

Public Assessment Report

Mutual Recognition Procedure

Salofalk 1g / Actuation rectal foam

UK/H/0527/001/E001

UK licence no: PL 08637/0003

Dr Falk Pharma GmbH

LAY SUMMARY

The MHRA has granted Dr. Falk Pharma GmbH a Marketing Authorisation (licence) for the medicinal product Salofalk 1g / Actuation rectal foam (PL 08637/0003).

This is a prescription only medicine (POM) for the treatment of active mild episodes of ulcerative colitis, particularly if located in the rectum and sigmoid or descending colon.

Salofalk 1g / Actuation rectal foam contains the active ingredient 5-aminosalicylic acid which is well characterised in the literature. 5-aminosalicylic acid was first used in the clinical therapy of ulcerative colitis in the 1940's in the azo compound form, suphasalazine consisting of sulphonamide and 5-ASA. It was not until 1977 that it was demonstrated that it was the 5-ASA that was the active component in the treatment of chronic inflammatory bowel diseases.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Salofalk 1g / Actuation rectal foam outweighs the risk, hence a Marketing Authorisation was granted.

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Module 6: Steps taken after initial procedure	Not applicable

Module 1

Product Name	Salofalk 1g / Actuation rectal foam
Type of Application	Article 10.1 [formerly Article 10.1 (a) (iii)]
Active Substance	Mesalazine (5-aminosalicylic acid)
Form	Rectal foam
Strength	1g
MA Holder	Dr. Falk Pharma GmbH, Leinenweberstr. 5, D-79108 Freiburg, Germany
RMS	UK
CMS	Germany
Procedure Number	UK/H/0527/0001/E001
Timetable	Day 90 – 26 th June 2006

Module 2

European Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Salofalk 1g/actuation Rectal Foam.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 actuation contains:
Mesalazine 1.0g
For excipients see 6.1

3. PHARMACEUTICAL FORM

Rectal foam.
White-greyish to slightly reddish-violet, creamy firm foam.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of active, mild ulcerative colitis of the sigmoid colon and rectum.

4.2 Posology and method of administration

Method of Administration: rectal.
Adults and adolescents above 12 years of age:

2 administrations once a day at bedtime. The canister is first fitted with an applicator and then shaken for about 15 seconds before the applicator is inserted into the rectum as far as comfortable. To administer a dose of Salofalk[®], the pump dome is fully pushed down and released. Note that the spray will only work properly when held with the pump dome pointing down. Following the first or second activation depending upon need (see below) the applicator should be held in position for 10-15 seconds before being withdrawn from the rectum. If the patient has difficulty in holding this amount of foam, the foam can also be administered in divided doses: one at bedtime and the other during the night (after evacuation of the first single dose) or in the early morning. The best results are obtained when the intestine is evacuated prior to administration of Salofalk[®].

In general, an acute episode of a mild ulcerative colitis subsides after 4-6 weeks. It is recommended to continue the maintenance therapy with an oral mesalazine preparation

e.g. Salofalk gastro-resistant prolonged release granules at a dosage recommended for this preparation.

Children below 12 years of age:

Salofalk rectal foam should not be used in children below 12 years of age because of insufficient experience with the rectal foam in this age group.

4.3 Contra-indications

Salofalk[®] is contraindicated in cases of:

- pre-existing hypersensitivity to salicylic acid and its derivatives or to any of the other constituents.
- severe impairment of hepatic and renal function
- pre-existing gastric or duodenal ulcers
- haemorrhagic diathesis

Salofalk should not be used for the treatment of children below the age of 12 years.

Caution:

Asthmatics should be treated with care with Salofalk[®] since sulphite contained in the foam may cause hypersensitivity reactions.

4.4 Special Warnings and Precautions for Use

Blood tests (differential blood counts; liver function parameters like ALT or AST; serum creatinine) and urinary status (dip sticks) should be determined prior to and during treatment, at the discretion of the treating physician. As a guideline, controls are recommended 14 days after commencement of treatment, then a further two to three times at intervals of 4 weeks.

If the findings are normal, control examinations should be carried out every 3 months. If additional symptoms occur, control examinations should be performed immediately. Caution is recommended in patients with impaired hepatic function. Salofalk is not recommended in patients with impaired renal function. Mesalazine-induced renal toxicity should be considered if renal function deteriorates during treatment.

Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment with Salofalk.

Patients with a history of adverse drug reactions to preparations containing sulphasalazine should be kept under close medical surveillance on commencement of a course of treatment with Salofalk. Should Salofalk cause acute intolerability reactions such as cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

Special notes:

In isolated cases hypersensitivity reactions principally in the form of respiratory problems may be experienced also by non-asthmatics due to the content of sulphite. This medicine contains propylene glycol that may cause lactic acidosis, hyperosmolality, haemolysis and CNS depression. Slight to mild skin irritation due to propylene glycol may occur. This medicine contains cetostearyl alcohol that may cause local skin reactions (e.g. contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction:

Specific interaction studies have not been performed.

Interactions may occur during treatment with Salofalk and concomitant administration of the following medicinal products. Most of these possible interactions are based on theoretical reasons:

- *Coumarin-type Anticoagulants*: possible potentiation of the anticoagulant effects (increasing the risk of gastro-intestinal haemorrhage)
- *Glucocorticoids*: possible increase in undesirable gastric effects
- *Sulphonylureas*: possible increase in the blood glucose-lowering effects.
- *Methotrexate*: possible increase in the toxic potential of methotrexate.
- *Probenecid/Sulphinpyrazone*: possible attenuation of the uricosuric effects.
- *Spirolactone/frusemide*: possible attenuation of the diuretic effects.
- *Rifampicin*: possible attenuation of the tuberculostatic effects.

In patients who are concomitantly treated with azathioprine or 6-mercaptopurine, possible enhanced myelosuppressive effects of azathioprine or 6-mercaptopurine should be taken into account.

4.6 Pregnancy and lactation

There are no adequate data from the use of Salofalk rectal foam in pregnant women.

However, data on a limited number of exposed pregnancies after oral application of mesalazine indicate no adverse effect on pregnancy or on the health of the fetus/newborn child. To date no other relevant epidemiological data are available. No animal reproductive studies with Salofalk rectal foam have been performed.

Previous animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Salofalk rectal foam should not be used during pregnancy unless the potential benefit outweighs the possible risk.

N-acetyl-mesalazine (N-Ac-5-ASA) and to a lesser degree mesalazine are excreted in breast milk. Only limited experience during lactation in women after oral application is available to date. Hypersensitivity reactions like diarrhoea can not be excluded.

Therefore, Salofalk rectal foam is not recommended in breast-feeding women. If treatment is necessary, breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Gastrointestinal undesirable effects (rare; $\geq 0.01\%$ - $< 0.1\%$):

Abdominal pain, diarrhoea, flatulence, nausea, vomiting.

CNS-related undesirable effects (rare $\geq 0.01\%$ - $< 0.1\%$):

headache, dizziness.

Renal undesirable effects (very rare $< 0.01\%$):

Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency.

Hypersensitivity reactions (very rare $< 0.01\%$):

Allergic exanthema, drug fever, bronchospasm, peri- and myocarditis, acute pancreatitis, allergic alveolitis, lupus erythematosus syndrome, pancolitis.

Musculoskeletal disorders (very rare $< 0.01\%$):

Myalgia, arthralgia.

Blood and the lymphatic system disorders (very rare $< 0.01\%$):

Altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, thrombocytopenia).

Hepato-biliary disorders (very rare $< 0.01\%$):

Changes in hepatic function parameters (increase in transaminases and parameters of cholestasis), hepatitis, cholestatic hepatitis.

Skin and appendage disorders (very rare $< 0.01\%$):

Alopecia.

General disorders and administration site conditions:

Abdominal distension (common $\geq 1\%$ - $< 10\%$);

Anal discomfort; application site irritation, rectal tenesmus (uncommon $\geq 0.1\%$ - $< 1\%$).

Special note:

Care should be taken when administering Salofalk to patients with diminished renal function.

4.9 Overdose

No cases of intoxication have been reported to date and no specific antidotes are known. If necessary, intravenous infusion of electrolytes (forced diuresis) should be considered in cases of overdose.

5. PHARMACOLOGICAL PROPERTIES.

5.1 Pharmacodynamic properties.

Pharmacotherapeutic group:

Aminosalicylic acid and similar agents mesalazine ATC Code: A07EC02.

The mechanism of the anti-inflammatory action is unknown. The results of *in vitro* studies indicate that inhibition of lipoxygenase may play a role. Effects on prostaglandin concentrations in the intestinal mucosa have also been demonstrated. Mesalazine may also function as a radical scavenger of reactive oxygen compounds. Mesalazine acts predominantly locally at the gut mucosa and in the submucosa tissue from the luminal side of the intestine. It is important therefore that mesalazine is available at the regions of inflammation. Systemic bioavailability / plasma concentrations of mesalazine therefore are of no relevance for therapeutic efficacy, but rather a factor for safety.

5.2 Pharmacokinetic properties.

General considerations of mesalazine:

Absorption:

Mesalazine absorption is highest in the proximal gut regions and lowest in distal gut areas.

