.d.: twice daily; o.d.: once daily

Study BUF-7/BIO

Pharmacokinetics and pharmacodynamics of budesonide after rectal application of Budenofalk foam to healthy male subjects.

Study design and objectives

This study was designed as a prospective, uncontrolled, single-centre, open-label and multiple-dose exploratory Phase I clinical trial:

- To investigate the pharmacokinetics of a single rectal dose of budesonide 2mg (Budenofalk) foam (2mg budesonide over 24 hours) in 18 healthy volunteers
- To assess the pharmacokinetics in the same subjects at steady state after administration of budesonide 2mg (Budenofalk) foam, given rectally b.i.d. over 5 days.
- To assess the observed systemic effects of lymphocytes and granulocytes, and on serum cortisol.

Criteria for Evaluation

The primary study variables were the pharmacokinetic parameters t_{max} , C_{max} and AUC after a single rectal dose at day 1 and after multiple dosing at day 5.

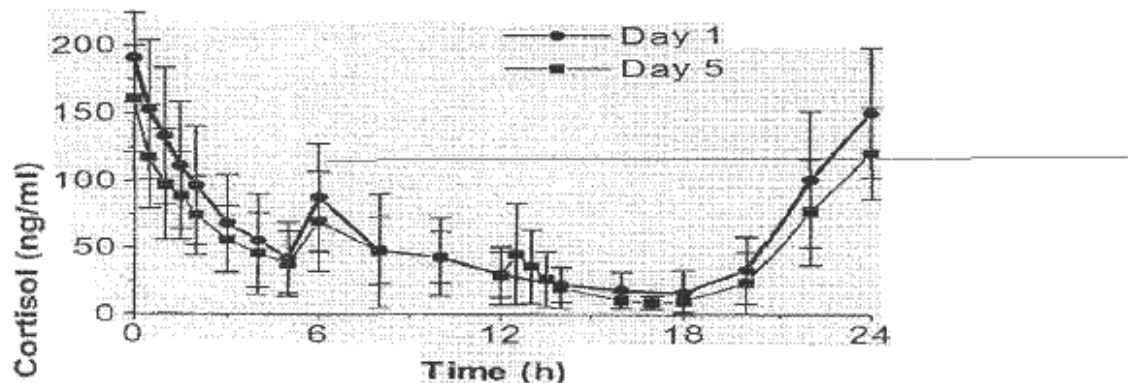
Study subjects, study conduct and methodology

The 18 eligible male healthy volunteers (age range: 20-31 years) received rectally one dose of 2mg budesonide foam in the morning (8am) of day 1. This was followed by b.i.d. dosing of 2mg budesonide foam (at 8am and 8pm) during days 2-5. On days 1 and 5, pharmacodynamic parameters (cortisol, lymphocytes and granulocytes) were assessed over 24 hours. Full pharmacodynamics profiles were established on days 1 and 5, while only the 8am and 8pm time points were included on days 2-4.

Pharmacodynamic Results

Effects on serum cortisol levels

The time course of mean serum cortisol levels after a single rectal dose of budesonide 2mg (Budenofalk) foam at 1 day and after b.i.d. multiple dosing at day 5 in healthy volunteers is depicted below:



Healthy Male Volunteers

Source: Study report BUF-7/BIO, Figure 4

Mean (±S.D.) Serum Cortisol levels after rectal administration of budesonide 2mg (Budenofalk) foam (single dose on day 1, b.i.d. on days 2 to 5) -BUF-7/BIO

Cumulative 24-hour serum cortisol levels on day 1 after single dosing of budesonide 2mg (Budenofalk) foam were about 20 % higher than those on day 5 after rectal administration of 2mg budesonide b.i.d. This difference was statistically significant (p=0.006)

Absolute serum levels of aldosterone at baseline and end of treatment –BUF-5/UCA

	Placebo n=76 Median (range)	Budesonide 2 mg n=70 Median (range)	Budesonide 4 mg n=76 Median (range)
Baseline at day 0*	132 ng/l (13-2000)	130 ng/l (13-478)	106 ng/l (13-2000)
End of treatment at day 42**	123 ng/l (13-890)	123 ng/l (13-456)	112 ng/l (13-1000)

* visit 1; ** visit 4

Source: Study Report BUF -5/UCA, Statistical Table 78

Absolute serum levels of electrolytes at baseline and end of treatment -BUF-5/UCA

