CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Budenofalk Schuim 2 mg, rectal foam
Dr. Falk Pharma Benelux B.V., the Netherlands

budesonide

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 102383

6 December 2012

Pharmacotherapeutic group:	intestinal antiinflammatory agents; corticosteroids acting locally
ATC code:	A07EA06
Route of administration:	rectal
Therapeutic indication:	active ulcerative colitis limited to the rectum and/or sigmoid colon
Prescription status:	prescription only
Date of authorisation in NL:	7 February 2011
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Budenofalk Schuim 2 mg, rectal foam from Dr. Falk Pharma Benelux B.V. The date of authorisation was on 7 February 2011 in the Netherlands.

The product is indicated for the treatment of active ulcerative colitis that is limited to the rectum and sigmoid colon.
A comprehensive description of the indications and posology is given in the SPC.

The exact mechanism of action of budesonide in the treatment of ulcerative colitis/procto-sigmoiditis is not fully understood. Data from clinical pharmacology studies and controlled clinical trials strongly indicate that the mode of action of budesonide is predominantly based on a local action in the gut. Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect. At a dosage of 2 mg budesonide, applied rectally, which is clinically equieffective to systemically acting glucocorticoids, budesonide leads to practically no suppression of the hypothalamus-hypophysis-adrenal cortex axis.
Budenofalk 2 mg rectal foam investigated up to the daily dosage of 4 mg budesonide showed virtually no influence on the plasma cortisol level.

This national procedure concerns a line extension to Budenofalk 3 mg controlled-release capsules (NL License RVG) of the same MAH, which has been authorised in the Netherlands since 8 March 2000.
The application represents a change in pharmaceutical form, strength and route of administration.

This national procedure concerns a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, pre-clinical and clinical data.

The active component of Budenofalk 2 mg rectal foam is considered to be well-known and the clinical pharmacology of budesonide has been extensively studied. Parts of the data in the dossier of Budenofalk rectal foam were already submitted in the dossier of the Budenofalk 3 mg capsules (NL License RVG 22557). The non-clinical documentation focuses only on new studies of single dose toxicity, genotoxicity and local tolerance.
The MAH submitted 5 clinical studies in support of the line extension. Two of these studies evaluated the pharmacokinetics (BUF-7/BIO, BUF-4/BIO). One phase IIb study compared two dosing regimens with placebo (BUF-5/UCA), and two phase III studies compared Budenofalk foam 2 mg o.d. with active comparators (a budesonide containing enema, BUF-9/UCA and a hydrocorticoid acetate containing rectal foam, BUF-6/UCA). These are discussed in section II.3 ‘Clinical aspects’.

The MAH sought scientific advice on this application in the UK in 1999 and in Germany in 2000.

No paediatric development programme has been submitted, as this is not required for a line extension.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is budesonide, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white crystalline powder, which is practically insoluble in water, freely soluble in methylene chloride and sparingly soluble in alcohol. The active substance is a mixture of the C-22*S* (epimer A) and C-22*R* (epimer b) epimers.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full-scale batches.

Stability of drug substance
Stability data have been provided on three full-scale batches of active substance stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. At both storage conditions no changes or trends are observed. The claimed retest period of 5 years without any special storage requirements is justified.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Budenofalk Schuim 2 mg is a white to white-greyish, creamy firm foam.

Budenofalk 2 mg rectal foam is formulated as emulsion plus propellant. It is available in one strength of 2 mg budesonide per puff and 48 mg budesonide per can (overfill). The pack includes 14 PVC applicators for rectal application (1.2 g foam per actuation), which are coated with an ointment of white soft paraffin and liquid paraffin for administration of the foam.

The excipients are: cetyl alcohol, emulsifying wax, macrogol stearyl ether, propylene glycol, disodium edetate, citric acid monohydrate and purified water. The propellant consists of a mixture of propane/butane 2.5 bar.

Pharmaceutical development

The development of the product has been described, the choice of excipients and package is justified and their functions explained. Pharmaceutical development studies were performed in relation to a suitable solvent, optimising pH (with citric acid), preservative effectiveness, optimising foam quality and choice of propellant and metering head. Due to the presence of propylene glycol, the drug product has self-preserving properties. Therefor sorbic acid was deleted as a preservative in the final formulation. The batches used for the clinical studies were performed with the initial formulation still containing sorbic acid. However, the effect of the deletion of sorbic acid on therapeutic effectiveness is considered negligible.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is subdivided in two main steps: preparation and filling of the basic emulsion and packaging. The manufacturing process has been adequately validated according to relevant European guidelines.
Process validation data on the product has been presented for 3 full-scale and 4 pilot-scale batches, of which 2 full-scale batches were manufactured according to the final formulation (without sorbic acid).

Control of excipients
The excipients comply with the Ph.Eur. or the USP-NF. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, filling weight, weight per puff, number of puffs, foam volume, duration of expansion, relative foam density, pH, pressure, leakage test, identification of budesonide and disodium edetate, related substances, assay of budesonide per puff and per can and assay for disodium edetate, microbial purity and examination of can interior. Most release specifications are similar to the end of shelf-life specifications except for the related substance, a degradation product, and the assay for disodium edetate per can. The specification has been sufficiently justified and is considered acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on 3 full-scale and 4 pilot-scale batches, demonstrating compliance with the release specification.

Container closure system
Sufficient specifications have been provided on the container closure system, consisting of aluminium monoblock cans with an inner lacquer fitted with a polyester metering head and valve system. Packaging materials are protective against light, leakage and microbial contamination.

Overfill
An overfill of up to ten puffs in excess is applied for the cans. This is sufficiently justified by the fact that some residue of the emulsion is always remaining on the inner surface of the container, and by the fact that the lower end of the valve stem is protruding into the emulsion in an upside-down position.

Microbiological attributes
In testing preservative effectiveness in the formulation without sorbic acid, the product is shown to comply with the Ph.Eur. requirements. Considering the result it is concluded that the antimicrobial activity of the preparation as such provides adequate protection from adverse effects that may arise from microbial contamination or proliferation during storage and use of the preparation. The presence of sorbic acid was therefore considered unnecessary.
All values obtained during long-term stability investigations and in-use stability tests were well below the required limits. No growth of microbial germs could be detected.

Stability of drug product
Stability data on the product has been provided three full-scale batches stored at 25°C/60% RH (2 batches for 24 months and one batch for 9 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). Intermediate and accelerated studies were only performed on two full-scale batches. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in aluminium pressurised containers with a plastic metered valve. At accelerated conditions out-of-specifications are observed after 6 months. A significant change in assay is observed after 12 month

storage at intermediate conditions (30°/65% RH). Although the long-term data shows variable results, no clear trends are observed for assay. The claimed shelf life of 2 years was granted with the applicable storage conditions “Store below 25°C” and “Do not refrigerate or freeze”.

In-use stability
Stability data has been provided for the drug product manufactured according to the initial formula. Based on the results, an in-use shelf life of 4 weeks after first opening was approved.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

Results of studies on single-dose toxicity and genotoxicity of budesonide are discussed below. Budesonide is a well-known compound which is already on the market also for rectal use (as an enema), at the same dose and a similar duration of treatment. Additional systemic toxicity of this product is therefore not expected. Local tolerance of budesonide foam was tested in dogs.

Good Laboratory Practice
The MEB has been assured that the non-clinical studies have been conducted in accordance with acceptable standards of Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Single-dose toxicity
Two studies investigating single-dose toxicity after i.v. administration were conducted in NMRI mice (BUF-11 and BUF-12). The tested substances were budesonide and its main degradation product 11β,16α-dihydroxy-androsta-1,4-diene-3,17-dione, respectively. This degradation product was detected in budesonide foam, and it was decided to investigate the toxicity and mutagenicity of it. The formation of this degradation product is time-dependent, and a maximum concentration of about 2 % is not reached until after 2 years of storage of budesonide foam.
The studies revealed that the degradation product of budesonide exhibits a somewhat higher acute toxicity following i.v. administration in comparison with budesonide (LD50: 150 mg/kg b.w. versus 320 mg/kg b.w.). A 70 kg adult person will apply 0.0286 mg/kg b.w. of budesonide daily. Assuming that the budesonide foam has been stored for 2 years and that 2 % of the amount of budesonide has degraded to 11β,16α-dihydroxy-androsta-1,4-diene-3,17- dione, a total dose of 0.04 mg of this degradation product would be applied by the patient, which would correspond to 0.00057 mg/kg b.w.. The highest non-lethal dose in mice was 68.1 mg/kg b.w. for the degradation product and 147 mg/kg b.w. for budesonide after i.v. administration in mice. This would theoretically yield a 119-fold safety factor for the degradation product and a 5-fold safety factor for budesonide for i.v. administration with respect to the highest nonlethal dose after i.v. administration.
However, as Budenofalk foam is administered rectally, the systemic concentrations of the active ingredient or its degradation product will be even lower than the concentrations used in the calculations above.
The limit of this impurity was finally reduced in the drug product to 0.8 %.