Biotransformation:

Mesalazine is metabolised both pre-systemically by the intestinal mucosa and the liver to the pharmacologically inactive N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). The acetylation seems to be independent of the acetylator phenotype of the patient. Some acetylation also occurs through the action of colonic bacteria. Protein binding of mesalazine and N-Ac-5-ASA is 43% and 78% respectively.

Elimination:

Mesalazine and its metabolite N-Ac-5-ASA are eliminated via the faeces (major part), renally (varies between 20 and 50%, dependant on kind of application, pharmaceutical preparation and route of mesalazine release, respectively), and biliary (minor part). Renal excretion predominantly occurs as N-Ac-5-ASA. About 1% of total orally administered mesalazine dose is excreted into the breast milk mainly as N-Ac-5-ASA.

Salofalk Foam Specific:

Distribution:

A combined pharmacoscintigraphic / pharmacokinetic study showed that spreading of Salofalk Foam is homogeneous and fast, and is almost complete within 1 hour. It reaches the gut regions rectum, sigmoid colon, and left-sided colon in dependence of extension of inflammation.

Absorption:

Absorption of mesalazine is fast, and peak plasma concentrations for mesalazine and its metabolite N-Ac-5-ASA are reached at about 4 hours. However, plasma concentrations of a 2g mesalazine rectal dose of foam are about comparable with an 250mg oral dose

mesalazine, reaching maximum concentrations of about 0.4 µg/ml. Pre-systemic metabolism is fast, and N-Ac-5-ASA reaches its maximum plasma concentrations also at about 4 hours, like mesalazine, but plasma concentrations are about 4-5 times higher, about 2µg/ml.

5.3 Preclinical safety data

With the exception of a local tolerance study in dogs, which showed good rectal tolerance, no preclinical studies have been performed with Salofalk Foam. Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenicity (rat) or toxicity to reproduction. Kidney toxicity (renal papillary necrosis and epithelial damage in the proximal convoluted tubule or the whole nephron) has been seen in repeat-dose toxicity studies with high oral doses of mesalazine. The clinical relevance of this finding is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite (E223),
cetostearyl alcohol,
polysorbate 60,
disodium edetate,
propylene glycol,
Propellants:
propane,
n-butane,
isobutane.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 years.
After first actuation: 12 weeks.

6.4. Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze. This is a pressurised container, containing 3.75% by mass of inflammable propellant. It should be kept away from any flames or sparks, including cigarettes. It should be protected from direct sunlight and must not be pierced or burned even when empty.

6.5 Nature and contents of container

Aluminium pressurised container with metering valve containing 80g (14 actuations) of suspension together with 14 PVC applicators coated with white soft paraffin and liquid paraffin for administration of the foam.

6.6 Instructions for use and handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

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D-79108 Freiburg
Germany
Phone: +49 (0) 761 1514-0

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

1 October 2001

10. DATE OF (PARTIAL) REVISION OF THE TEXT

May 2006

Module 3 Patient Information Leaflet

If you forget to use Salofalk® rectal foam

Do not take a larger than normal dose of Salofalk® rectal foam next time, but continue treatment at the prescribed dosage.

If you stop using Salofalk® rectal foam

Do not stop taking this product until you have talked to your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Salofalk® rectal foam can cause side effects, although not everybody gets them.

All medicines can cause allergic reactions although serious allergic reactions are very rare. If you get any of the following symptoms after taking this medicine, you should contact your doctor immediately:

- Allergic skin rash
- Fever
- Breathing difficulties.

The following side effects have also been reported:

Common side effects (that affect less than 1 in 10 patients):

- Abdominal discomfort.

Uncommon side effects (that affect less than 1 in 100 patients):

- Anal discomfort, anal irritation and painful urgent need to empty the bowels.

Rare side effects (that affect less than 1 in 1,000 patients):

- Abdominal pain, diarrhoea, wind, nausea and vomiting
- Headache, dizziness.

Very Rare side effects (that affect less than 1 in 10,000 patients):

- Changes in kidney function, sometimes with swollen limbs or flank pain because of renal disorders
- Chest pain, breathlessness or swollen limbs because of heart disorders
- Severe abdominal pain because of acute inflammation of the pancreas
- Severe breathlessness because of allergic inflammation of the lung
- Severe diarrhoea and abdominal pain because of allergic inflammation of the intestine
- Skin rash or inflammation
- Muscle and joint pain
- Fever, sore throat, or malaise because of blood count changes

- Jaundice or abdominal pain because of liver and bile flow disorders
- Hair loss and the development of baldness.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE SALOFALK® RECTAL FOAM

Keep out of the reach and sight of children.

Do not use Salofalk® rectal foam after the expiry date which is stated on the carton and the spray can. The contents of the container must be used within 12 weeks after first opening.

Do not store above 25°C.

Do not refrigerate or freeze.

The container is pressurised and contains 3.75% by weight of flammable propellant. Protect from sunlight and temperatures over 50°C. Do not force open, pierce or burn empty containers, even after use. Do not spray near a flame or incandescent material.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Salofalk® rectal foam contains

The active substance of Salofalk® rectal foam is mesalazine and each spray actuation contains 1 g of mesalazine.

The other ingredients are sodium metabisulphite (E223), disodium edetate, cetostearyl alcohol, polyorbate 60, propylene glycol and propane, n-butane, isobutane as propellants.

What Salofalk® rectal foam looks like and contents of the pack
Salofalk® rectal foam is a white-greyish to slightly reddish-violet and creamy firm foam.

Salofalk® rectal foam is available in packs containing 1 spray can and 14 applicators. Each spray can of Salofalk® rectal foam contains 60 grams of foam, which is sufficient for 14 spray actuations (equivalent to 7 doses).

Marketing Authorisation Holder and Manufacturer

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e-mail: zentrale@drfalkpharma.de

Salofalk® rectal foam is approved in the following EU countries under the trademark Salofalk®:

Austria, Germany, Great Britain, Luxembourg, Netherlands and Portugal.

This leaflet was last approved in 09/2006

PL 08637/003

PACKAGE LEAFLET: INFORMATION FOR THE USER

Salofalk® 1g Rectal Foam mesalazine

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Salofalk® rectal foam is and what it is used for
2. Before you use Salofalk® rectal foam
3. How to use Salofalk® rectal foam
4. Possible side effects
5. How to store Salofalk® rectal foam
6. Further information

GB/08.06

1. WHAT SALOFALK® RECTAL FOAM IS AND WHAT IT IS USED FOR

Salofalk® rectal foam contains the active substance mesalazine, an anti-inflammatory agent used to treat inflammatory bowel disease.

Salofalk® rectal foam is used for the treatment of:

- Inflammation of the large intestine (colon) and rectum (back passage) known by doctors as ulcerative colitis.

2. BEFORE YOU USE SALOFALK® RECTAL FOAM

Do not use Salofalk® rectal foam

- If you are or have been told you are allergic (hypersensitive) to salicylic acid, to salicylates such as Aspirin® or to any of the other ingredients of Salofalk® rectal foam (these are listed in section 6, Further information).
- If you have a serious liver and/or kidney disease.
- If you have a stomach or duodenal ulcer.
- If you have a tendency to bleed easily or you have ever been told that there is a problem with the clotting of your blood.

Do not give Salofalk® rectal foam to children under 12 years of age,

because there is very limited experience with Salofalk® rectal foam in this age group.

Take special care with Salofalk® rectal foam.

Before you start using this medicine you should tell your doctor:

- If you have a history of problems with your lungs, particularly if you suffer from bronchial asthma.
- If you have a history of allergy to sulphasalazine, a substance related to mesalazine.
- If you suffer with problems of your liver.
- If you suffer with problems of your kidney.

Further precautions:

During treatment your doctor may want to keep you under close medical supervision, where you will have regular blood and urine tests.

Using other medicines

Please tell your doctor if you take or use any of the medicines mentioned below as the effects of these medicines may change (interactions):

- Certain agents that inhibit blood clotting (medicines for thrombosis or to thin your blood)
- Glucocorticoids (certain steroid-like anti-inflammatory agents, such as prednisolone)
- Sulphonyl ureas (substances used to control your blood sugar, such as glibenclamide)

- Methotrexate (an agent used to treat leukaemia or immune disorders)
- Probenecid/sulphinpyrazone (agents used to treat gout)
- Spironolactone/furosemide (agents used to treat heart problems)
- Rifampicin (substance used against tuberculosis)
- Medicines containing azathioprine or 6-mercaptopurine (used to treat immune disorders).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It may still be all right for you to use Salofalk® rectal foam and your doctor will be able to decide what is suitable for you.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

You should only use Salofalk® rectal foam during pregnancy if your doctor tells you to.

Salofalk® rectal foam should not be used during breast-feeding as the drug and its metabolite may pass into breast milk.

Driving and using machines
There are no effects on the ability to drive and use machines.

Important information about some of the ingredients of Salofalk® rectal foam

This medicine contains sulphite which may very rarely cause allergic reactions, which may be experienced in the form of breathing problems.

This medicine contains propylene glycol, which can cause certain blood changes, and may cause slight to mild skin irritation.