	Placebo n=76 Mean (range)	Budesonide 2 mg n=70 Mean (range)	Budesonide 4 mg n=76 Mean (range)
Chloride (mmol/l) Baseline at day 0* End of treatment at day 42**	105 (95-114) 106 (94-115)	105 (93-115) 106 (96-114)	106 (95-115) 106 (87-114)
Potassium (mmol/l) Baseline at day 0* End of treatment at day 42**	4.4 (3.4-5.9) 4.4 (3.2-5.9)	4.3 (3.3-5.3) 4.6 (3.1-22.9)	4.4 (3.7-5.7) 4.7 (3.4-25.8)
Sodium (mmol/l) Baseline at day 0* End of treatment at day 42**	142 (132-151) 141 (123-147)	141 (127-150) 141 (131-149)	141 (135-154) 141 (128-149)

* visit 1; ** visit 4

Source: Study Report BUF -5/UCA,, Text Table XXIV

Normal Ranges of serum electrolytes were defined as follows: Chloride 98-107 Mmol/l; potassium 3.6-5 mmol/l; sodium 135-145 mmol/l.

From the results it can be seen that there were no significant changes in serum cortisol, aldosterone or electrolyte levels on rectal administration of budesonide foam at doses of 2 mg or 4 mg daily.

Study BUF-6/UCA was a randomised, open-label, active-controlled, Phase III study of the efficacy and safety of (Budenofalk) foam (2 mg o.d.) compared to hydrocortisone acetate foam (100 mg o.d.) in the eight week treatment of proctitis and proctosigmoiditis. In total, 248 patients received study medication, of whom 120 patients received budesonide and 128 patients received hydrocortisone acetate.

Conclusion

Changes in serum cortisol, osteocalcin and bAP levels were similar for both treatments; no statistically significant differences were observed.

No significant adrenal suppression was detected as serum cortisol levels remained within the normal range during rectal administration of budesonide 2 mg (Budenofalk) foam o.d. Moreover, budesonide 2 mg (Budenofalk) foam o.d. showed no effect on serum bAP and serum osteocalcin levels, both markers of bone metabolism.

Study BUF-9/UCA

This Phase III study was a prospective, controlled, multicentre, randomised, double-blind, double-dummy, parallel-group trial to compare the efficacy and safety of budesonide 2 mg (Budenofalk) foam o.d. and budesonide 2 mg enema 0.d. in patients with active proctitis or proctosigmoiditis.

The 541 patients included were randomly allocated to receive budesonide 2 mg (Budenofalk) foam or budesonide 2 mg enema (Entocort) o.d. for a treatment period of 4 weeks. Serum cortisol concentrations were monitored at baseline and final visit (day 28) to assess the level of adrenal and pituitary suppression.

Frequency of cortisol deteriorations -BUF -9/UCA

Number (%) of patients with cortisol deteriorations			
Budesonide 2 mg (Budenofalk®) foam 2 mg o.d.		Budesonide 2 mg enema 2 mg o.d.	
Below 'normal'	Above 'normal'	Below 'normal'	Above 'normal'
All Samples			
3/248 (1%)	22/248 (9%)	2/248 (1%)	15/248 (6%)
Samples taken between 7:00a.m. and 9:00 a.m.			
1/180 (1%)	16/180 (9%)	2/183 (1%)	11/183 (6%)

Safety Population

Source: Study Report BUF-9/UCA, Table 50

Deterioration of serum cortisol values below the normal range, as could indicate adrenal and pituitary suppression, was only observed in 3 patients in the budesonide 2 mg foam group and in 2 patients in the budesonide 2 mg enema group.

The Frequency of serum cortisol deteriorations was similar for both treatments. From the results it is possible to conclude that budesonide 2mg foam does not suppress the HPA axis when administered once daily for up to 4 weeks -a period suggested by the German regulatory authority BfArM.

Overall, from analysis of all the studies, it is clear that no significant adrenal suppression was observed and that, likewise, there were no effects on serum aldosterone or electrolyte levels, nor on serum osteocalcin or bone-specific alkaline phosphatase.

7. Efficacy

The Efficacy of the budesonide 2mg foam in the treatment of active distal ulcerative colitis (UC) was assessed in the two phase III clinical trials BUF-6/UCA and BUF- 9/UCA already discussed. The foam was shown to be efficacious in patients with distal UC and was not inferior to the marketed budesonide 2mg enema Entocort, as well as being therapeutically equivalent to Colifoam containing 100mg hydrocortisone acetate.