Genotoxicity
The degradation product of budesonide, 11β,16α-dihydroxy-androsta-1,4-diene-3,17-dione, was tested in one adequately performed Ames test with and without metabolic activation in the recommended strains of *Salmonella typhimurium* TA 98, TA 100, TA 102, TA 1535, and TA 1537 (BUF-13). No mutagenic effect was observed for 11β,16α-dihydroxyandrosta-1,4-diene-3,17-dione at 5 concentrations up to the highest concentration of 5000 µg/plate, carried out without and with metabolic activation. Cytotoxicity was only observed at a concentration of 5000 µg/plate in test strain TA 98 without metabolic activation. In the experiment with metabolic activation no cytotoxicity was observed in any of the tested strains. In summary, no mutagenic effect of 11β,16α-dihydroxy-androsta-1,4-diene-3,17-dione was seen in the Ames test.

Local tolerance
The local tolerance of budesonide foam after rectal application was tested in two studies with twice-daily application for 14 days in beagle dogs (BUF-1 and BUF-8). In an additional study with twice-daily rectal application for 4 weeks, local and systemic tolerance of an old foam batch showing some degradation products and a new budesonide foam batch were compared (BUF-14).
In all three studies, budesonide foam was applied twice daily, resulting in daily doses between 3.0 mg and 3.4 mg. In humans, 2 mg budesonide foam is applied once daily. With this twice daily dosing regimen, the potential of budesonide and/or its degradation product for local irritancy could have been detected earlier than with a once-daily dosing scheme. However, no signs of local intolerance reactions (signs of discharge, erythema, or irritation) were noted in any of the animals treated in these studies. Macroscopic and microscopic examination of the bowel did not reveal pathological findings considered to be related to rectal treatment with budesonide foam.
In study BUF-14, with 4-week duration, endoscopic inspection of the recto-sigmoid region (performed prior to sacrifice) revealed no test-item related changes in the budesonide foam-treated groups as compared to placebo foam-treated group. Furthermore, no clinical signs of systemic toxicity were detected, and no test item-related effect was noted on the body weight or food consumption of budesonide foam-treated animals. In this study, no difference between the tolerability of the old budesonide foam batch (produced in November 1997), containing degradation products, the new budesonide foam batch (produced in May 2003), and the vehicle control could be detected.

Environmental risk assessment
Although this concerns a new pharmaceutical form for rectal use, there is already a budesonide enema for rectal use, for the same indication. A substantial increase in the use of budesonide is therefore not expected following the registration of this product. No additional environmental risk assessment is required.

II.3 Clinical aspects

The clinical documentation in support of this application includes five studies. Two of these studies evaluate the pharmacokinetics (BUF-7/BIO, BUF-4/BIO). One phase IIb study compares two dosing regimens with placebo (BUF-5/UCA), and two phase III studies compare Budenofalk foam 2 mg o.d. with active comparators (a budesonide containing enema, BUF-9/UCA and a hydrocorticoid acetate containing rectal foam, BUF-6/UCA).

Quality of clinical studies, compliance with GCP
The MEB has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

Clinical pharmacology
As is stated in the Clinical Pharmacology summary, budesonide, a non-halogenated glucocorticosteroid (16*a*, 17*a* -butylidendioxy-l Iβ, 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. The two main metabolites, 6β-hydroxy budesonide and 16a-hydroxy prednisolone show considerably less glucocorticoid activity than the parent drug.

Clinical Pharmacokinetics
Study BUF-7/BIO (1998):
In this study healthy volunteers received Budenofalk foam for 5 days. Pharmacokinetics were evaluated at day 1 and at day 5, while trough budesonide plasma concentrations were measured at day 2 – 5.

18 male subjects, aged 20-31 years, were included and completed the study. Budenofalk foam 2 mg (Dr. Falk Pharma, Freiburg) was administered at day one at 8 a.m., at day 2–5 at 8 a.m. and 8 p.m. At day 1 and day 5 subjects remained fasted, and received a standardised meal 5 h after application. Blood samples were taken at day 1 at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 hours after administration, at day 2–5 in the morning (pre-dose) and 12 h their after (before second dose), and at day 5 at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h after the morning dose, and at 0.5, 1, 1.5, 2, 4, 5, 6, 8, 10, and 12 h after the second dose.
Budesonide plasma levels were analysed by HPLC/MS. The pharmacokinetic variables and the C-t curves are shown below.

Table 1: Mean (+ S.D.) pharmacokinetic parameters of 2 mg budesonide after rectal administration as Budenofalk foam, given as a single rectal dose on day 1 and twice daily on day 2 to 5 in healthy males.

	Day 1		Day 5		t-test
	Mean	S.D.	Mean	S.D.	p
n	18		18		
Dose (mg)	2.0		2.0		
$t_{½}$ (h)	4.05	1.28			
k_e (h^{-1})	0.19	0.07			
MRT (h)	6.36	1.73			
$AUC_{0\text{-}12h}$ (ng*h/ml) or AUC_{ss} (ng*h/ml)	4.59	2.94	4.30	2.58	0.299
AUC_{∞} or AUC_{ss} (ng*h/ml)	5.36	3.60	4.30	2.58	0.051
AUC_{∞}/D (ng*h/(ml*mg) or AUC_{ss}/D (ng*h/(ml*mg)	2.68	1.80	2.15	1.29	0.051
Cl/f (L/min)	9.33	8.36	10.10	5.14	0.346
T_{max} (h)	2.14	1.28	1.81	0.88	0.172
C_{max} (ng/ml)	0.84	0.55	0.90	0.49	0.313
C_{max}/D (ng/(ml*mg)	0.42	0.28	0.45	0.24	0.313
$C_{average}$ (ng/ml)			0.36	0.21	

After single dose maximal plasma concentrations are obtained at about 2 hours after administration. At day 2- 5, pre-dose concentrations were just above the limit of quantitation (LOQ) of 0.1 ng/ml. As can be observed from the AUC at day 1 and at day 5, no accumulation occurs.

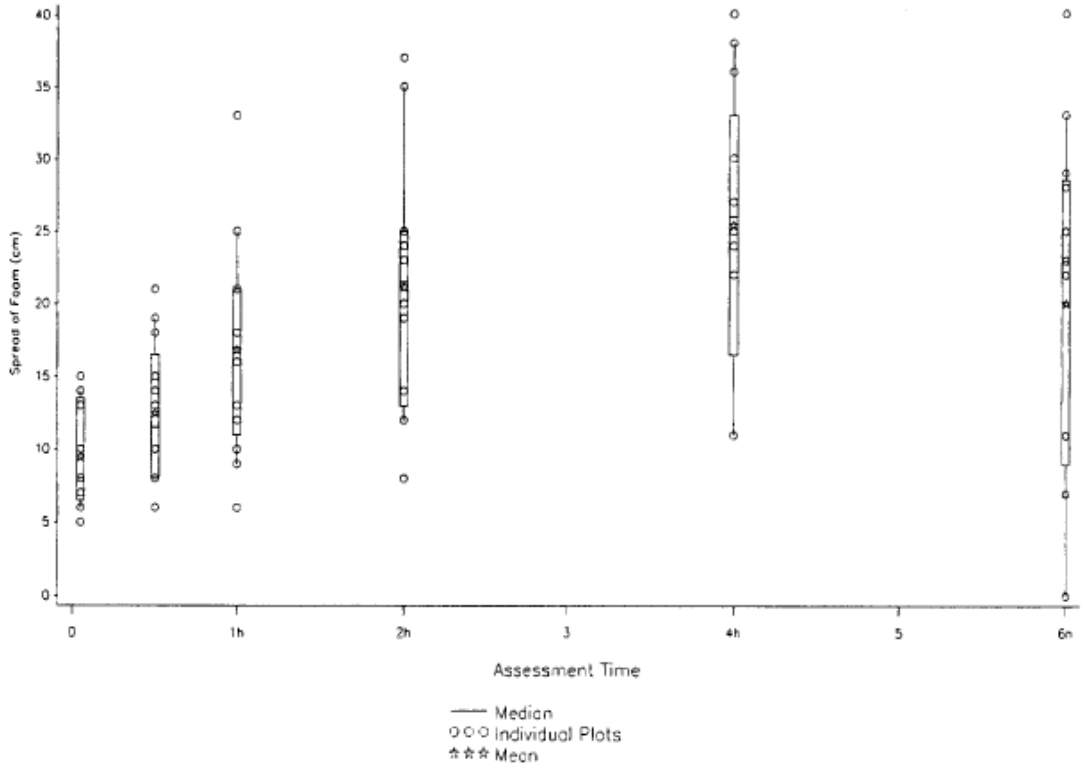
The Board noted that compared to capsules, comparable C_{max} levels are observed (C_{max} capsules 1 – 4 ng/ml, as indicated in the SPC of Budenofalk capsules). The values are also in the range of C_{max} values obtained in previous studies after administration of the capsule, but dose corrected values indicated higher values for the foam. In addition, C_{max} and AUC values are in the range of those observed after administration of 2 mg budesonide as a enema[1] (C_{max} 0.9 ng/ml, AUC 4.2 ng.h/ml).
Based upon the clearance after i.v. dosing (about 84 l/h)[2] and the clearance values after rectal administration, bioavailability is estimated to be ca. 14%, which is somewhat higher than the bioavailability after oral administration (ca. 11%).