This medicine contains cetostearyl alcohol which may cause local skin reactions (e.g. contact dermatitis).

3. HOW TO USE SALOFALK® RECTAL FOAM

Always use Salofalk® rectal foam exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Method of administration:

This medicine may only be used rectally, so it has to be inserted through the anus. It is not intended to be taken by mouth. Do not swallow.

Dosage:

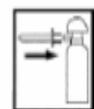
Dose for adults and children over 12 years of age:
The usual dose is 2 spray actuations once a day at bedtime. If you have

difficulty retaining this amount of foam, it may also be administered in two separate doses: one at bedtime and the other during the night or early in the morning (after excreting the first dose).

Emptying your bowels before using Salofalk® rectal foam produces the best results.

Children under 12 years of age:
Salofalk® rectal foam should not be used in children under 12 years of age, because there is very limited experience with Salofalk® rectal foam in this age group.

Preparing to use the foam:



Push the applicator firmly onto the spout of the spray can. Shake the spray can for about 15 seconds to mix the contents.



Before first use, remove the safety lock (plastic flap) from under the pump dome.



Twist the dome on the top of the spray can until the semi-circular gap underneath is in line with the nozzle. The spray can is now ready for use.

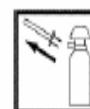
Using the foam:



Place your index finger on the top of pump dome and turn the can upside down. Please note that the spray can will only work properly when held with the pump dome pointing down.



Insert the applicator into your rectum as far as possible. The best way to do this is to place one foot on a chair or stool. To administer a dose of Salofalk® rectal foam, push down fully the pump dome once and slowly release it. For the second spray, push the dome again and release slowly. Wait 10-15 seconds before withdrawing the applicator as the foam still expands a little and would otherwise drop out of the applicator.



After administering the foam, remove the applicator and dispose of it as household waste in the plastic bag provided. Use a new

applicator for another administration.

- Please wash your hands and try not to empty your bowels until the next morning.
- If you go to hospital or see another doctor, tell them you are using this medicine.

You should use Salofalk® rectal foam regularly and consistently to achieve the desired effect.

Duration of treatment:

How long you will use the medicine depends upon your condition. Your doctor will decide how long you are to continue the medication. Mild acute episodes of inflammatory bowel disease (ulcerative colitis) generally subside after 4-6 weeks. If long-term treatment is required, your doctor will prescribe you an oral form of mesalazine, e.g. Salofalk® granules.

If you think that the effect of Salofalk® rectal foam is too strong or too weak, talk to your doctor.

If you use more Salofalk® rectal foam than you should
Contact a doctor if you are in doubt, so he or she can decide what to do. If you use too much Salofalk® rectal foam on one occasion, just take your next dose as prescribed. Do not use a smaller amount.

Module 4 Labelling

Salofalk® 1g rectal foam

mesalazine

Rectal use

Each can of Salofalk 1g rectal foam contains 80 grams of foam, which is sufficient for 14 spray actuations (equivalent to 7 doses).

Each actuation contains 1 g mesalazine.

Sodium metabisulphite (E223), disodium edetate, cetylstearyl alcohol, polysorbate 60, propylene glycol and propane, n-butane, isobutane as propellants.

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

DR. FALK PHARMA GmbH
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78041 Freiburg
Germany



The container is pressurised and contains 3.75% by weight of flammable propellant. Protect from sunlight and temperatures over 50°C. Do not force open, pierce or burn empty containers, even after use. Do not spray near a flame or incandescent material.

The contents of the container must be used within 12 weeks after first opening.

Medicinal product subject to medical prescription.

Keep out of the reach and sight of children.

Read the package leaflet before use.

blue box

Expiry Date:

Batch No:

CXP/08.06

Salofalk 1g rectal foam for Europe
label of the spray can

Falk-Datumscode/Falk code: CXP/08.06

Lohnhersteller/Producer: ASM

Format/Size: 105 x 85 mm

Druckfarben/Printing colours:

- Schwarz
- Pantone 2945
- Pantone 290

Salofalk 1g rectal foam for EU
 Label of the outer pack with Braille
 (package for sale)

Falk-Datumscode/Falk code: CXP/08.06
 Lohnhersteller/Producer: ASM

Format/Size: 155 x 98 x 80 mm
 Konstruktionsnr.: Kd4611b1 (K+D, CH-St. Gallen)

Druckfarben/Printing colours:
 ■ Schwarz
 ■ Pantone 2945
 □ Pantone 290

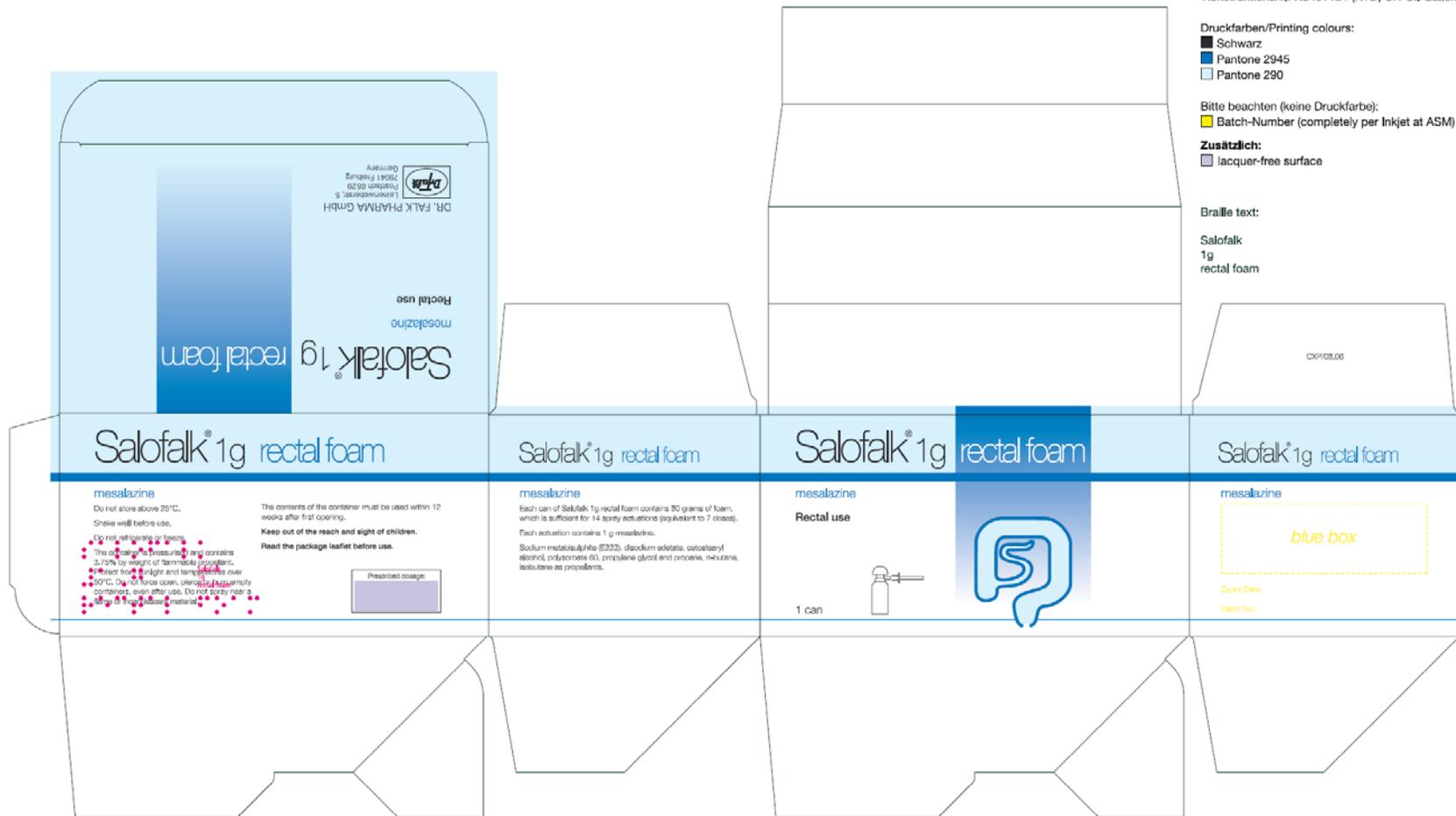
Bitte beachten (keine Druckfarbe):
 ■ Batch-Number (completely per Inkjet at ASM)

Zusätzlich:
 □ lacquer-free surface

Braille text:

Salofalk
 1g
 rectal foam

CXP/08.06



Aerosol Kd4611b1 view on printing dat. 5.1.05

Module 5

Scientific discussion during initial procedure

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK considered that the application for Salofalk 1g / Actuation rectal foam in the treatment of mild episodes of ulcerative colitis, particularly if located in the rectum and sigmoid or descending colon, could be approved. A national marketing authorisation was granted on the 1st October 2001.

This repeat use application is submitted by Dr Falk Pharma GmbH via the Decentralised (Mutual Recognition) Procedure, based upon Mutual Recognition of United Kingdom Product Licence PL 08637/0003 held by the applicant and approved on 1 October 2001.