Patients' rating of handling of the device and overall preference was in favour of the budesonide foam. Thus 84% of the patients preferred the foam, with only 6% preferring the enema. The foam was also found easier to handle by 89% of patients.

8. Safety

Rectal budesonide as an enema (Entocort) has been shown to be safe and well- tolerated in active distal UC in a number of clinical studies. Safety data on budesonide foam have been generated in the company's one phase IIb and two phase III studies involving in all 1,005 patients with active distal UC who were treated for periods of 4, 6 & 8 weeks. Of these, 533 were exposed to budesonide 2mg foam, 76 to placebo and 396 to an active comparator, 128 to 100 mg hydrocortisone acetate foam (Colifoam) and 268 to budesonide 2 mg enema- Entocort

Rectally administered budesonide 2mg foam (Budenofalk) was found to be safe and well tolerated throughout. As the study medication was applied locally, the incidence of treatment-emergent adverse events (AEs) was, as expected, low.

Systemic AEs usually associated with corticosteroids were virtually absent. The serious adverse events (SAEs) reported were not related to the study medication.

There were no deaths.

Overall, budesonide 2mg foam, in the form of Budenofalk, applied once daily was assessed as safe and well tolerated, being easy to handle and administer.

9. Expert Report

There is a satisfactory clinical expert report by a suitably qualified individual.

His curriculum vitae is included as are those for the preclinical expert and the pharmaceutical expert.

10 Summary of Product Characteristics

The Summary of product characteristics is satisfactory.

11. Patient Information Leaflet

The Patient Information Leaflet is satisfactory.

12. Labelling

The labelling is satisfactory

13. Application Form (MAA)

The MAA is satisfactory

14. Discussion

The applicant has shown that their Budenofalk rectal foam is as effective as hydrocortisone rectal foam and budesonide enema in the treatment of recto- sigmoid ulcerative colitis. It is a line extension of their currently marketed 3mg budesonide capsules.

15. Medical Conclusions

A product licence may be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Budenofalk 2mg/dose Rectal Foam 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.

PRECLINICAL

Toxicology studies were presented which were assessed in relation to a named impurity, which could have been present in the finished product at levels requiring toxicological qualification. This issue was resolved and there are no outstanding preclinical issues arising from this application.

EFFICACY

Budesonide is a well-known drug and has been used in the treatment of active distal ulcerative colitis (UC) for over 10 years. It has been demonstrated that the applicant's product is efficacious in patients with distal UC and was not inferior to the marketed budesonide 2mg enema Entocort, as well as being therapeutically equivalent to Colifoam containing 100mg hydrocortisone acetate.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no outstanding preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product is as effective as hydrocortisone rectal foam and budesonide enema in the treatment of recto- sigmoid ulcerative colitis. Clinical experience with budesonide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