Study BUF-4/BIO (2004):
In this study patients with mildly to moderately active ulcerative colitis received a single rectal dose of 2 mg ^{99m}Tc-labelled budesonide foam. Twelve patients, 8 males and 4 females, aged 28-58 years, were included and completed the study. The foam (20 ml) was administered in the morning after defecation. Gamma scintigraphic examination was performed immediately after dosing and at 0.05, 0.5, 1, 2, 4 and 6

[1] Danielsen et al., Aliment. Pharmacol. Ther. 1992, 7: 401-407.
[2] Ryrfeldt et al., Eur. J. Respir.Dis. 1982, 63 (suppl. 122) : 86-95.

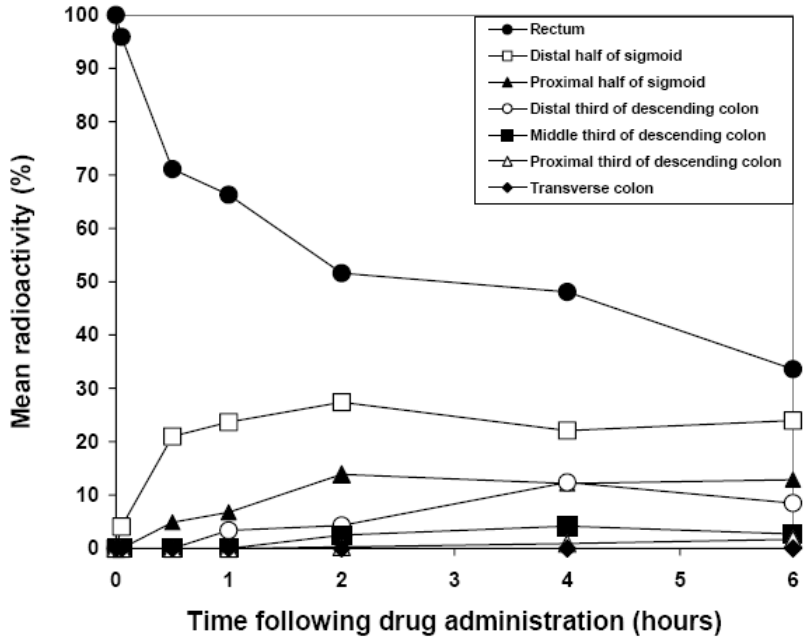
hours after administration to determine the extent of distribution of the foam within the colon. Blood samples were taken at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6 and 8 h after administration, and budesonide plasma levels were analysed by HPLC/MS.
The spread of the budesonide foam ranged between 11 and 40 cm with a mean (± SD) of 25.4 ± 10.3 cm (see figure below). The maximal spread was obtained between 2 to 6 hours.

OVERALL SPREAD OF BUDESONIDE FOAM



The distal half of the sigmoid was reached in all patients on average after 2 h, and accounted for about 27% of the radio-labelled budesonide foam (see figure below). The budesonide foam reached the proximal half of the sigmoid and the distal third of the descending colon in 9 and 6 patients, respectively. The radioactivity was detected in the middle descending colon in three patients and in the proximal third of the descending colon in one patient. The transverse colon was never reached. Overall, the radio-labelling was homogenous in the rectum and the distal sigmoid and was less homogenous or rare in the other part of the colon.

SPREAD OF BUDESONIDE FOAM ACROSS THE COLON

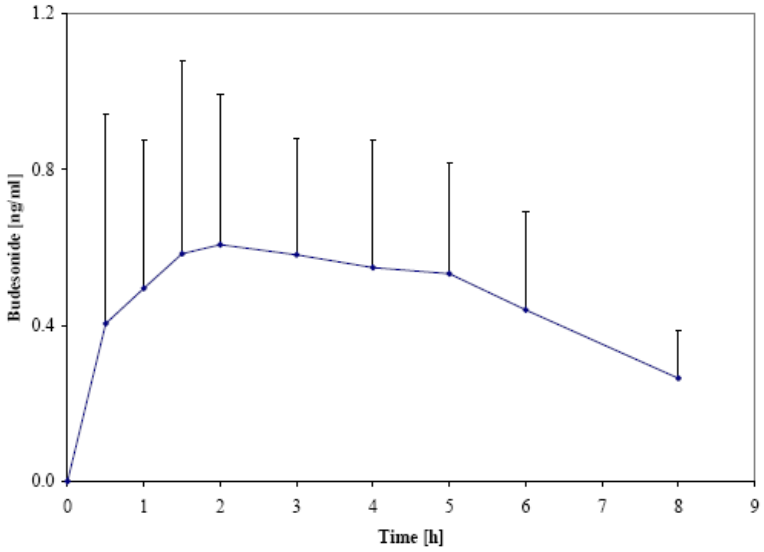


The mean C-t curve and the pharmacokinetic variables for budesonide are shown in the table below. C_{max} was reached after about 3 h, with mean C_{max} values of 0.77 ng/ml.

Parameter	Mean ± S.D.	Median	Maximum	Minimum
C_{max} (ng/ml)	0.767 ± 0.456	0.600	1.790	0.165
$AUC_{0\text{-}8\,h}$ (ng x h/ml)	3.70 ± 1.89	2.97	7.27	0.918
$AUC_{0\text{-}24\,h}$ (ng x h/ml)	5.18 ± 2.42	4.75	9.73	1.84
t_{max} (h)	3.08 ± 1.43	3.00	6.00	1.50
k_e (h^{-1})	0.232 ± 0.103	0.210	0.392	0.086
$t_{½}$ (h)	3.66 ± 1.83	3.41	8.08	1.77

Patients with active distal UC

MEAN (± SD) SERUM CONCENTRATION OF BUDESONIDE VS TIME



The scintigraphic examination indicated that, as expected, the foam was spread in the lower part of the colon/rectum. The AUC and C_{max} values observed in this study were in line with those observed in study BUF-7/BIO in healthy volunteers.

Conclusion

After rectal administration of budesonide as foam, the foam is spread mainly in the lower part of the colon (sigmoid) and rectum, and remained there for about 2 – 6 hours. Rectum and sigmoid are also the treatment areas, as indicated in the SPC.

Budesonide is absorbed with peak plasma concentrations at about 2-3 h after administration. Cmax and AUC values after daily dosing of 2 mg were in the range of those observed after oral administration of the controlled release Budenofalk capsule (3 mg). Bioavailability was estimated to be about 14%. No accumulation is observed after b.i.d. dosing.

The studies indicate that budesonide is locally available and partly absorbed. No unexpected findings have been observed. The studies are considered supportive to the submitted clinical studies.

The SPC recommends a daily dose of 2 mg. This dose was not studied at steady state in the intended population, but as observed after 2 mg b.i.d. dosing in healthy volunteers, no accumulation is expected.

Clinical studies

The MAH has developed a foam formulation as alternative to the registered budesonide 2 mg enemas (Entocort®) in order to provide an 'easy-to-handle' rectal formulation of budesonide.