The original application for Salofalk foam was submitted to the UK Licensing Authority as an abridged application, according to Directive 65/65/EEC, article 4.8 (hybrid). The current mutual recognition application is submitted under article 10.1.(a)(iii) last paragraph of Directive 2001/83/EC as amended. The original abridged application referred to Pentasa Mesalazine Enema (Ferring Pharmaceuticals Limited, PL 03194/0027) while the repeat use application refers to Salofalk 1000 mg gastro-resistant prolonged release granules in sachets (Dr Falk Pharma GmbH, PL 08637/0008, MRP no.: DE/H/0363/002) as the original product.

The product has successfully gone through a first-wave MRP in Austria, Luxembourg, Portugal and the Netherlands.

Mesalazine, the active substance in Salofalk foam, falls under the ATC classification “intestinal antiinflammatory agents: aminosalicic acid and similar” (A07E C02).

With the UK as reference member state in this decentralised mutual recognition procedure (MRP), the marketing authorisation holder (Dr Falk Pharma GmbH) is applying for a marketing authorisation in Germany.

In the repeat use procedure the applicant is seeking the authorisation to market Salofalk foam for treatment of active, mild ulcerative colitis of the sigmoid colon and rectum.

The relevant data were presented to the Committee on Safety of Medicines referring to the indications originally approved by the MHRA. The clinical dossier was amended by an additional pivotal comparator controlled clinical study confirming the efficacy and safety of Salofalk rectal foam. The indication (treatment of active, mild ulcerative colitis of the sigmoid colon and rectum) and the additional clinical study were considered acceptable and a repeat use procedure was started.

The product contains 5-aminosalicylic acid (5-ASA or mesalazine) as the active ingredient. Therefore, its action is similar to that of other Salofalk products containing the same active substance already on the market, namely Salofalk tablets, Salofalk suppositories, Salofalk enemas and Salofalk granules. Moreover, Salofalk foam is similar in composition to Salofalk, Colitofalk, Rafassal, and Rowasa enemas.

Salofalk foam represents a new pharmaceutical formulation, which allows accurate rectal dosing and offers improved patient convenience over Salofalk enemas, especially for those patients who cannot hold the liquid enemas. Thus, compliance in patients with ulcerative colitis can be enhanced.

Presentation form: Foam

Constituents:

Active ingredient: 1 puff contains 1g 5-aminosalicylic acid in 17.5 to 30ml foam

Other constituents: Emulsifying wax (Polawax™ - now the individual compounds of this wax, namely polysorbate 60 and cetostearyl alcohol, are used).

Sodium metabisulphite

Titriplex

Propylene glycol

Propellant: mixture of propane, n-butane, and isobutane

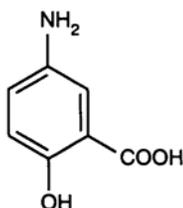
Protecting gas: nitrogen

Chemical name: 5-amino-2-hydroxybenzoic acid

Chemical formula: C₇H₇NO₃

Molecular weight: 153.1

Structural formula:



Description: White or grey voluminous powder, with some pink coloration

Melting point: From 265°C, with decomposition

pKa: 5.31

Only one new preclinical study was reported in the documentation supplied by the applicant. This Good Laboratory Practice (GLP) compliant study showed that repeat daily rectal doses of Salofalk foam were well tolerated by female dogs.

Adequate justification for the concentration of the excipient propylene glycol in Salofalk foam was provided and appropriate warnings included in the SPC.

Salofalk foam has been shown to be more efficacious than placebo in patients with mild ulcerative colitis affecting the rectum and the sigmoid colon. In addition Salofalk foam has proven to be non-inferior to a recently registered mesalazine-containing rectal foam. The formulation appears to be generally well tolerated.

There are no GMP (Good Manufacturing Practice) issues. The manufacturing site is in Switzerland and batch-release site is in Germany. These sites are satisfactory for the purposes nominated.

The UK was assured that acceptable standards of GMP are in place for this product at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

All product related text (SPC, PIL and labels) are satisfactory from the clinical, preclinical and pharmaceutical point of view for a product of this nature.

The quality of the product is satisfactory in relation to its safety and efficacy. The data have demonstrated the efficacy and safety of the product to the extent that the overall risk/benefits of the product is favourable for the proposed indications.

PHARMACEUTICAL ASSESSMENT

Drug substance

A drug master file for the active substance Mesalazine, was first submitted to the MHRA in 1984. Various updates have since been submitted, and at the time of the national Salofalk foam application the relevant update was assessed. A more recent update, dated July 2005, has since been submitted. An appropriate specification according to the Ph.Eur. monograph is provided for mesalazine.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported.

Mesalazine from this source is currently included in a variety of products on the UK market (including Salofalk enemas and suppositories). Certificates of analysis taken from three batches of drug substance generally confirm that mesalazine from this source is of suitable quality.

Drug product

The proposed commercial manufacturer is in Switzerland and EU batch release takes place in Germany. The applicant has provided an assurance that the product will be tested to the full finished product specification on entry into the EU. A satisfactory manufacturing formula has been provided, which is the normal production batch size.

The aim was to develop a formulation capable of easily distributing mesalazine over the entire mucosal surface of the lower colon. A target volume of approximately 35-60 ml was chosen, which is readily achieved using foam due to the rapid expansion that takes place during/after propellant evaporation.

The manufacturing procedure has been successfully validated. Some excipients are European Pharmacopoeial grade, the rest are USP/NF grade. There are no European pharmacopoeial monographs for control of the propellants, so conformance to USP/NF specification is acceptable. Relevant certificates of analysis for the excipients have been provided.

The suspension is packaged in internally coated aluminium monoblock canisters, with a dose metering valve. Compatibility trials have been performed using a variety of lacquers, which were stored in contact with the suspension at 40°C for 6 months. No discolouration or damage was observed following storage and suspension appearance remained unchanged. Only the lacquers tested in the formal stability trial will be used in the marketed product.

The applicant has provided results of testing for clinical efficacy/safety and a study of the distribution of foam within the colon. This is in line with EC requirements for the clinical dossier on locally applied products. The updated clinical assessment report provides a thorough review of four studies:

- (i) Double blind, randomised, comparative study to the tolerability of Salofalk foam vs. Salofalk placebo foam in patients with mildly to moderately active proctitis, proctosigmoiditis and left-sided ulcerative colitis.
- (ii) Open, randomised, crossover, comparative study of the acceptability, efficacy and tolerability of mesalazine foam (2g/60ml bid) vs. mesalazine enema (2g/60ml bid) in patients with proctitis, proctosigmoiditis and left-sided ulcerative colitis.
- (iii) Open, single dose, two way crossover scintigraphic study on the spread of samarium (¹⁵³Sm) labelled mesalazine foam in the colon vs. mesalazine enema in healthy volunteers and patients with ulcerative colitis.
- (iv) Single-blind (investigator blinded), randomised, multicentre, comparative study of the efficacy and tolerability of mesalazine foam (2x 1g/30ml) vs. mesalazine foam (2x 1g/60ml) in patients with active ulcerative proctitis or proctosigmoiditis

The proposed finished product specifications are in compliance with the general pharmacopoeial requirements and the batch data submitted, and are controlled with valid methods. Stability studies have been undertaken with stability data results supporting a shelf life of 36 months for the drug product and 12 weeks after first actuation.

Description and composition of the drug product

A single canister holds sufficient suspension to produce 14 doses of foam plus a 20% overage to accommodate losses in the can and applicator. The applicant states that the formulation used in clinical trials was consistent with that proposed for market. The applicant has confirmed that although nitrogen was included as propellant in early batches produced as part of development work it was not included in the batches used for clinical trials.

The propellant consists of an isobutane/propane/butane mix. The relative proportions of individual propellants are not specified as the important factor is the total pressure exerted and not the amount of each individual propellant per can.

The composition of Salofalk foam is shown below:

Mesalazine (5-aminosalicylic acid)
Cetostearyl alcohol
Polysorbate 60
Propylene glycol
Sodium metabisulphite
Disodium edetate
Propane/iso-butane/n-butane 2.5 bar
Nitrogen

Aluminium pressurised container with metering valve containing 80g (14 actuations) of suspension together with 14 PVC applicators coated with white soft paraffin and liquid paraffin for administration of the foam.

Pharmaceutical Development

Formulation Development

The aim was to develop a formulation capable of easily distributing mesalazine over the entire mucosal surface of the lower colon. Although not justified, a target volume of approximately 35-60 ml was chosen, which is readily achieved using foam due to the rapid expansion that takes place during/after propellant evaporation.

Foams may be prepared from aqueous or non-aqueous bases or a mixture of the two. A non-aqueous formulation was developed because mesalazine is insoluble in water at the required pH range and aqueous suspensions form less stable foams. An emulsion-type, propylene glycol foam, containing polysorbate 60 and cetostearyl alcohol (which together form an emulsifying wax), was chosen because such formulations are known to produce dense and stable foams.

Manufacturing Process Development

The manufacturing process has been described satisfactorily. During the development process batches were produced which were (i) not milled, (ii) milled once, and (iii) milled twice. All batches were used for stability testing and all results were within specification. The manufacturing process for all new batches includes a milling stage.

In-process control of filling weight is performed and each container is filled with propellant through the valve.