SUMMARY OF PRODUCT CHARACTERISTICS

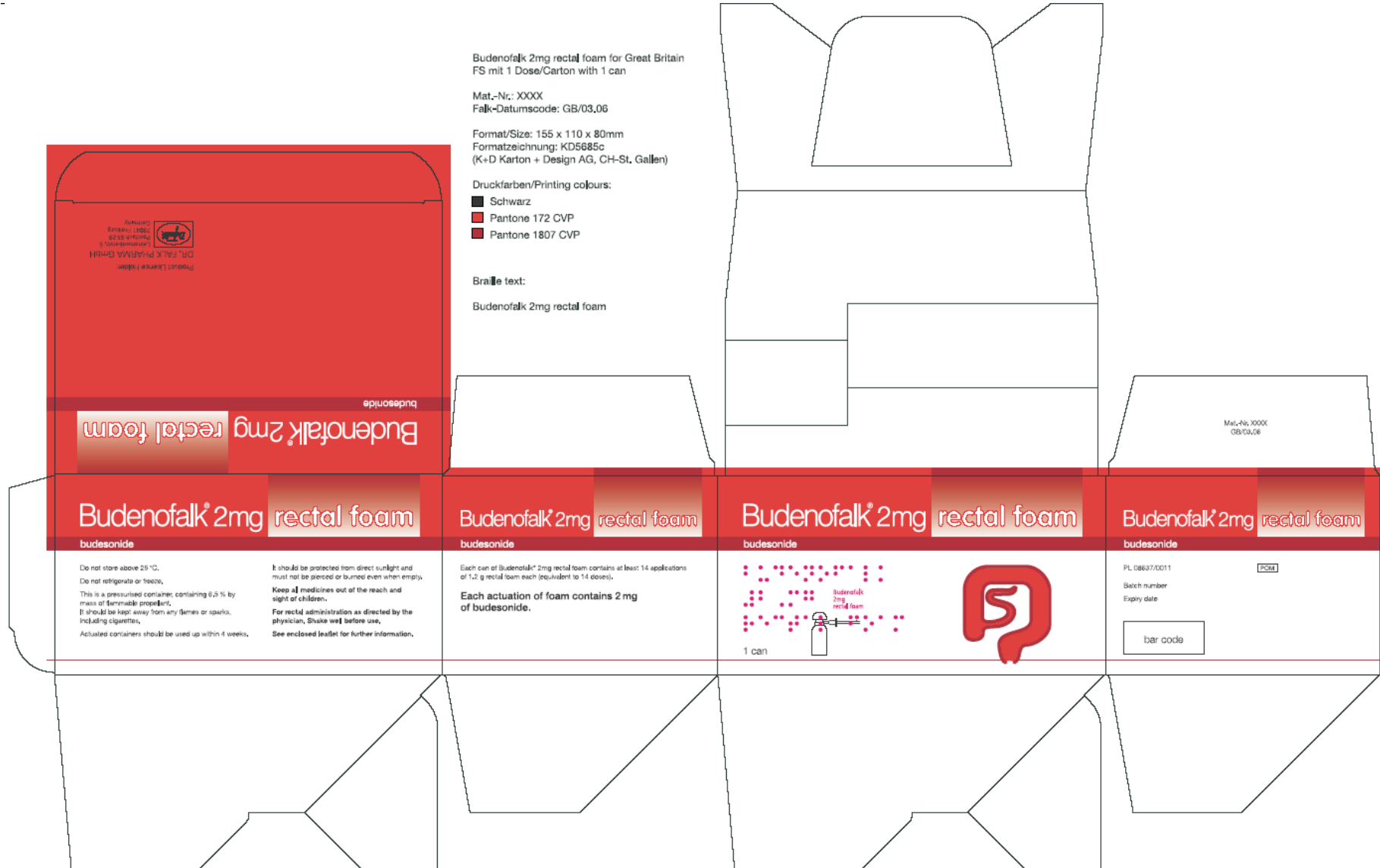
In accordance with Directive 2010/84/EU, the current version of the SmPC is available on the MHRA website.

PRODUCT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the current version of the Patient Information Leaflet is available on the MHRA website.

LABELLING

CARTON



CONTAINER

Budenofalk® 2mg rectal foam

budesonide

Each can of Budenofalk® 2mg rectal foam contains at least 14 applications of 1.2 g rectal foam each (equivalent to 14 doses).

Each actuation of foam contains 2 mg of budesonide.

Do not store above 25 °C.
Do not refrigerate or freeze.

This is a pressurised container, containing 6.5 % by mass of flammable propellant. It should be kept away from any flames or sparks, including cigarettes.

Mat.-Nr. XXXX GB/03.06

Actuated containers should be used up within 4 weeks.

It should be protected from direct sunlight and must not be pierced or burned even when empty.

PL 08637/0011

POM

Keep all medicines out of the reach and sight of children.

For rectal administration as directed by the physician. Shake well before use.

See enclosed leaflet for further information.

Batch number/Expiry date: see can bottom

Product Licence Holder: Dr. Falk Pharma GmbH, D-79041 Freiburg, Germany

Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/no n approval	Assessment report attached
To update sections 2 (Qualitative and quantitative composition), 4.3 (Contraindications), 4.6 (Fertility, pregnancy and lactation), 4.7 (Effects on ability to drive and use machines) and 4.8 (Undesirable effects) of the Summary of Product Characteristics (SmPC) and consequentially the Patient Information Leaflet (PIL) and labelling in line with the Quality review of Documents (QRD) template.	UK/H/0334/002/IB/030	SmPC, PIL and labelling	04/11/2014	28/11//2014	Approval	Yes (Annex 1.1)

Annex 1.1

Our Reference:	PL 08637/0011, Application 26
Product:	Budenofalk 2mg/dose Rectal Foam
Marketing Authorisation Holder:	Dr Falk Pharma GmbH
Active Ingredient(s):	Budesonide
Type of Procedure:	Mutual Recognition
Submission Type:	Variation
Submission Category:	Type IB
Submission Complexity:	Standard
EU Procedure Number (if applicable):	UK/H/0334/002/IB/030

Reason:

To update sections 2 (Qualitative and quantitative composition), 4.3 (Contraindications), 4.6 (Fertility, pregnancy and lactation), 4.7 (Effects on ability to drive and use machines) and 4.8 (Undesirable effects) of the Summary of Product Characteristics (SmPC) and consequentially the Patient Information Leaflet (PIL) and labelling in line with the Quality Review of Documents (QRD) template.