The *Guideline on the development of new medicinal products for the treatment of ulcerative colitis* (CHMP/EWP/18463/2006) is applicable for this application.

In total, three clinical trials were submitted by the MAH in support of the use of Budenofalk foam 2 mg o.d. in the treatment (induction of remission) of proctosigmoiditis and proctitis:

- One clinical Phase IIb dose-finding study to determine whether budesonide 2 mg foam o.d. or budesonide 2 mg foam b.i.d. is the most suitable dose in active distal UC. In order to control spontaneous remission, a part of patients was randomly allocated to placebo (BUF-5/UCA).
- Two active-controlled, randomised trials vs. comparator treatments in order to investigate the efficacy and safety of budesonide 2 mg foam (BUF-6/UCA, BUF-9/UCA).

In study BUF-6/UCA, budesonide 2 mg foam o.d. was compared to hydrocortisone acetate 100 mg foam o.d. in order to demonstrate therapeutic equivalence and a potentially more advantageous safety and tolerability profile.
In study BUF-9/UCA, budesonide 2 mg foam o.d. was compared to budesonide 2 mg enema o.d. in order to demonstrate non-inferiority of budesonide foam to budesonide enema. Moreover, the different pharmaceutical forms /drug devices (foam can, enema) were compared in terms of acceptance, application problems, handling of the devices, and patients' preference.
As the recently approved guideline on the development of new medicinal products for the treatment of ulcerative colitis (CHMP/EWP/18463/2006) mentions, corticosteroids may be used as active control for evaluating topical treatments of proctitis and left sided colitis. Budesonide enema (Entocort®) is registered in the Netherlands under RVG 15660. Hydrocortisone-acetate foam is not registered in the Netherlands.

The efficacy of Budenofalk foam is based mainly upon demonstrating therapeutic equivalence between *budesonide enema* and *budesonide foam*. Budesonide enema was shown to be more effective than placebo (Danielsson et al. 1992, Hanauer et al. 1998) and equally effective to 5-ASA (Lamers et al., 1991, Lémann et al., 1995), thus forming an effective treatment for distal UC. Also, unlike prednisolone, budesonide appears not to affect plasma cortisol levels, demonstrating favourable safety (Lofberg et al. 1996). As the MAH claims therapeutic equivalence with budesonide enema, the main focus of this assessment lies on the comparison between budesonide foam and budesonide enema. BUF-5/UCA and BUF-6/UCA are considered to be supportive.
An overview of the characteristics of the clinical trials submitted by the MAH can be found in the table below. The methodology of BUF-5/UCA and BUF-6/UCA will only be summarized. The methodology of BUF-9/UCA will be discussed in detail.

Overview of clinical trials:

STUDY	*Ph.*	*Year*	*Main Objective*	*Design*	*N r¶*	*N tt*	*# cent -res*	*Poso- logy bude- nofalk foam*	*duration*	*Control*	*Blinded*	*Primary endpoint*	*Other*
BUF-5/UCA	IIb	1997/ 1998	To evaluate efficacy & safety of Budenofalk foam (2 mg o.d. vs. 2 mg b.i.d.) in inducing remission in proctosigmoidi- tis and proctitis	Randomised placebo- controlled double-blind trial	223	70*	7	2 mg o.d. / 2 mg b.i.d.	42 days	Placebo	Double	% CAI ≤ 4	
BUF-6/UCA	III	1998/ 2000	Demonstrate equivalence of Budenofalk foam to hydrocortisone acetate foam	Randomised, open-label, active controlled non-inferiority trial	251	120	38	2 mg o.d.	56 days	Hydroco -rtisone acetate (100 mg o.d.)	Open	% DAI ≤ 3	δ= ± 0.10
BUF-9/ UCA	III	2001/ 2003	Compare efficacy of 2 mg o.d. rectal budesonide administered either as an enema or as foam in patients with active ulcerative proctitis or proctosigmoidi- tis.	Double blinded, double dummy, randomised controlled non-inferiority trial	541	268	52	2 mg o.d.	28 days	Budeso- nide enema (2 mg o.d.)	Double	% CAI ≤ 4	δ= - 0.15

¶ N^r = Number of patients that were randomised
† N^t = Number of patients that were treated with Budenofalk foam 2 mg o.d.
* In addition, 76 patients received 2 mg b.i.d.

Dose selection
The dose of 2 mg o.d. was selected upon publications of dose finding trials with budesonide enema (Hanauer *et al.*, 1995; Hanauer *et al.*, 1998; Lindgren *et al.*, 1997; Matzen *et al.*, 1991). A daily dose of 2 mg budesonide was found to be superior to either placebo or lower daily dosages of budesonide (*i.e.* 0.5 mg/day and 1 mg/day, respectively) . Furthermore, higher daily dosages of budesonide (i.e., 4 mg/day and 8 mg/day, respectively) did not offer a clinically relevant superiority over a daily dosage of 2 mg budesonide. In the clinical documentation a study in 22 patients is mentioned, in which Budenofalk foam 2mg b.i.d. reduced the CAI by an average of 48% (Falk Pharma GmbH, 1996).

In addition the MAH submitted a clinical trial (BUF-5/UCA) in which 2mg budesonide o.d. was compared to 2 mg budesonide b.i.d. and a placebo arm. This trial will be discussed in more detail. In this study the 2 mg o.d. group achieved a clinical remission rate of 56%, the 4 mg b.i.d. group achieved clinical remission rate of 62%. This difference was not statistically significant. Moreover, the clinical remission rate in the placebo group was similarly high (61%). This trial did not provide any evidence that 2mg b.i.d. is more effective than 2 mg o.d.. Moreover, Lindgren et al. (1997) found that 2 mg budesonide given twice daily was not superior to 2 mg budesonide given once daily.

The Board reckons that the selected dose of 2 mg o.d. is supported by several publications and thus is likely to be appropriate.

Supportive studies

<u>BUF-5/UCA - budesonide 2 mg foam o.d./b.i.d. vs. placebo</u>
Study BUF-5/UCA was a placebo-controlled, multi-centre, randomised, double-blind parallel-group trial. The treatment period comprised a total of 6 weeks (42 days) in order to determine the safe and optimal dose for the induction of clinical remission of proctitis or proctosigmoiditis.
The study was conducted in several centres in the Russian Federation and Ukraine.
Patients were included who had a confirmed (by endoscopy, histology, microbiology, case history) diagnosis of proctitis or proctosigmoiditis of mildly to moderately active phase. The Clinical Activity Index had to be between >4 to ≤ 12 on admission.
It was calculated that with a two-sided α=0.05 and 80% power, 61 patients were needed per treatment arm to detect a difference between treatments assuming 55% response in the active treatment groups and 25% response in the placebo arm. Respectively 76, 71 and 76 patients were randomised to receive placebo, and 2mg o.d./b.i.d., of which 63, 59 and 62 were included in the per protocol population.
The dose of rectal budesonide selected for evaluation (i.e. 2 mg) was based on previous experience. Due to the rapid elimination of budesonide from plasma, it was assumed that a twice-daily regime might be more effective than a once-daily regime of 2 mg rectal budesonide. A placebo control was included to determine the spontaneous remission rate. Clinical remission was determined as CAI≤4.

<u>BUF-6/UCA - budesonide 2 mg foam o.d. vs. hydrocortisone acetate 100 mg foam o.d.</u>
Study BUF-6/UCA was designed as a randomised, open-label, multi-centre, active-controlled phase III study to investigate the efficacy and safety of budesonide foam (2 mg o.d.) compared to hydrocortisone acetate foam (100 mg o.d.) in the 8-week treatment of proctitis and proctosigmoiditis.
Patients aged between 18 and 70 years, with a clinical diagnosis of proctitis or proctosigmoiditis with macroscopic lesions exclusively distal to the sigma up to 40 cm ab ano, a DAI (Disease Activity Index) score of ≥ 4 on admission, and ulcerative colitis confirmed by histology, microbiology and case history were eligible to enter the study.
Of the 251 patients who were randomised, 248 patients received study medication, of whom 120 patients received budesonide and 128 patients received hydrocortisone acetate. The treatment period was 8 weeks. The primary endpoint was the clinical remission rate. Clinical remission was determined as DAI ≤ 3.