Description of Manufacturing Process & Process Controls

Details are provided as both a narrative and a flow chart of the manufacturing process including the in-process controls.

Controls of Critical Steps & Intermediates

In process controls are set and a rationale is provided for the controls proposed at various stages in the process.

Process validation & evaluation

Process validation was carried out on full-scale batches made at the proposed manufacturing site. The data provided confirm that the process is well controlled and reproducible.

Control of excipients

All excipients are adequately controlled before use during the manufacturing process.

Justification of Specifications

No justification was deemed necessary for those excipients that are controlled by the Ph.Eur. and the USPNF national formulary. There are no European pharmacopoeial monographs for control of the propellants, so conformance to USPNF specification is acceptable. Relevant certificates of analysis for the excipients have been provided. The necessary tests required confirming the quality of the material is deemed to be covered by the specification provided.

Excipients of Human or Animal Origin

It has been confirmed that the cetostearyl alcohol is derived from non animal sources and so complies with current TSE requirements.

Control of Drug Product**Specifications**

Suitable tests and limits are proposed for the control of preparations of this 1g presentation.

Analytical Procedures & Validation of Analytical Procedures

An in-house HPLC method has been developed to determine the content of mesalazine and related substances in the suspension. The technique has been validated for determination of mesalazine and related substances. Content of active ingredient per unit dose is determined by UV spectroscopy against a mesalazine reference standard. The method has been validated in terms of specificity, linearity and accuracy, and intermediate precision has been demonstrated.

Sodium metabisulphite is determined using a suitable technique. A satisfactory method is used to determine the content of sodium EDTA. The method has been satisfactorily validated. A comprehensive validation package has been submitted for all the analytical methods.

Batch Analyses

Appropriate batch analytical data has been provided on batches of product manufactured at a production scale in the designated facility. These demonstrate compliance with the proposed release specification.

Justification of Specification(s)

The specification for this 1g rectal foam has been adequately justified in the application.

Container Closure System

Aluminium pressurised container with metering valve containing 80g (14 actuations) of suspension together with 14 PVC applicators coated with white soft paraffin and liquid paraffin for administration of the foam.

Stability**Stability of the active**

Data on stability of the active ingredient are included in the drug master file. The drug substance is highly stable and the proposed shelf-life (three years) and re-test date (two years) are appropriate.

Stability of the finished product

Stability trials have provided enough data to indicate that a stable product has been developed. Since no photostability or cold storage testing has been carried out, the following storage instructions are included in the SPC “Keep container in the outer carton. Do not refrigerate or freeze.” The quality of the product can be expected to be assured up to the end of the expiry period if storage recommendations are followed.

BIOAVAILABILITY

The applicant has provided results of testing for clinical efficacy/safety and a study of the distribution of foam within the colon. This is in line with EC requirements for the clinical dossier on locally applied products. The clinical assessment report provides a thorough review of the following studies:

- (i) Double blind, randomised, comparative study to the tolerability of Salofalk foam vs. Salofalk placebo foam in patients with mildly to moderately active proctitis, proctosigmoiditis and left-sided ulcerative colitis.
- (ii) Open, randomised, crossover, comparative study of the acceptability, efficacy and tolerability of mesalazine foam (2g/60ml bid) vs. mesalazine enema (2g/60ml bid) in patients with proctitis, proctosigmoiditis and left-sided ulcerative colitis.
- (iii) Open, single dose, two way crossover scintigraphic study on the spread of samarium (¹⁵³Sm) labelled mesalazine foam in the colon vs. mesalazine enema in healthy volunteers and patients with ulcerative colitis.

(iv) Single-blind (investigator blinded), randomised, multicentre, comparative study of the efficacy and tolerability of mesalazine foam (2x 1g/30ml) vs. mesalazine foam (2x 1g/60ml) in patients with active ulcerative proctitis or proctosigmoiditis

EXPERT REPORT

The proposed expert provides a satisfactory pharmaceutical expert report.

PRODUCT NAME AND APPEARANCE

The product name “Salofalk foam” is satisfactory. The suspension is contained in an aluminium can and is described as a white-grey to lightly reddish-violet foam

PATIENT INFORMATION LEAFLET

The PIL is satisfactory.

LABELLING

The labels are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is satisfactory.

CONCLUSION

The product appears to be stable, highly pure, and of proven efficacy (albeit in only limited indications – see clinical assessment report). The grant of a licence is recommended.

Pharmaceutical Assessor
March 2006

PRECLINICAL ASSESSMENT

INTRODUCTION

This is an outgoing mutual recognition application for Salofalk foam containing the active ingredient mesalazine for treatment of acute attacks of mild ulcerative colitis (especially in the rectum and sigmoid colon). Salofalk foam is intended for rectal administration.

Each metered dose (each puff) of Salofalk foam contains 1g of the active ingredient mesalazine (5-amino-salicylic acid or 5-ASA) in sodium metabisulphite, cetostearyl alcohol, polysorbate 60, disodium edetate and propylene glycol. Propane, n-butane and isobutane are used as propellants and nitrogen as protecting gas. The maximum recommended human daily dose (MRDD) of 4 puffs (2 puffs at bedtime and 2 puffs early in the morning) of Salofalk foam has been proposed which is equivalent to a daily dose of 4g 5-ASA (*ca* 57mg 5-ASA per kg for a person weighing 70kg).

COMMENT

The historical preclinical studies carried out with oral and rectal (suppositories or enemas) formulations of 5-ASA (different from Salofalk foam) were discussed. These data will not be reiterated and only an overview of 5-ASA toxicity in animals will be given as a reference point.

The mechanism of action of 5-ASA is still poorly understood. 5-Amino-salicylic acid is generally thought to have a local effect (rather than a systemic effect) on the inflamed intestinal tissue and the systemic availability of 5-ASA has not been related to its therapeutic efficacy. However, systemic availability of 5-ASA is related to its safety (see below).

5-Amino-salicylic acid is metabolised by N-acetyl-transferase (NAT; a cytosolic enzyme present in the liver, lung, kidneys and the entire gastrointestinal mucosa) to its major metabolite, N-acetyl-mesalazine, in most species (rats, mice, guinea pigs, rabbits and man, but not dogs which are poor acetylators of aromatic amines including 5-ASA). In animals, there has been evidence of saturation of NAT and reduction of renal elimination caused by renal function impairment when high doses of 5-ASA were administered. The main target organs of toxicity are the kidneys. Chronic toxicity studies with various oral formulations of 5-ASA have shown that in rats and dogs, nephrotoxicity (mainly renal papillary necrosis) is produced at doses in excess of 80 and 40mg/kg/day (highest NOEL for nephrotoxicity), respectively. The nephrotoxic potential of salicylates has been related to an exaggeration of their pharmacological action, resulting in local ischaemia or uncoupling of oxidative phosphorylation in the medulla, with subsequent oxidative damage at suprathreshold doses. According to the Expert, dogs, and to lesser extent rats, are considered to be sensitive models for iatrogenic renal papillary necrosis. According to the ER, terminal elimination half-life of N-acetyl-mesalazine was at least 6h. A plasma mesalazine elimination half-life of 1h has been quoted in the literature.

Systemic exposure to 5-ASA and/or N-acetyl-mesalazine is related to its toxicity and therefore safety. The Expert did not compare the extent of exposure to 5-ASA and/or N-acetyl-mesalazine in experimental animals with that in humans following rectal application of Salofalk foam. Kinetic parameters (for mesalazine and its major metabolite) were calculated in a clinical bioequivalence study in healthy volunteers and patients with ulcerative colitis. The Clinical Expert claims that there were no statistical differences in kinetic parameters between Salofalk foam and Salofalk enema. In addition, the reporting of the study contained some flaws, which had the effect of making interpretation of the results somewhat difficult. In general the study confirms the well-known fact that 5-ASA plasma levels are lower following rectal application compared to orally administered mesalazine.

Plasma of rats and dogs were not assayed at NOEL for nephrotoxicity quoted above. Peak plasma concentrations (C_{max}) and AUCs for 5-ASA and N-acetyl-mesalazine following oral administration of 5-ASA have been estimated in rat and dog assuming dose-proportionality up to the NOELs in these species. These kinetic parameter estimates are compared with those obtained in the single dose bioequivalence study with Salofalk foam and enemas in Table 1 below.

Table 1 Inter-species comparison of plasma C_{max} and AUC values for 5-ASA and its major metabolite. (Assessor's table)

Species	Dose (mg/kg)	Route/formulation /number of doses	C_{max} (µg/ml)		AUC (µg.h/ml)	
			5-ASA	N-acetyl-ASA	5-ASA	N-acetyl-ASA
Rat	80	oral suspension, eight consecutive daily doses	67 ^a	103 ^a	42 ^a	97 ^a
Dog	40	oral capsule, single dose	176 ^a	0 ^a	291 ^a	0 ^a
Human	29 ^b	rectal Salofalk foam, single dose	0.45	2.0	1.94 ^c	10.0 ^c
Human	29	rectal Salofalk enema, single dose	0.37	1.9	1.73 ^c	9.0 ^c

^a Estimated assuming dose proportionality up to 80mg/kg and 40mg/kg in rats and dogs, respectively.