Linked / Related Variation(s) or Case(s):

Not applicable

Supporting Evidence

Revised SmPC fragments, PIL and labelling have been provided.

Evaluation

The updated sections of the SmPC, PIL and labelling are satisfactory.

Conclusion

The amended SmPC sections, PIL and labelling have been provided and are acceptable.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The revised labelling is presented below:

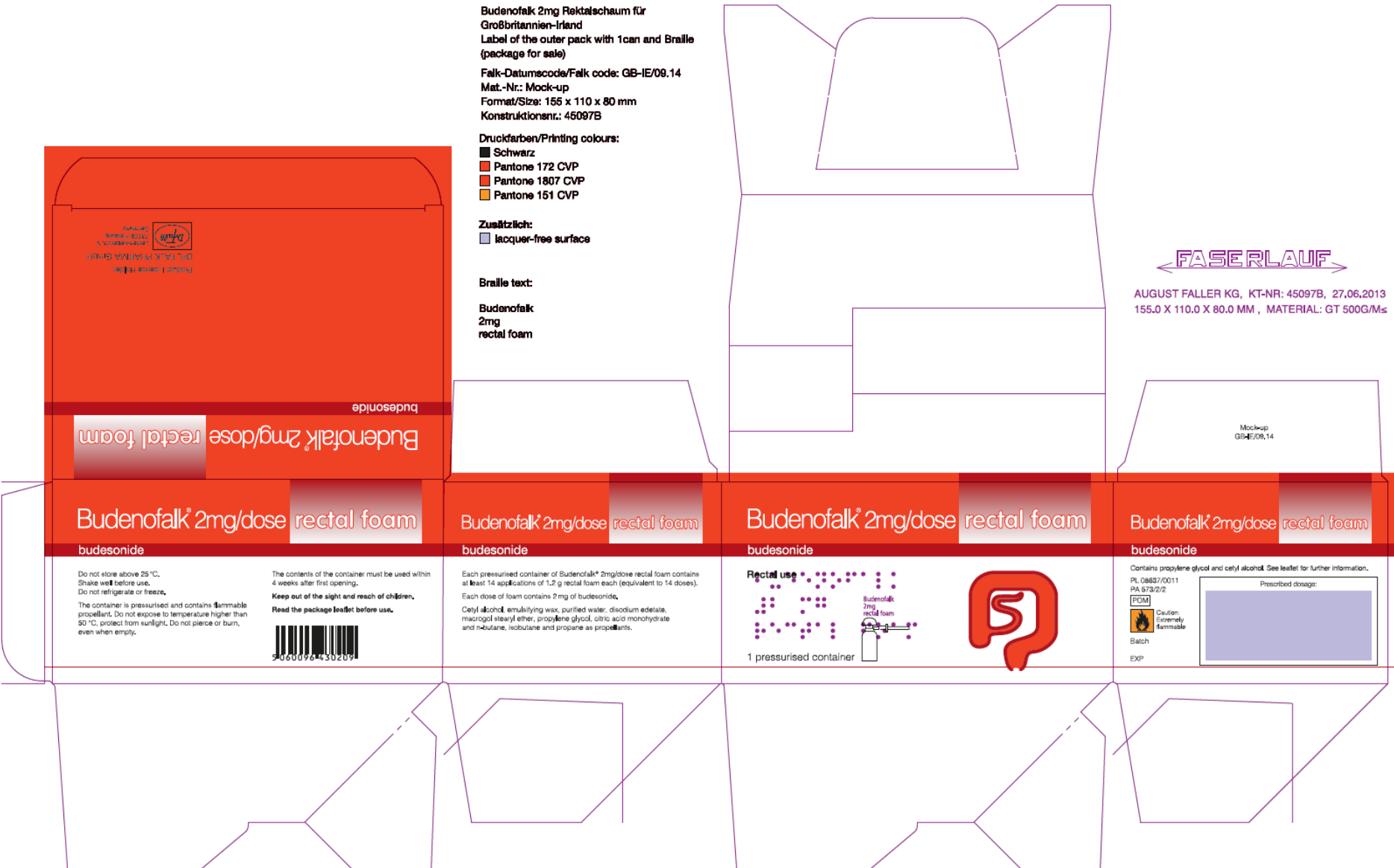
Budonofalk 2mg Rektalschaum für Großbritannien-Irland
 Label of the outer pack with 1can and Braille (package for sale)
 Falk-Datumscode/Falk code: GB-IE/08.14
 Mat.-Nr.: Mock-up
 Format/Size: 155 x 110 x 80 mm
 Konstruktionsnr.: 45097B