Main Study

BUF-9/UCA - budesonide 2 mg foam o.d. vs. budesonide 2 mg enema o.d.
Study BUF-9/UCA was an active-controlled, multi-centre, randomised, double-blind, double-dummy, parallel-group trial. The study was designed following a four group-sequential adaptive design with three interim analyses planned (thus four analyses in total) in order to have the possibility of increasing the sample size during the trial if this was deemed necessary.

The objectives were:
- To compare the efficacy of a daily dose of 2 mg rectal budesonide administered either as an enema or as foam in patients with active proctitis or proctosigmoiditis
- To evaluate patient's preference regarding acceptance and handling of study drugs
- To study tolerability in the form of adverse events and of laboratory parameters.

Participants

Main inclusion criteria
– Male and female adult patients aged between 18 and 70 years
– Ulcerative proctitis or proctosigmoiditis, established or newly diagnosed (first attack: bloody stools ≥14 days prior to baseline visit), confirmed by endoscopy (EI), histology, negative stool culture*, case history
– CAI >4
– Endoscopic Index (EI) ≥4
– Macroscopic lesions only within 40 cm *ab ano*

** For exclusion of causative pathogens*

Main exclusion criteria
Concomitant / previous morbidity
- Crohn's disease
- Prior bowel operation, except appendectomy,
- Toxic megacolon,
- Bacteriologically or virally induced bowel disease,
- Active colorectal cancer or a history of colorectal cancer,
- Presence of symptomatic organic disease of the gastrointestinal tract (with the exception of rectal haemorrhoids or hiatal hernia)
- Serious secondary illnesses of an acute or chronic nature
Concomitant / previous therapy
- Oral/rectal steroids within 1 month prior to baseline
- Immunosuppressant within 3 months prior to baseline
- Long-term NSAID treatment

Patients could withdraw from the trial following a lack of efficacy, intolerable adverse events, a lack of cooperation or having a different diagnosis than distal ulcerosa colitis.

The main inclusion criteria are in line with the recommendations as stipulated in the earlier mentioned CHMP guideline. Patients included in the study, i.e. patients with moderate to severe active distal disease, reflect patients that would be expected to be treated with budesonide foam or enema in practice; however one would expect only to treat those who do not respond to 5-ASAs. This was not a criterion in the study, yet is thought to be of little influence to the overall conclusion (i.e. therapeutic equivalence between enema and foam) and is thus deemed acceptable.

Treatment
A rectally applied budesonide comparator (budesonide 2 mg enema [Entocort®]), which is a registered standard treatment, was used to compare budesonide 2 mg (Budenofalk®) foam, a new budesonide rectal application form.
Both treatment groups were stratified according to the sequence of study drug application (i.e. foam in the morning, enema in the evening vs enema in the morning) leading to four parallel groups.
A treatment period of 4 weeks was considered appropriate to allow for an improvement of clinical symptoms in the target indication.

Randomisation & blinding
Randomisation into 2 treatment groups and 2 strata was performed in blocks of four using automated randomisation lists. The study was double-blind: neither the investigator nor the patient was aware whether the patient applied budesonide foam and placebo enema or budesonide enema and placebo foam.

Outcomes/endpoints:
Primary Endpoint: Clinical remission, defined as a CAI ≤ 4 at the final visit.
The total score of the Clinical Activity Index (CAI) according to Rachmilewitz was calculated as the sum of the scores of seven variables. The scores for four variables were based on data of the patient's diary during the last 7 days before the visit.

Secondary Endpoints:
- Change of CAI
- Change of number of stools per day
- Change of number of bloody stools per day
- Clinical improvement based on CAI
- Time to first clinical remission
- Change of the Disease Activity Index (DAI)
- Clinical remission and improvement based on DAI
- Endoscopic remission and improvement
- Histological improvement
- Therapeutic success and benefit based on global assessment (PGA)
- Patient’s acceptance of the study drug

Safety:
- Adverse Events (AEs)
- Vital signs (blood pressure, heart rate, body weight)
- ESR, haematology, blood chemistry, cortisol, urinalysis
- Assessment of tolerability by investigator and patient

The chosen endpoints are considered to be appropriate in order to address the selected objectives, and follow the earlier mentioned CHMP guideline.

Sample size & underlying assumptions
The calculation of the planned sample sizes for the group sequential test design was based on the primary efficacy variable, the remission rates for Budenofalk® foam and budesonide enema, respectively. Based on literature data, the remission rate was expected to be 0.55 in the Budenofalk® foam and in the budesonide enema group. The non-inferiority margin was set at 15%. For (one-sided) $\alpha = 0.025$ and assumed remission rates of 0.55 in both groups,$1-\beta \approx 80\%$ the study would have 80% power to yield a statistically significant result with a sample size of 172 for each group (344 patients in total),

The chosen approach for the group sequential adaptive design, and the assumptions underlying the sample size determination are acceptable. Considering the average placebo effect lies around 25% (11%-42%) a margin of 15% can be accepted, although it should be taken into account that the placebo effect has been found to be as low as 11%.

Planned analyses
Three analysis sets were defined for the statistical evaluation; safety data set, intention to treat population (ITT) and per protocol population (PP). The final definition and the assignment of patients to these analysis sets were fixed before the final data analysis. The main analysis population was the PP.

Primary endpoint:
The primary goal of the study was to test the null (H0) against the alternative hypothesis (H1):
H0: p(budesonide foam) – p(budesonide comparator) < - Δ
H1: p(budesonide foam) – p(budesonide comparator) > - Δ
Δ > 0 specifies the tolerated inferiority.
The hypotheses were tested using a Farrington-Manning type non-inferiority chi^2 test for difference of proportions with Mantel-Haenzel stratification for treatment sequence considering a non inferiority margin of 15%. Covariates were analysed by logistic regression.

Interim analyses
The plan was to perform the first interim analysis after observation of 86 patients (43 in each group). H0 would have been rejected and the study might have been stopped if the shifted one-sided test for H0 vs. H1 yielded a p-value lower than 0.00003. Otherwise, the study had to be continued with 86 further patients (ca. 43 patients per group) or with a possibly recalculated sample size, based on the observed effect sizes (remission rates) at the interim analysis. Similar stopping rules were put in place for the second and third interim analysis, with predefined critical values for the test statistic.

Secondary efficacy evaluation:
Change of CAI, Clinical Improvement (CAI):
The mean and median CAI was calculated for baseline, for every follow-up examination and for the last documented value on treatment (individual end of therapy) in each treatment group. The mean decrease of the CAI from baseline to the last value on treatment was also calculated and exploratively compared between the two treatment groups. The frequency of patients with clinical improvement in CAI (i.e., improvement by >1 point from baseline) at the final/withdrawal examination was analysed descriptively.

Change of number of stools / Change of number of bloody stools:
The mean and median number of (bloody) stools was calculated for baseline, for every follow-up examination and for the last documented value on treatment (individual end of therapy) in each treatment group. The mean decrease of the number of stools from baseline to the last value on treatment was also calculated and exploratively compared between the two treatment groups. A 95%-confidence interval for the difference of the decrease between the two treatments was calculated.

Time to first clinical remission:
If a patient demonstrated remission (maximally 3 stools and no blood) at “Day X”, then this time was taken for analysis, even if the patient failed to demonstrate remission at subsequent days. The median time to remission, in days, and the corresponding 95%-confidence interval was calculated for each treatment group. Treatment groups were compared by calculating the relative risk and the corresponding 95%-confidence interval.

The planned analyses are deemed appropriate in addressing the objective.

Clinical Efficacy

Supportive studies

BUF-5/UCA - budesonide 2 mg foam o.d. / b.i.d. vs. placebo
After 42 days the following response rates were seen in each treatment group:

	Budesonide 2 mg (Budenofalk®) foam n (%)		Comparator n (%)
Study BUF-5/UCA (clinical remission based on CAI ≤4 associated with a CAI reduction of ≥2 points)			
	2 mg o.d.	**2 mg b.i.d.**	**Placebo**
ITT population	n=70	n=76	n=76
No. of patients with clinical remission#	39 (56 %)	47 (62 %)	46 (61 %)
Odds ratio vs. placebo	0.80	1.05	-
95 % CI	(0.40, 1.59)	(0.50, 2.19)	-
PP population	n=59	n=62	n=63
No. of patients with clinical remission#	31 (53 %)	40 (65 %)	40 (63 %)
Odds ratio vs. placebo	0.59	1.17	-
95 % CI	(0.27, 1.28)	(0.49, 2.76)	-

There was no significant difference in clinical remission rate between the treatment groups and the placebo arm. The clinical remission rate in the placebo group was higher than assumed a-priori, making the study insufficiently powered to detect a difference between treatment and placebo. Several plausible explanations for the high placebo effect were explored by the applicant but no satisfactory clarification was found.