^b A dose of 2g of 5-ASA/60ml of foam is equivalent to a dose of 29mg/kg for a 70kg person.

^c These are only 0-12h AUC values.

Systemic exposure to 5-ASA and N-acetyl-ASA at the non-nephrotoxic oral doses in animals are more than 22 and 10 fold higher, respectively, than the corresponding exposures achieved following a single therapeutic rectal dose of Salofalk foam (2g 5-ASA/60ml). Given this safety margin, it is considered that systemic exposure to 5-ASA and its major metabolite following rectal application of Salofalk foam is unlikely to present a safety concern. Salofalk foam is appropriately contra-indicated in patients with severe renal and hepatic impairment and monitoring of patients for kidney and liver impairment has been recommended in section 4.4 of the SPC.

In dogs, 5-ASA also produced ocular lesions characterised as keratoconjunctivitis sicca. However, these ocular lesions appeared to be a species-specific effect of mesalazine that has not been reported in man.

Oral doses of 5-ASA up to 320mg/kg/day (rats) and 495mg/kg/day (rabbits) were neither teratogenic nor embryotoxic. In addition, oral mesalazine did not affect fertility and

reproductive function of rats. N-Acetyl-mesalazine and to a lesser degree 5-ASA have been shown to cross the placenta or enter breast milk. This medicine should therefore not be used during pregnancy or breastfeeding unless in the opinion of the physician, the likely benefits of treatment outweigh the potential hazards. According to data in the literature, 5-ASA is not potentially mutagenic, clastogenic nor carcinogenic.

LOCAL TOLERANCE

A 14 day, local tolerance study by rectal administration of Salofalk foam was carried out. This study appeared to be GLP compliant although the deviation to study protocol was not included in the raw data documents and was provided by the applicant only when requested during this assessment. Two daily rectal doses of either 2g of Salofalk foam (according to raw data, 2g of foam was equivalent to 10ml) or an equivalent dose volume of 0.9% saline solution as control. Test animals received 4g (2 x 2g) of foam per day corresponding to 880mg (2 x 440mg) 5-ASA per day (nominally 60mg 5-ASA/kg per day). Slight reduction in body weights of both test and control dogs were observed but were associated with the stress induced by the rectal application. Macroscopic and histopathological examinations of the rectum and colon (serial sections) revealed no changes considered to be related to rectal treatment with Salofalk foam. In fact, microscopic findings *ie* granulocytic infiltration, glandular dilatation, haemorrhage, lymphadenitis, epithelial cysts filled with mucous and cellular detritus seen in both test and control animals, were considered to be spontaneous in nature and within the normal background pathology commonly found in dogs of this strain and age.

IMPURITIES/DEGRADATION PRODUCTS

The impurity profile of the proposed product was not discussed in the dossier. The source of active ingredient is described. Drug substance specification (DSS) limits proposed for the impurities/related substances are in accordance with the current EP specifications.

The proposed finished product specification (FPS) limits for 4-AP and for other individual related substances are considered acceptable.

EXCIPIENTS

Each puff of Salofalk foam contains propylene glycol (PG). An adequate review of the literature on the toxicity of propylene glycol (PG) in animals and humans has been provided by Dr Falk Pharma.

Propylene glycol has low acute toxicity. The potential safety concern is whether propylene glycol will cause toxicity (CNS depression, lactic acidosis, haemolysis or increased osmolality) following repeat rectal administration of Salofalk foam. In 2 year chronic feeding studies the NOELs for PG are approximately 7-10 times higher than the maximum daily dose of PG anticipated with Salofalk foam. These findings support that the repeat rectal administration of Salofalk foam is safe.

The National Institute for Public Health and Environmental Hygiene (in the Netherlands) considered the safety of propylene glycol when used as a solvent in oral cough mixtures.

The Institute concluded that daily oral doses of propylene glycol up to 400mg/kg (adults) and 200mg/kg (children) were safe, if taken for not longer than 2 weeks. This safe dose of PG in adults is higher than anticipated with Salofalk foam, but Salofalk foam may be used long term and therefore the limit proposed by the Institute may not be suitable in this case.

In humans, an oral dose of PG is rapidly absorbed from the gastrointestinal tract and metabolised primarily in the liver and kidneys and between 20-50% of the dose is excreted as unchanged PG within 24h post-dose.

The applicant estimated plasma C_{max} values for PG after a rectal dose of Salofalk foam by assuming dose linearity for PG absorption/plasma concentrations. However, according to Speth *et al* (1987), PG has non-linear pharmacokinetics because of saturable clearance. Therefore the above C_{max} estimations may be inappropriate.

According to Speth *et al*, there was no evidence of lactic acidosis, haemolysis or increase in osmolality in cancer patients after a single 4h iv infusion of 5-21g PG (equivalent to 82-488mg PG/kg). However, blood chemistry results were not presented in this paper.

During multiple oral dosing there was evidence that accumulation of PG in humans was significant enough to cause toxic effects (Yu *et al*, 1985), but no clear relationship between plasma PG concentrations and CNS toxicity was evident. The elimination half-life of PG was in the same range after single (*ca* 4h) and repeat (3.8-4.1h) oral doses and after single rectal dose (*ca* 3h). Considering the MRDD of PG with Salofalk foam, its short half-life after rectal administration, its rapid metabolism to substances of low toxicity (ultimately lactic acid and glucose), rapid excretion of PG and metabolites, and the 7-10 fold safety margin (estimated above), accumulation of PG with the proposed formulation and hence toxicity is not expected.

However, propylene glycol has been associated with CNS toxicity in children (when used as a solvent in some oral vitamin preparations) and increased serum osmolality especially in small infants and in patients with diminished renal function (when given as an iv infusion). Patients with renal impairment exposed to PG have also developed lactic acidosis possibly because of hepatic metabolism of propylene glycol to lactic acid and its subsequent accumulation in such patients. Section 4.4 of the SmPC therefore contains a warning specifying that Salofalk foam is best avoided in patients with established renal impairments. A further precautionary warning: "This medicine contains propylene glycol that may cause lactic acidosis, hyperosmolality, haemolysis and CNS depression. Care should be taken when administering Salofalk foam to patients with diminished renal function. Slight to mild skin irritation due to propylene glycol may occur" is also included in section 4.4 of the SmPC. Since Salofalk foam is not recommended for use in babies and infants, a warning on effects of propylene glycol in this age group may not be necessary.

SUMMARY OF PRODUCT CHARACTERISTICS

The summary of product characteristics is acceptable

PATIENT INFORMATION LEAFLET

The patient information leaflet is acceptable.

EXPERT REPORT

The applicant has submitted a pharmaco-toxicological Expert Report (ER) and an addendum to the ER both written by a suitably qualified expert.

DISCUSSION

Salofalk foam is intended for rectal administration and in line with other 5-ASA formulations is thought to have a local effect rather than a systemic effect. Systemic exposure to 5-ASA and/or its metabolites is associated with safety but not with therapeutic efficacy of such formulations. The only pre-clinical study performed with Salofalk foam was a rectal tolerance study which showed that repeat daily rectal doses equivalent to the human therapeutic dose (nominally 60mg 5-ASA/kg/day) were well tolerated. In fact, macroscopic and histopathological examinations of the rectum and colon revealed no changes considered to be related to rectal treatment with Salofalk foam.

In the dossier, a comparative pharmacokinetic study with Salofalk foam and enema (in patients and volunteers) was presented. Given the safety margin of more than 10 fold estimated by the present assessor, systemic exposure to 5-ASA and its major metabolite following rectal application of Salofalk foam is not considered to raise a safety concern.

Salofalk foam contains propylene glycol as an excipient. Appropriate warnings regarding the possible toxic effects of propylene glycol (e.g. hyperosmolality, lactic acidosis, haemolysis and CNS depression), particularly in patients with diminished renal function, have been included in the SPC.

CONCLUSIONS

Grant of a Marketing Authorisation for Salofalk foam is recommended.

Pre-clinical Assessor

March 2006

CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

The application is for Salofalk foam (1 puff = 1g 5-aminosalicylic acid (5-ASA)/17.5 to 30 ml foam) for rectal administration in the treatment of mild episodes of ulcerative colitis. Although this represents a new delivery system for the company, there is a foam enema preparation already available in the UK (Asacol Foam Enema Suspension, PL 00002/0222 granted 3/5/94). The applicant does not claim essential similarity to this product but rather compares its new preparation to that of Claversal rectal foam) a drug product that was recently registered in Germany (Reg-No: 42197.00.00), Belgium (Reg-No: 0404 IS 23 F 11) and Luxembourg (Reg-No: 0210817). Claversal rectal foam and Asacol rectal foam, are foam preparations containing mesalazine as the active pharmaceutical ingredient (API) which is administered in a dosage of 1g per puff (60ml). The qualitative compositions are almost identical and agree in API, solvents, propellant, preservatives, complex formers, anti-oxidant and viscosity arising agent. The emulsifiers used to generate the pharmaceutical form are very similar. Therefore the same type of emulsion is to be expected.