Druckfarben/Printing colours:
 ■ Schwarz
 ■ Pantone 172 CVP
 ■ Pantone 1807 CVP
 ■ Pantone 151 CVP

Zusätzlich:
 □ lacquer-free surface

Braille text:

Budonofalk
 2mg
 rectal foam



Budenofalk 2mg Rektalschaum für Großbritannien-Irland
Label of the outer pack with 1 can and Braille (package for sale)

Falk-Datumscode/Falk code: GB-IE/09.14
Mat.-Nr.: Mock-up
Format/Size: 155 x 110 x 80 mm
Konstruktionsnr.: 45097B

Druckfarben/Printing colours:

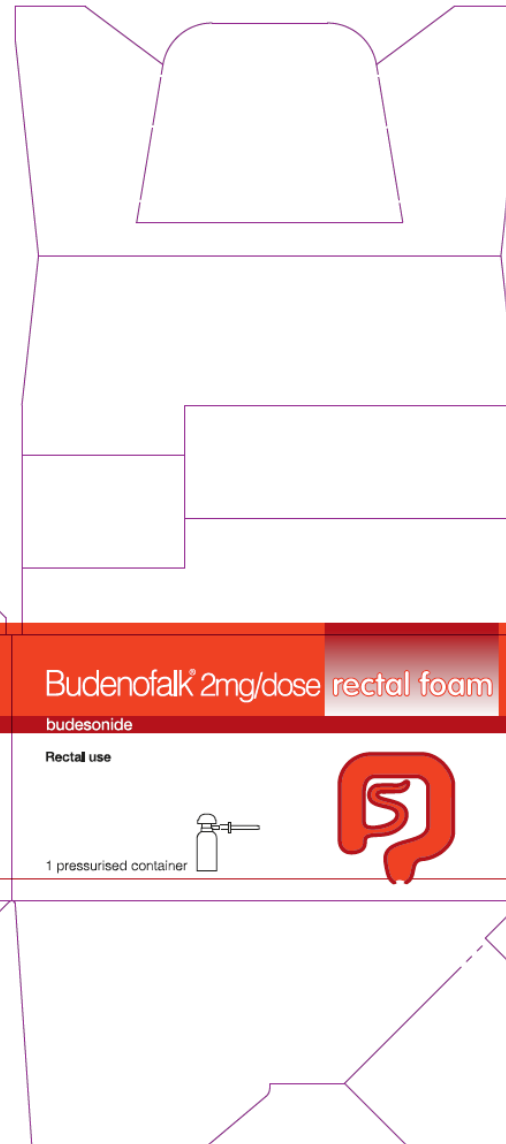
- Schwarz
- Pantone 172 CVP
- Pantone 1807 CVP
- Pantone 151 CVP

Zusätzlich:

- lacquer-free surface

Braille text:

Budenofalk
2mg
rectal foam



← FASERLAUF →

AUGUST FALLER KG, KT-NR: 45097B, 27.06.2013
155.0 X 110.0 X 80.0 MM, MATERIAL: GT 500G/M²

Mock-up
GB-IE/09.14

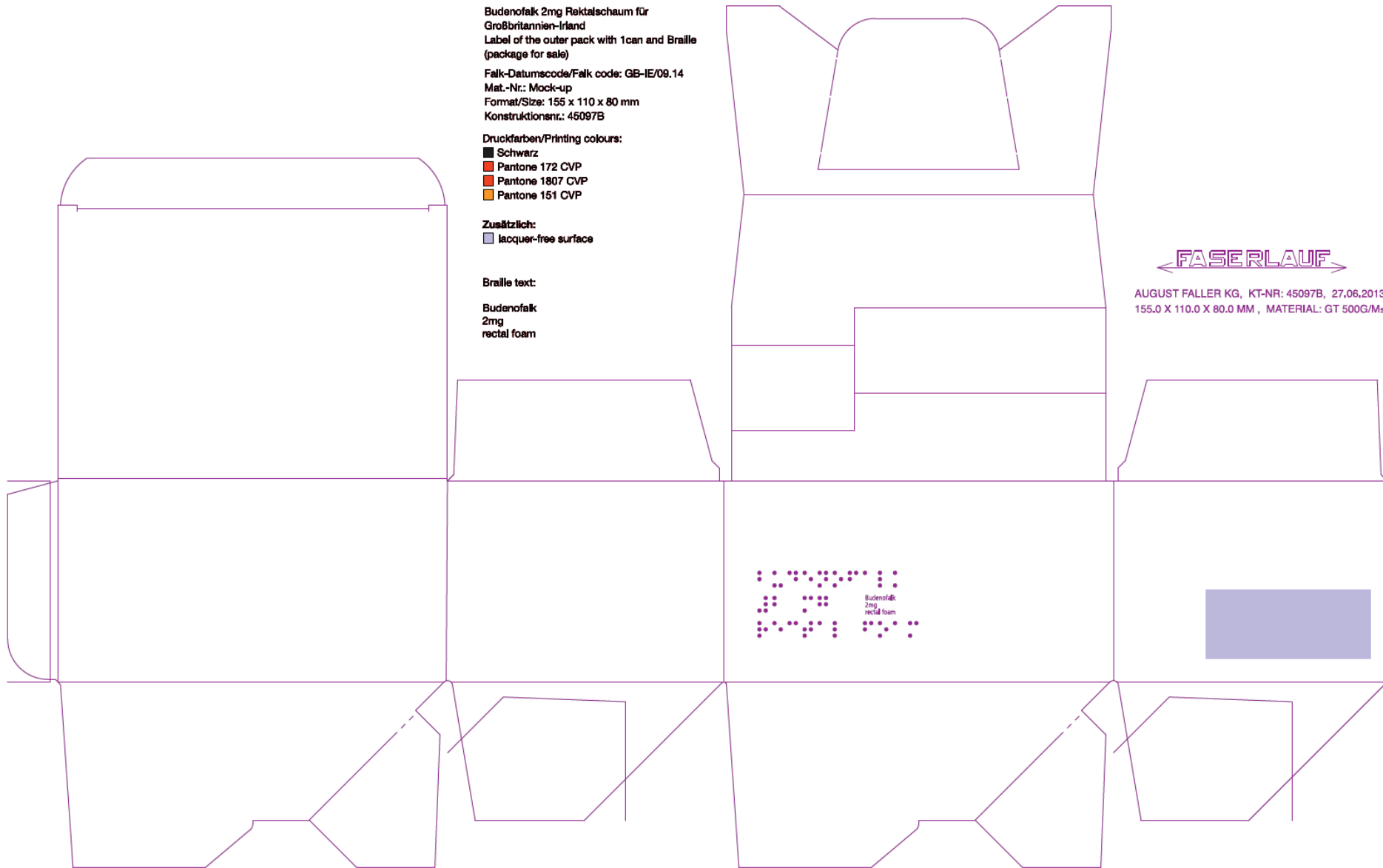
Budenofalk 2mg Rektalschaum für
Großbritannien-Irland
Label of the outer pack with 1can and Braille
(package for sale)
Falk-Datumscode/Falk code: GB-IE/08.14
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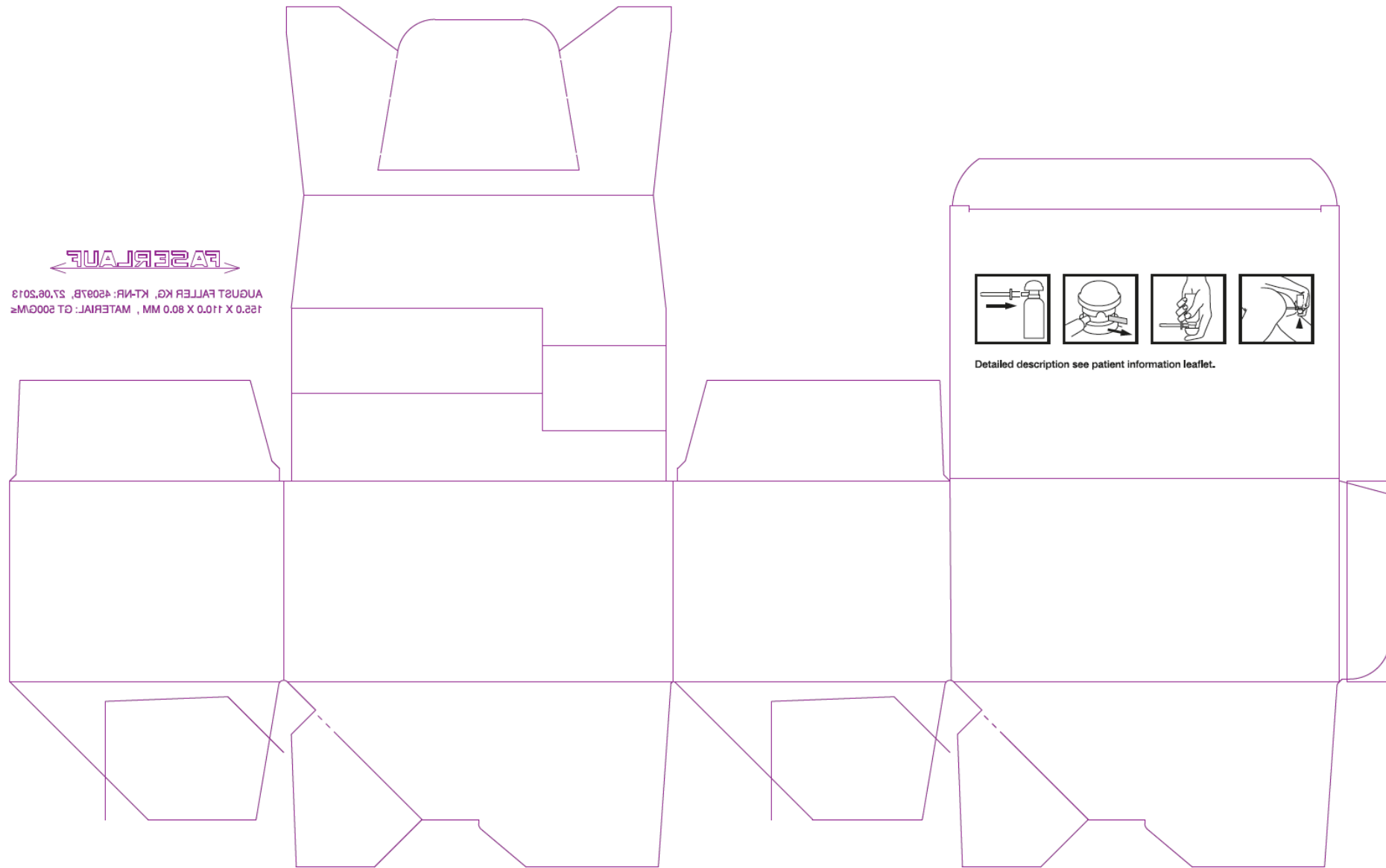
Druckfarben/Printing colours:
■ Schwarz
■ Pantone 172 CVP
■ Pantone 1807 CVP
■ Pantone 151 CVP