As the efficacy of rectal budesonide has been well established in other trials (Lamers et al., 1991; Danielsson et al. 1992; Lémann et al., 1995; Hanauer et al. 1998), this finding is at least remarkable. It is agreed with the MAH that this finding does not necessarily mean that budesonide foam is ineffective, however since the trial appears to be well conducted and baseline characteristics seem to be well balanced over the different arms the treatment, it does appear to be ineffective within this trial setting. It is most likely that this is due to a combination of known and unknown factors – i.e. low levels of disease activity, possible genetic factors etc.

BUF-6/UCA - budesonide 2 mg foam o.d. vs. hydrocortisone acetate 100 mg foam o.d.

After 8 weeks of treatment the following clinical remission rates were seen:

Study BUF-6/UCA (clinical remission based on DAI ≤3)		
	2 mg o.d.	**Hydrocortisone acetate 100 mg foam o.d.**
ITT population	n=120	n=128
No. of patients with clinical remission#	63 (53 %)	67 (52 %)
Difference in proportion (%) of response vs. comparator	0.16*; -2.63**	-
95 % CI	(-12.3, 12.6)* (-15.8, 10.5)**	-
PP population	n=88	n=91
No. of patients with clinical remission#	48 (55 %)	46 (51 %)
Difference in proportion (%) of response vs. comparator	4.00*; 0.99**	-
95 % CI	(-10.6, 18.6)* (-14.5, 16.5)**	-

*# LOCF; * Response is experiencing clinical remission, with 'Not recorded' taken to be "Lack of remission"; ** Response is experiencing clinical remission, excluding data classified as 'Not recorded'*

The difference in proportion of responses for budesonide patients compared to hydrocortisone acetate patients was 4.0 % (95 %CI: -10.6 %, 18.6 %), and thus budesonide 2 mg foam was at least as effective as hydrocortisone acetate 100 mg foam in the treatment of active proctitis and procto-sigmoiditis. Improvement was comparable between both treatment groups and confirms that budesonide 2 mg foam is efficient in active distal UC.

As hydrocortisone acetate is not registered, the results of this trial are considered merely supportive to the results of trial BUF-9/UCA and the established efficacy of rectal budesonide.

Main Study

BUF-9/UCA - budesonide 2 mg foam o.d. vs. budesonide 2 mg enema o.d.

Patient disposition:

A total of 541 patients were randomised; 537 patients were treated, with 482 patients completing the study. Two patients were lost to followed-up. 53 patients were withdrawn prematurely during treatment; primarily for lack of efficacy (23), lack of co-operation (20), intolerable adverse events (6), not satisfying the entry criteria (3) and due to device malfunction (1). The primary population for efficacy analysis was the PP population (449 patients).

The following table presents the baseline characteristics per treatment group at baseline.

Demography and anamnesis (ITT population)		Budenofalk foam [n=265]	Budesonide enema [n=268]	Total [n=533]
Sex				
Male	n (%)	117 (44.2%)	134 (50.0%)	251 (47.1%)
Female	n (%)	148 (55.8%)	134 (50.0%)	282 (52.9%)
Ethnic origin				
Caucasian	n (%)	264 (99.6%)	267 (99.6%)	531 (99.6)
Negroid	n (%)	0	1 (0.4%)	1 (0.2%)
Caucasian/Asian	n (%)	1 (0.4%)	0	1 (0.2%)
Age [years]	mean (STD)	44.4 (12.9)	43.1 (13.7)	43.8 (13.3)
Weight [kg]	mean (STD)	71.7 (15.2)	71.2 (14.1) [n=267]	71.5 (14.6) [n=532]
Height [cm]	mean (STD)	168.8 (8.4)	170.1 (9.1)	169.5 (8.8)
Smoking habits				
Non-smoker	n (%)	188 (70.9%)	195 (72.8%)	383 (71.9%)
Ex-smoker	n (%)	57 (21.5%)	50 (18.7%)	107 (20.1%)
Smoker	n (%)	20 (7.5%)	23 (8.6%)	43 (8.1%)
Type of disease				
New	n (%)	55 (20.8%)	69 (25.7%)	124 (23.3%)
Established	n (%)	210 (79.2%)	199 (74.3%)	409 (76.7%)
Course of disease				
Unknown (initial)	n (%)	54 (20.4%)	69 (25.7%)	123 (23.1%)
Continuous	n (%)	11 (4.2%)	11 (4.1%)	22 (4.1%)
Recurrent	n (%)	200 (75.5%)	188 (70.1%)	388 (72.8%)
Duration of UC [years]	median (range)	4.9 (0 – 39.8)	3.3 (0 – 36.4)	4.0 (0 – 39.8)
Time since first diagnosis [years]	median (range)	3.5 (0 – 39.8)	2.3 (0 – 31.8)	2.6 (0 – 39.8)
Number of previous episodes	mean (STD)	5.6 (6.5) [n=205]	4.9 (5.5) [n=194]	5.3 (6.0) [n=399]
Duration of present acute episode [weeks]	median (range)	5.0 (0 – 837.3) [n=264]	5.7 (0.3 – 687.6)	5.4 (0 – 837.3) [n=532]
Stool frequency in remission	mean (STD)	1.3 (0.7) [n=264]	1.3 (0.7)	1.3 (0.7) [n=532]
Length of inflammation [cm]	mean (STD)	23.6 (10.4)	24.3 (10.7)	24.0 (10.5)
CAI	mean (STD)	7.6 (2.0)	7.5 (2.0)	7.5 (2.0)
DAI	mean (STD)	7.2 (1.8)	7.3 (2.0)	7.2 (1.9)
Endoscopic Index (EI)	mean (STD)	7.7 (1.9)	7.7 (1.8)	7.7 (1.9)

The different treatment arms appear to be well balanced for the different measured baseline characteristics. The patients receiving the budesonide foam have overall been suffering from UC for slightly longer compared to the patients receiving budesonide enema.

Primary efficacy endpoint:
After four weeks of treatment the following remission rates were:

Study BUF-9/UCA (clinical remission based on CAI ≤4)		
	2 mg o.d.	**Budesonide 2 mg enema o.d.**
ITT population	n=265	n=268
No. of patients with clinical remission[#]	150 (56.6 %)	173 (64.6 %)
Adjusted p value	0.07340	
PP population	n=210	n=239
No. of patients with clinical remission[#]	125 (59.5 %)	157 (65.7 %)
Adjusted p value	0.02362	

The primary analysis was the analysis adjusted for the randomised treatment sequence (stratum). The adjusted p-value obtained for this analysis was p = 0.02362 (PP analysis). The corresponding 95% confidence interval was [-0.149; 0.038]. Thus, the shifted null hypothesis of an inferior effect of

Budenofalk® foam was rejected at the experiment-wise significance level of 0.025, using the pre-specified non-inferiority margin of 15%. For the unstratified PP analysis (neglecting the treatment sequence), the p-value was 0.02 (95% CI: [-0.147; 0.040]). A stratified PP analysis that allocated patients to sequences as treated resulted in a p-value of 0.03 (95% CI: [-0.151; 0.037]).
The results of the ITT analysis were similar but showed confidence intervals that exceeded the non-inferiority margin: a 95% CI of [-0.168; 0.005] (p = 0.07) was found.

The confidence interval approach to determining non-inferiority compares the lower bound of the 95%CI with the determined non-inferiority margin. By applying this approach the lower bound of the 95%CI is within the 15% margin – however when stratifying the analysis by sequence this is not the case. When considering the ITT analysis the lower bound of the 95%CI exceeds the determined non-inferiority margin – however, the main focus is on the PP analysis.
After stratification by covariates one would naturally expect the precision of the estimate to increase, thus the confidence interval to become narrower. Here it widens slightly – therefore the sequences are unlikely related to the outcome.