There are a range of other formulations for mesalazine on the market including Salofalk tablets (PL 10341/0004, granted 13/9/91) and Salofalk suppositories (PL 10341/0009, originally granted 22/1/96).

The exact cause of ulcerative colitis is still unclear. It has been suggested that it is related to genetic disposition, micro-organisms, lifestyle and/or nutritional factors. Ulcerative colitis usually begins in the rectum and can spread proximally into the colon to any length. The effects are restricted to the mucosa and sub-mucosal layer.

The natural history consists of episodes of high and low inflammatory activity. In the absence of a known cure, treatment is aimed at suppressing acute episodes and preventing recurrences.

5-aminosalicylic acid was first used in the clinical therapy of ulcerative colitis in the 1940's in the azo compound form, sulphasalazine consisting of sulphonamide and 5-ASA. It was not until 1977 that it was demonstrated that it was the 5-ASA that was the active component in the treatment of chronic inflammatory bowel diseases.

It is thought that it is the local availability of 5-ASA, rather than its systemic plasma concentration, which determines its efficacy. As a result of its rapid absorption in the upper gastro-intestinal tract, conventional oral preparations provide little active substance to the distal small intestine and the large intestine. A number of delayed release oral formulations have been developed to overcome this problem and rectal preparations can be used to ensure local availability.

The rationale of this application is that, while enemas are generally well accepted, some patients complain of difficulties with self-administration or retention of the enema. Based on the experience of steroid foam preparations used for the same condition, the applicant seeks to market a therapeutic alternative to 5-ASA enemas.

INDICATIONS

The indications as proposed by the applicant in the original application were:
“Therapy and prophylaxis of acute attacks of mild to moderate ulcerative colitis, especially in the rectum and sigmoid colon and also in the descending colon”.

Given the paucity of clinical data on patients with moderate disease and patients with ulcerative colitis in the ascending colon it was judged that the proposed indications were too broad. The applicant was advised to amend the indications to: “Treatment of active, mild ulcerative colitis of the sigmoid colon and rectum.”

DOSE & DOSE SCHEDULE

The proposed dose schedule is for 2 puffs (equivalent to 2g) once a day at bedtime.

The majority of trials with 5-ASA enemas used doses of 1-4g/day. While some studies showed a dose-dependent response, the dose effect was not demonstrated in others. Of the three studies with Salofalk foam described below, two used 2g/day (as 2 puffs at night) and one used 2g twice a day.

Given the results of the trials and the clinical experience of use with mesalazine, the proposed dosage regimen seems appropriate.

The wording of the dose and dose schedule for children states:
“Salofalk rectal foam should not be used in children below 12 years of age because of insufficient experience with the rectal foam in this age group”.
This is satisfactory.

TOXICOLOGY

See above.

CLINICAL PHARMACOLOGY

Despite the length of time that the product has been available there remains some controversy over its mode of action. The low plasma concentration and the efficacy of locally applied preparations would appear to confirm its topical mechanism of action.

The inflammation associated with ulcerative colitis is triggered and maintained by a number of inflammatory mediators. Various mediators, such as prostaglandins, thromboxanes, leukotrienes, platelet activating factor (PAF), cytokines and oxygen

radicals have been found in increased concentrations in patients. Although 5-ASA would appear to affect the action of some, if not all, of these mediators the precise mechanism is unclear. Its relatively well understood inhibition of prostaglandin synthesis would appear to be a minor influence on its therapeutic effect.

The clinical expert report, with its accompanying references, discusses possible modes of action including its effect as (amongst others): a scavenger of free radicals, an inhibitor of leukotriene production, its inhibition of PAF secretion, its inhibition of interleukin-1 synthesis, its effect on the aggregation of tumour necrosis factor, its inhibition of neutrophil chemotaxis, its inhibition of nitric oxide, its inhibition of immunoglobulin from mononuclear leucocytes and its suppression of histamine release.

PHARMACOKINETICS

5-ASA's therapeutic efficacy is not related to its systemic availability. However, some of the adverse effects appear to be related to the plasma concentration and therefore the pharmacokinetic profile is still of significance.

With the increase in the availability of modified delivery preparations, scintigraphic techniques have been developed to assess the progress of radio-labelled samples within the bowel.

Orally administered doses of 5-aminosalicylic acid are well absorbed. However, it appears that the absorption of 5-ASA decreases from proximal to distal sites in the intestine and that absorption from the colon is relatively low. This is confirmed by data from 5 clinical studies that demonstrate that, when administered as an enema, 5-ASA is poorly absorbed. In patients with ulcerative colitis the recovery rates in urine are significantly lower following administration by enema than in healthy volunteers. Furthermore, there is greater absorption with a neutral pH of the formulation compared to an acidic pH and that absorption increases with increasing volumes of formulation administered.

Study SAF-2/BIO

Open, single dose, two way cross-over scintigraphic study on the spread of samarium (¹⁵³Sm) labelled mesalazine foam (2g mesalazine in 60ml foam) in the colon versus mesalazine enema (2g mesalazine in 60ml suspension) in healthy volunteers and patients with ulcerative colitis (unpublished).

The six male healthy volunteers had an average age of 36 years (range 28-46 years). The six patients with ulcerative colitis had an average age of 41 years (range 29-74 years). They had an average Clinical Activity Index of 5.2 (range 4-7) and an average Endoscopy Index of 6.5 (range 5-8).

Several protocol violations, although well documented, add to the difficulty in interpreting the results.

From the information presented it is not possible to confirm that an effective randomisation scheme was in place.

The washout period proposed was seven days which, given the short half-life of the active component, would have been sufficient. For reasons not fully explained, for three subjects the washout period was only 4 days.

For the assessment of the distribution within the intestine, scintigraphic scans were performed at 5mins, 0.5hr, 1hr, 2hr, 4hr, 6hr and 12hr. The abdomen was divided into 5 regions: ascending colon, transverse colon, descending colon, sigmoid colon and rectum. A percentage of the originally administered radioactivity in each region was calculated at each time.

Results

Given the changes in the protocol, the exclusions due to protocol violations, the problems with retention experienced by some subjects and the small number of subjects recruited, meaningful interpretation of the data is difficult.

However, it can be noted that in healthy volunteers, no radioactivity was detected in the proximal colon (ascending and transverse). In patients and healthy volunteers the retrograde spread of both the foam and the enema preparation was essentially similar. Both formulations fully covered the rectum and sigma. In 3 of 6 patients both preparations reached also the descending colon, although only in a relatively small percentage.

Conclusions

The results from the healthy volunteers are of limited value. The results from the small number of patients investigated suggest that the systemic bioavailability of rectally administered mesalazine foam is limited and not meaningfully different from the enemas for which a low absorption rate is known.

Summary of other data on the pharmacokinetics of mesalazine

5-ASA diffuses widely through the body tissues and fluids, although diffusion into the CSF only occurs if the meninges are inflamed. Approximately 43% of 5-ASA is bound to plasma proteins.

The main metabolite of 5-aminosalicylic acid is N-acetyl-5-aminosalicylic acid. Acetylation occurs mainly in the intestinal mucosa but also in the liver. The acetylation rate does not appear to be affected by the different acetylation phenotypes.

Because of the low absorption rates after rectal administration, the main elimination route is via the faeces. Absorbed 5-ASA and N-Ac-5-ASA are eliminated mainly in the urine. It is stated that there are no published studies on the pharmacokinetics of 5-ASA in the elderly.

EFFICACY

The efficacy of rectally administered 5-aminosalicylic acid is well established. Rectal administration has become a popular approach for patients with distal ulcerative colitis as it is a very effective means of delivering adequate quantities of a locally acting substance to the inflamed areas.

Rectally administered 5-ASA has been studied in placebo-controlled trials, and in trials comparing it to active alternatives. In patients with mild to moderate distal ulcerative colitis doses of 1-4g/day have been demonstrated to be significantly more effective than placebo. In a meta-analysis by Marshall and Irvine (1995), five studies were identified where 5-ASA had been compared to placebo. The proportion of patients who improved symptomatically with rectal 5-ASA ranged from 60-94% compared to 14-42% in the placebo groups (Odds Ratio for symptomatic improvement: 7.36; 95% C.I. 4.7-11.5). The equivalent rates for symptomatic remission were 31-80% with 5-ASA compared with 7-11% receiving placebo. These results were supported by endoscopic and histological investigations carried out in 4 of the 5 studies.

A further meta-analysis by the same authors (1997) reviewed studies which compared a number of active treatments in patients with distal ulcerative colitis. The combined results of seven studies showed that rectal 5-ASA (enema and suppositories) was significantly better than rectal corticosteroids for inducing remission of symptoms, as well as endoscopic and histological signs of ulcerative colitis. Pooled Odds Ratios were 2.42 (95% C.I. 1.72-3.41), 1.89 (1.29-2.76) and 2.03 (1.28-3.20) respectively.

As the current application is for a new formulation, three new studies have been presented. These investigated the therapeutic efficacy and tolerability of the applicant's product.

Study SAF-4/UCA

Double blind, randomised, comparative study of the efficacy and tolerability of Salofalk[®] foam (2 x 1g) vs. Salofalk[®] placebo foam in patients with mild to moderately active proctitis, proctosigmoiditis and left-sided ulcerative colitis.