Zusätzlich:
□ lacquer-free surface

Braille text:

Budenofalk
2mg
rectal foam





Budenofalk 2mg/dose rectal foam

budesonide

Rectal use

Each pressurised container of Budenofalk® 2mg/dose rectal foam contains at least 14 applications of 1.2 g rectal foam each (equivalent to 14 doses). Each dose contains 2 mg of budesonide.

Cetyl alcohol, emulsifying wax, purified water, disodium edetate, macrogol stearyl ether, propylene glycol, citric acid monohydrate and n-butane, isobutane and propane as propellants.

Do not store above 25 °C. Shake well before use. Do not refrigerate or freeze.

The container is pressurised and contains flammable propellant. Do not expose to temperature higher than 50 °C, protect from sunlight. Do not pierce or burn, even when empty.

The contents of the container must be used within 4 weeks after first opening.


Keep out of the sight and reach of children. Read the package leaflet before use.


Batch number/Expiry date: see can bottom

Contains propylene glycol and cetyl alcohol. See leaflet for further information.

PL 08637/0011 POM

PA 573/2/2

 Caution: Extremely flammable





 DR. FALK PHARMA GmbH

Linenweberstr. 5
79108 Freiburg
Germany

Budenofalk 2mg Rektalschaum
Etikett für Großbritannien-Irland

Item No.: Mock-up (ASM)
Falk code: GB-IE/09.14
Size: 105 x 47 mm

Printing colours:

-  **Black**
-  **Pantone 172 CVP**
-  **Pantone 1807 CVP**
-  **Pantone 151 CVP**

105 mm

47 mm

Mockup_BUF_Label_GB-IE.indd 1

25.09.14 13:13

Decision – Approved on 28 November 2014.