Secondary efficacy evaluation
The secondary endpoints (efficacy) are presented in the following table:

Secondary Efficacy Evaluation (ITT Analysis set):

		Treatment group		Difference between changes* [CI]
		Budenofalk foam	Budesonide enema	
Change of CAI	mean	-3.7	-3.9	-0.200 [-0.792, 0.391]
Change of number of stools per week	mean	-11.6	-12.6	-0.963 [-3.954, 2.029]
Change of number of bloody stools per week	mean	-12.9	-13.7	-0.724 [-3.847, 2.401]
Change of DAI	mean	-3.5	-3.9	-0.433 [-0.927, 0.061]
Time to first clinical remission	median [CI]	9 [7, 12]	7 [5, 10]	**Hazard ratio** 1.109 [0.911, 1.350]
				Difference between proportions* [CI]
Clinical improvement rates (CAI)	n/N_t (%)	211/265 (80%)	223/267 (84%)	-0.039 [-0.105, 0.027]
Clinical remission rates (DAI)	n/N_t (%)	134/241 (56%)	158/248 (64%)	-0.081 [-0.168, 0.006]
Clinical improvement rates (DAI)	n/N_t (%)	200/241 (83%)	215/247 (87%)	-0.041 [-0.104, 0.023]
Endoscopic remission rates	n/N_t (%)	127/243 (52%)	134/248 (54%)	-0.018 [-0.106, 0.071]
Endoscopic improvement rates	n/N_t (%)	179/243 (74%)	197/248 (79%)	-0.058 [-0.133, 0.017]
Histological improvement rates	n/N_t (%)	117/241 (49%)	134/242 (55%)	-0.068 [-0.157, 0.021]
Therapeutic success rates (PGA)	n/N_t (%)	141/263 (54%)	163/267 (61%)	-0.074 [-0.158, 0.010]
Therapeutic benefit rates (PGA)	n/N_t (%)	205/263 (78%)	221/267 (83%)	-0.048 [-0.116, 0.019]

N_t: group total; CI: 95% confidence interval; * Budenofalk® foam – budesonide enema

The findings of the secondary analyses follow those of the primary analysis. Overall the point estimate of clinical improvement of patients using budesonide foam is slightly lower than those patients using budesonide enema, suggesting that budesonide foam is slightly less effective compared to budesonide enema.

The degree to which the improvement of patients using budesonide enema is greater than that of patients using budesonide foam is small, but consistent across the several variables taken into account. However, the difference in improvement rates was of such a degree that it can be deemed clinically not relevant.

Clinical Remission (CAI) – Baseline Covariate Effects

A summary of the influence of baseline covariates on the clinical remission rates for the ITT analysis set is displayed in the table below:

	Number (%) of patients in clinical remission (CAI) at Visit 3 (LOCF)		Adjusted odds ratio* [95%-confidence interval]
	Budenofalk foam	Budesonide enema	
Baseline CAI			1.430 [1.005, 2.041]
<= 8	118/199 (59%)	137/193 (71%)	
> 8	32/66 (49%)	35/74 (47%)	
Localisation			1.404 [0.991, 1.994]
Proctitis	61/105 (58%)	68/99 (69%)	
Proctosigmoiditis	89/160 (56%)	105/169 (62%)	
Duration of disease			1.371 [0.967, 1.949]
<= 5 years	79/135 (59%)	107/159 (67%)	
> 5 years	71/130 (55%)	66/109 (61%)	
Smoking history			1.404 [0.991, 1.995]
non-smoker	101/188 (54%)	126/195 (65%)	
ex-smoker	37/57 (65%)	32/50 (64%)	
smoker	12/20 (60%)	15/23 (65%)	
Extraintestinal manifestations			1.391 [0.980, 1.977]
absent	146/249 (59%)	165/254 (65%)	
present	4/16 (25%)	8/14 (57%)	
Non-response to rectal mesalazine (present episode)			1.398 [0.986, 1.986]
no	134/226 (59%)	149/229 (65%)	
yes	16/39 (41%)	24/39 (62%)	
Non-response to oral mesalazine (present episode)			1.350 [0.950, 1.921]
no	117/198 (59%)	148/218 (68%)	
yes	33/67 (49%)	25/50 (50%)	
Non-response to rectal mesalazine (previous episodes)			1.391 [0.982, 1.975]
no	137/240 (57%)	161/246 (65%)	
yes	13/25 (52%)	12/22 (55%)	
Non-response to oral mesalazine (previous episodes)			1.391 [0.982, 1.975]
no	128/221 (58%)	148/230 (64%)	
yes	22/44 (50%)	25/38 (66%)	

Source: Appendix 8.1, Table D.3.5 to D.3.13; Appendix 8.3, Statistical Outputs 1d-1l
* odds ratio for treatment groups enema versus foam, adjusted for covariate

The baseline CAI showed a clear influence on the remission rates: patients with low CAI achieved clinical remission more frequently than patients with high CAI (p-value in logit model: 0.0003).
The adjusted odds ratios for the two treatment groups are approximately 1.4, with the 95% CI approaching [1 – 2].

Many of the covariates do not seem to influence treatment effect. Adjusted odds ratios are not appropriate in these cases.
The odds ratio adjusted for baseline CAI indicates that patients using budesonide enema have 1.43 the odds of achieving clinical remission compared patients using budesonide foam. It appears that patients with lower baseline CAI fare better when using budesonide enema.

Overall conclusion on clinical efficacy

The MAH submitted three clinical studies in support of the current application. A randomised placebo controlled trial (BUF-5/UCA) found similar efficacy between the placebo-arm (61%) compared to the patients treated with budesonide foam (56%-62%). This is remarkable, as the efficacy of rectal budesonide in distal UC has been demonstrated in several randomised controlled trials, and therefore this finding is considered to be inherent to this particular study. A second trial demonstrated that budesonide 2 mg foam is at least as effective as hydrocortisone acetate 100 mg foam in the treatment of active distal UC (response rates 53% vs 52% respectively).

The pivotal trial (BUF-9/UCA) compared budesonide foam (2 mg o.d.) with budesonide enema (2 mg o.d.). Regarding the primary objective, budesonide foam was found to be non-inferior to budesonide enema (59.5% compared to 65.7% respectively, 95%CI of difference: -14.7% - 4%, δ=-15%). Overall, patients using budesonide enema seem to have a higher degree of improvement compared to patients using budesonide foam. This was consistent across all the variables taken into account – however, the difference in improvement rates between the two treatments was so small that it can be deemed not clinically relevant. Therefore, it can be concluded that budesonide foam is therapeutically equivalent to the registered budesonide enema in the treatment of distal ulcerosa colitis.

In one clinical study administration in the morning was investigated versus administration in the evening. There is not enough evidence that administration in the morning is as effective as application in the evening. Therefore, the SPC states 'Budenofalk foam should be applied at bedtime'.

Clinical Safety

Systemically active glucocorticoids often cause massive adverse effects restricting their use. As budesonide undergoes extensive first-pass metabolism only a small fraction of the active substance is systemically available, therefore it demonstrates a comparably favourable safety and tolerability profile. Rectal budesonide (2 mg enema) has been proven to be safe and well tolerated in active distal UC in a considerable number of clinical studies. Fewer side effects have been observed compared to conventional corticosteroids. The most frequent events reported are gastrointestinal, including increased bowel frequency and colorectal bleeding. Laboratory abnormalities do not usually develop, and no signs of significant adrenal suppression have been detected during treatment with budesonide enemas.

Experience within the current application

Within the context of this application there were 1005 patients evaluable in the safety population with active distal UC exposed to budesonide. In study BUF-5/UCA, 37 patients reported a total of 83 treatment-emergent Adverse Events (AEs), with 12 patients reporting 23 AEs in the placebo group; 11 patients experiencing 31 AEs in the budesonide 2 mg group and 14 patients experiencing 29 AEs in the budesonide 4 mg group. In study BUF-6/UCA, 86 patients reported 156 treatment-emergent AEs. A total of 36 (30 %) patients in the budesonide group experienced 67 AEs compared to 50 (39 %) patients experiencing 89 AEs in the hydrocortisone acetate group. In study BUF-9/UCA, a total of 143 AEs occurred in the budesonide 2 mg foam group compared to 133 in the budesonide 2 mg enema group.