This was a double blind, placebo-controlled, randomised study comparing the efficacy and tolerability of two puffs of 1g administrations of Salofalk[®] foam (2 x 1g) with "Salofalk[®] placebo" in patients with mildly to moderately active proctitis, proctosigmoiditis and left-sided ulcerative colitis (Clinical Activity Index >4, Endoscopic Index \geq 4).

The primary efficacy endpoint was the induction of clinical remission at the end of the study, defined by a CAI score of \leq 4 and associated with at least a 2-point decrease. Secondary efficacy endpoints were intermediary evaluations at day 14 and 28, an

evaluation of efficacy on day 42 by calculation of the Endoscopic Index and Histological Index, global assessment of efficacy by the patient and the investigator on days 14, 28 and 42 and patient preference on day 42.

Conclusion

This trial suggests that Salofalk foam is an effective treatment for mild ulcerative colitis. The foam formulation was generally well tolerated and did not appear to be related to any formulation specific adverse events. Due to the small number of patients in the moderate ulcerative colitis and left-sided ulcerative colitis subgroups this study cannot be used to support the use of Salofalk foam in these subgroups.

Study SAF-3/UCA

Multicentre, open, randomised, cross-over, comparative study of the acceptability, efficacy and tolerability of mesalazine foam (2g/60ml, twice a day) vs. mesalazine enema (2g/60ml, twice a day) in patients with proctitis, proctosigmoiditis and left-sided ulcerative colitis.

This was designed as a multicentre, open, randomised, cross-over study comparing the acceptability, efficacy and tolerability of mesalazine foam (2g/60ml, twice a day) vs. mesalazine enema (2g/60ml, twice a day) in patients with proctitis, procto-sigmoiditis and left-sided ulcerative colitis.

Acceptability was measured with patient preference and Quality of Life scores; safety was assessed through adverse event reporting and laboratory investigations; efficacy was assessed using the Clinical Activity Index and the Endoscopic Index, with remission defined as a CAI < 4 and an EI < 6.

The primary objective was to compare the acceptability of mesalazine foam and mesalazine enema. Secondary objectives were to evaluate the clinical efficacy of mesalazine foam and mesalazine enema in this patient group and to record the tolerability of the two preparations.

Study conclusion

The poor study design and the change of the primary endpoint hinders the interpretation of the study. Therefore this study cannot be considered as a pivotal study to convincingly demonstrate efficacy.

Based simply on remission rates this study did demonstrate some efficacy of Salofalk foam. As this clinical study was not adequately powered for the demonstration of non-inferiority, equivalence of Salofalk foam and Salofalk enema could not be shown. In fact, for the primary endpoint of Quality of Life the evidence suggests that Salofalk foam was significantly worse than Salofalk enema, while the secondary endpoint of remission was only numerically inferior. The majority of patients in this study had mild ulcerative colitis. Due to the small number of patients with moderate ulcerative colitis it is not possible to comment on the efficacy, safety and acceptability of Salofalk foam in this group.

While being associated with some minor local reactions in some patients, the mesalazine foam was generally well tolerated.

Study SAF-6/UCA

Single-blind (investigator blinded), randomised, multicentre, comparative, phase III clinical trial. The study was conducted with two arms in the form of a parallel-group comparison comparing two different rectal mesalazine foam formulations: 5-ASA foam 1 g/30 ml (Salofalk[®] foam; 2 g 5-ASA/day) and 5-ASA foam 1 g/60 ml (Claversal[®] rectal foam; 2 g 5-ASA/day).

Patients with mild to moderate active ulcerative proctitis or proctosigmoiditis (max 40 cm *ab ano*, confirmed by endoscopy, histology, and negative stool culture, disease activity at baseline: Clinical Activity Index (CAI) > 4, Endoscopic Index (EI) ≥ 4) were included. They received 60 ml (Salofalk) or 120 ml (Claversal) foam (2 g 5-ASA) rectally o.d. in the evening.

The primary efficacy endpoint was clinical remission, defined as a CAI ≤ 4, at the final / withdrawal examination.

Secondary efficacy endpoints were CAI in the course of the study, clinical improvement (CAI), number of stools in the course of the study, number of bloody stools in the course of the study, patient's acceptance and preference of the study drugs, time to first clinical remission, Disease Activity Index (DAI), Endoscopic Index (EI), Histological Index (HI), Physician's Global Assessment (PGA), and quality of life (QoL).

The primary population for efficacy analysis was the PP population.

Study conclusion

Based on clinical remission defined as a CAI ≤ 4, Salofalk foam proved to be non-inferior compared to Claversal foam for the treatment of ulcerative proctitis or proctosigmoiditis (p = 0.00153 [PP analysis set]; p = 0.00004 [ITT analysis set]).

Both rectal treatments were highly efficacious, inducing clinical, endoscopical, and histological remission in about 70%, 60%, and 50% of the patients, respectively, and led to clinically meaningful improvement in patient's QoL. Overall, no difference between patients treated with Salofalk or Claversal could be observed. In addition, both foams were preferred by the patients as compared to former use of enema. However, Salofalk foam was associated with less severe discomfort, pain, and retention problems as compared to Claversal foam.

SAFETY

The low systemic absorption of rectally administered 5-ASA contributes to the fact that it is generally well tolerated with a low incidence of side effects. Also in the newly submitted clinical study SAF-6/UCA no relevant difference in safety and tolerability in comparison with Claversal foam could be observed. The clinical expert report summarises the main safety concerns that have been raised over the years of clinical experience. These are covered in the proposed SPC.

In the studies described above, there were 18 local adverse reactions with the use of the foam formulation. They are adequately reflected in the updated SPC in Section 4.8, “General disorders and administration site conditions”.

EXPERT REPORTS

The updated clinical expert report is well referenced.

PATIENT INFORMATION LEAFLET (PIL)

The PIL was generally well written and clear. An adequate User Testing according to European Guidelines was provided and passed a readability index of 92%. Following some revisions the PIL was considered to be acceptable.

LABELLING

Following revisions the labelling was considered to be acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS

Following revisions the SPC was considered to be acceptable.

APPLICATION FORM (MAA)

This is acceptable from a medical perspective.

POSTMARKETING EXPERIENCE

In conclusion:

Salofalk foam is safe and well tolerated. The safety profile of the 5-ASA foam enemas is comparable to that of 5-ASA (Salofalk) liquid enemas and 5-ASA rectal foam (Claversal). The available safety data generated in controlled clinical studies and the most recent PSUR confirm the known favourable safety profile of all Salofalk formulations. No Salofalk formulation-specific type of adverse drug reaction was noted. No cases of 5-ASA intoxication have been reported to date. The clinical use of Salofalk (liquid and foam) enemas in the therapy of acute exacerbation of distal UC, in conjunction with the reports of side effects during controlled clinical trials, show that the rectal preparations are, in general, extremely well tolerated.

MEDICAL CONCLUSION

Marketing authorisation may be granted for this product.

DISCUSSION

This is an application for a new formulation of mesalazine foam for the treatment of ulcerative colitis. The application is supported by four studies.

The first (SAF-2/BIO) was a scintigraphic and pharmacokinetic study.

The product covers the rectum and sigmoid colon, and reaches in 3 of 6 patients also the left splenic flexure. The retrograde spread is comparable to that of the 60 ml enema.

In the second study (SAF-4/UCA), the applicant demonstrated that the mesalazine foam is more efficacious than placebo for the treatment of mild ulcerative colitis. The paucity of patients with moderate attacks or left-sided disease precludes conclusions relating to the product's efficacy in moderate disease or in disease of the descending colon. The preparation appeared to be well tolerated.

The third study (SAF-3/UCA) was poorly designed and contained an important change of primary endpoint. Despite the inadequate design, the study did demonstrate some efficacy of Salofalk foam. However, the study also showed that Salofalk foam is less acceptable to patients and produces numerically lower remission rates than Salofalk enema. Equivalence of Salofalk foam to Salofalk enema could not be demonstrated, as no appropriate non-inferiority design was used. Due to the small numbers of patients with moderate disease and disease of the descending colon no conclusions regarding the efficacy of mesalazine foam in these sub-groups can be drawn.

In the fourth study (SAF-6/UCA) the applicant demonstrated that Salofalk foam is non-inferior to a recently registered mesalazine containing foam (Claversal) for the treatment of mild to moderate ulcerative colitis. Moreover Salofalk foam was associated with less severe discomfort, pain, and retention problems as compared to Claversal foam.

CONCLUSIONS

Salofalk foam has been shown to be more efficacious than placebo in patients with mild ulcerative colitis affecting the rectum and the sigmoid colon. Furthermore Salofalk foam is therapeutically equivalent to a high volume mesalazine containing foam. Despite the reporting of a small number of local adverse events, the formulation appears to be generally well tolerated.

The clinical evidence of the original application based on the studies SAF-3/UCA and SAF-4/UCA was not sufficient to recommend the granting of a licence for prophylaxis of the disease, for moderate disease or for disease of the descending colon. It is recommended that a licence be granted only for treatment of active, mild ulcerative colitis of the sigmoid colon and rectum.

Medical Assessor
March 2006