The most common treatment-emergent adverse events observed during the clinical trials submitted are presented in the following table:

	Budesonide 2 mg foam n (%)		Comparator n (%)
BUF-5/UCA*	**2 mg o.d. (n=70)**	**2 mg b.i.d. (n=76)**	**Placebo (n=76)**
Headache	4 (6 %)	4 (5 %)	4 (5 %)
Application site reaction	2 (3 %)	5 (7 %)	4 (5 %)
Nausea	3 (4 %)	1 (1 %)	1 (1 %)
Fever	2 (3 %)	1 (1 %)	0
Vomiting	2 (3 %)	0	2 (3 %)
Back pain	2 (3 %)	0	0
Dyspepsia	0	2 (3 %)	0
BUF-6/UCA*	**2 mg o.d. (n=120)**		**Hydrocortisone acetate 100 mg foam o.d. (n=128)**
Abdominal pain	7 (6 %)		9 (7 %)
Diarrhoea	5 (4 %)		2 (2 %)
Headache	4 (3 %)		6 (5 %)
Infection	4 (3 %)		2 (2 %)
Sedimentation rate increased	3 (3 %)		4 (3 %)
Gastrointestinal disorder	3 (3 %)		3 (2 %)
Bronchitis	0		4 (3 %)
BUF-9/UCA**	**2 mg o.d. (n=267)**		**Budesonide 2 mg enema o.d. (n=268)**
Headache	10.5 %		10.8 %
Abdominal pain	3.0 %		2.2 %
Nausea	3.0 %		0.7 %
UC colitis aggravated	1.5 %		3.7 %

* ITT / SAF population; ** SAF population

Systemic AEs commonly associated with corticosteroids were not observed. Reactions at the site of application were a relevant observation in study BUF-5/UCA, in studies BUF-6/UCA and BUF-9/UCA. Compared to budesonide 2 mg enema there was no relevant difference.
Regarding causally related adverse drug reactions, no significant differences between the different treatment groups in the three trials were seen – although in study BUF-9/UCA slightly more ADRs were experienced in the patients using budesonide foam as compared to those using budesonide enema. An overview is given in the following table:

Table 2.5-14: Incidence of adverse events causally related to study treatment across all clinical studies

	Safety population	No. of patients with ADR	No. of ADRs
BUF-5/UCA - budesonide 2 mg foam o.d. / b.i.d. vs. placebo			
Total	222*	12 (5 %)	13
Budesonide 2 mg foam o.d.	70	3 (4 %)	4
Budesonide 2 mg foam b.i.d.	76	5 (7 %)	5
Placebo	76	4 (5 %)	4
BUF-6/UCA - budesonide 2 mg foam o.d. vs. hydrocortisone acetate 100 mg foam o.d.			
Total	248*	16 (6 %)	26
Budesonide 2 mg foam o.d.	120	8 (7 %)	15
Hydrocortisone acetate 100 mg foam o.d.	128	8 (6 %)	11
BUF-9/UCA - budesonide 2 mg foam o.d. vs. budesonide 2 mg enema o.d.			
Total	535	46 (9 %)	63
Budesonide foam 2 mg o.d.	267	27 (10 %)	40
Budesonide enema 2 mg o.d.	268	19 (7 %)	23

* corresponds with ITT population
All AEs classed as having a 'definite/certain', 'probable', 'possible' causal relationship to study medication.

Within the three trials 12 patients reported 13 AEs that were considered serious adverse events (SAEs). Three SAEs were recorded in patients treated with budesonide 2 mg foam o.d.: persistent diarrhoea, UC aggravated and angina unstable. None of these were considered to be causally related to the treatment. There were no reported deaths.
Most abnormalities of laboratory values were rated as 'not clinically significant' or 'related to the underlying disease'. In study BUF-5/UCA monitoring of serum electrolytes and aldosterone levels revealed no change of electrolyte or aldosterone levels. No significant adrenal suppression was detected over a treatment period of 8 weeks. In BUF-6/UCA, alterations in serum cortisol levels, and the markers of bone metabolism, osteocalcin and bone-specific AP (bAP), were similar for both treatments, with no statistically significant differences observed. In study BUF-9/UCA, 3 patients in the budesonide 2 mg foam and 2 patients in the budesonide 2 mg enema group showed a deterioration of serum cortisol values below the normal range after a 4-week treatment.
There was no evidence that the rectal administration of 2 mg budesonide does induce any adrenal suppression when administered for a short period of e.g., 4 to 8 weeks.
In none of the different treatment groups throughout the clinical studies a clinically significant effect on the systolic or diastolic blood pressure, pulse rate, weight and body temperature was observed.
There were no specific withdrawal or rebound phenomena.

Overall conclusion on clinical safety
The safety profile of rectal budesonide is well known; fewer side effects have been observed compared to conventional corticosteroids. The most frequent events reported are gastrointestinal, including increased bowel frequency and colorectal bleeding. Within the context of this submission there were 1005 patients evaluable in the safety population with active distal UC exposed to budesonide. Systemic AEs commonly associated with corticosteroids were not observed. Compared to budesonide 2 mg enema there was no relevant difference, aside from a slightly higher occurrence of ADRs. The safety data from the clinical trials included in this current submission revealed no new safety concerns regarding rectal budesonide. Overall, 2 mg budesonide foam o.d. appears to demonstrate a similar safety profile to 2 mg budesonide enema o.d.; most common adverse events were headache and gastrointestinal disturbances, which is in line with the information currently included in section 4.8 of the SPC.

Overall conclusion on clinical aspects

This line-extension is based mainly upon demonstrating therapeutic equivalence between *budesonide enema* and *budesonide foam*. In study BUF-9/UCA it was found that along all the measured parameters, including the main primary efficacy endpoint, patients using budesonide enema seem to have greater improvement compared to those using budesonide foam. However, the difference in improvement rates was of such a degree that it can be deemed clinically not relevant. Moreover – the main aim of this study, to demonstrate non-inferiority of budesonide foam 2 mg o.d. compared to budesonide enema 2 mg o.d., was achieved. Therefore therapeutic equivalence can be assumed based upon the results of this study.

In this trial it was found that the baseline CAI had an influence on the remission rates – also the odds ratio adjusted for baseline CAI indicated that patients using budesonide enema have 1.43 the odds (95% CI:1.005-2.041) of achieving clinical remission compared patients using budesonide foam. It appears that patients with lower baseline CAI fare better when using budesonide enema.

The safety data from the clinical trials included in this current submission revealed no new safety concerns regarding rectal budesonide. Overall, 2 mg budesonide foam o.d. appears to demonstrate a similar safety profile to 2 mg budesonide enema o.d.; most common adverse events were headache and gastrointestinal disturbances, which is in line with the information currently included in section 4.8 of the SPC.

Risk management plan

Budesonide was first approved in 1992, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of budesonide can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the national procedure is in accordance with that accepted for the product Budenofalk 9 mg granules.

Readability test

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 test consisted of two rounds with 10 participants each. People with distal ulcerative colitis and other inflammatory colon diseases were chosen to participate in this user test. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The PIL achieved an Independent Readability Index (IRI) of 99.3 in the first cycle with 10 participants and an IRI of 97.8 in the second cycle with 10 participants. Due to the good results no additional changes were deemed necessary between the cycles. The results indicate that the user will be able to find and understand the necessary information in the PIL. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Budenofalk Schuim 2 mg, rectal foam has a proven chemical-pharmaceutical quality and is a legitimate line extension to Budenofalk 3 mg controlled-release capsules. Budenofalk capsules is a well-known medicinal product with an established favourable efficacy and safety profile.

The MAH has shown that their Budenofalk rectal foam is as effective as hydrocortisone rectal foam and budenoside enema in the treatment of ulcerative colitis that is limited to the rectum and sigmoid colon. The safety data from the clinical trials revealed no new safety concerns regarding rectal budesonide.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other budesonide containing products.

In the Board meeting of 16 October 2008, the application was discussed. The Board followed the positive evaluation of the assessors. The MEB, on the basis of the data submitted, considered the benefit/risk balance positive and granted a marketing authorisation. Budenofalk Schuim 2 mg, rectal foam was authorised in the Netherlands on 7 February 2011.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CAI	Clinical Activity Index
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
DAI	Disease Activity Index
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Marketing Authorisation transfer.	--	MA transfer	9-12-2009	30-12-2009	Approval	N
Change in any part of the (primary) packaging material not ¡n contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)).	--	IA	7-4-2011	18-4-2011	Approval	N
Extension of the current shelf-life of the finished product from 24 months to 36 months. The variation is supported by additional stability data.	--	IB	2-5-2011	10-8-2011	Approval	N
Change of the deputy Qualified Person for Pharmacovigilance (QPPV). Minor textual changes have been made in the Detailed Description of the Pharmaco-vigilance System (DDPS).	--	IA/G	15-6-2011	22-6-2011	Approval	N
Submission of a new or updated Ph. Eur. certificate of suitability for the active substance.	--	IB	4-4-2012	10-5-2012	Approval	N