



Public Assessment Report

Decentralised Procedure

Salofalk 1g Suppositories

PL 08637/0018

UK/H/1746/01/DC

Dr. Falk Pharma GmbH

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Dr. Falk Pharma GmbH a Marketing Authorisation (licence) for the medicinal product Salofalk 1g Suppositories (product licence number: PL 08637/0018). This medicine is available on prescription only.

Salofalk 1g Suppositories are used to treat mild to moderate acute episodes of an inflammatory disease affecting the rectum (back passage) known by doctors as ulcerative colitis or ulcerative proctitis.

The data submitted in support of this application for Salofalk 1g Suppositories raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about decentralised procedure

Name of the product in the Reference Member State	Salofalk 1g Suppositories
Type of application (Eudratrack details)	Level 1 Abridged Level 2 Initial Level 3 8(3) Level 4 Chemical substance Level 5 Prescription only
Name of the active substance (INN)	Mesalazine
Pharmacotherapeutic classification (ATC code)	Aminosalicylic acid and similar agents (A07EC02)
Pharmaceutical form and strength	1g, suppositories
Reference numbers for the decentralised Procedure	UK/H/1746/01/DC
Reference Member State	United Kingdom
Member States concerned	AT, BE, BG, CY, CZ, DE, DK, EL, ES, FI, HU, IE, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI, and SK
Date of start of the procedure	28 July 2008
End date of decentralised procedure	22 April 2010
Marketing Authorisation Number	PL 08637/0018
Name and address of the authorisation holder	Dr. Falk Pharma GmbH Leinenweberstr. 5 79108 Freiburg Germany

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Salofalk 1g Suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 1 g mesalazine.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Suppositories

Appearance: light beige coloured, torpedo-shaped suppositories

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute mild to moderate ulcerative colitis that is limited to the rectum (ulcerative proctitis).

4.2 Posology and method of administration

Adults and elderly:

One Salofalk 1g Suppository once daily (equivalent to 1g mesalazine daily) inserted into the rectum.

Children

There is little experience and only limited documentation for an effect in children.

General instructions for use:

Salofalk 1g Suppositories should be administered preferably at bedtime.

Treatment with Salofalk 1g Suppositories must be administered regularly and consistently, because only in this way can healing be successfully achieved.

The duration of use is determined by the physician.

4.3 Contraindications

Salofalk 1g Suppositories are contraindicated in patients with:

- known hypersensitivity to salicylates or the excipient
- severe impairment of hepatic or renal function

4.4 Special warnings and precautions for use

Blood tests (differential blood count; liver function tests such as ALT or AST; serum creatinine) and dip-stick urinalysis should be determined prior to and during treatment, at the discretion of the treating physician. As a guideline, further testing is recommended 14 days after commencement of treatment, then a further two to three times at intervals of 4 weeks.

If the findings are normal, further testing should be carried out every 3 months. If additional symptoms occur, tests should be performed immediately.

Caution is recommended in patients with impaired hepatic function.

Salofalk 1g Suppositories are 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 1g Suppositories.

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 1g Suppositories. Should Salofalk 1g Suppositories cause acute intolerance reactions such as cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

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 1g Suppositories 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 gastrointestinal 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 |
| - Spironolactone/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 1g Suppositories in pregnant women. However, data on a limited number of exposed pregnancies indicate no adverse effect of mesalazine on pregnancy or on the health of the fetus/newborn child. To date no other relevant epidemiologic data are available. In one single case after long-term use of a high dose mesalazine (2-4 g, orally) during pregnancy, renal failure in a neonate was reported.

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 1g Suppositories should only be used during pregnancy if the potential benefit outweighs the possible risk.

N-acetyl-5-aminosalicylic acid and to a lesser degree mesalazine are excreted in breast milk. Only limited experience during lactation in women is available to date. Hypersensitivity reactions like diarrhea can not be excluded. Therefore, Salofalk 1g Suppositories should only be used during breast-feeding if the potential benefit outweighs the possible risk. If the suckling neonate develops diarrhea, the 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

In clinical studies involving 248 participants, approximately 3% experienced adverse reactions while receiving Salofalk 1g Suppositories. The most commonly reported ADRs were headache, in approximately 0.8%, and gastrointestinal side effects (constipation in approximately 0.8%; nausea, vomiting and abdominal pain in 0.4% each).

The following side effects have been reported with the use of mesalazine:

<i>System organ class</i>	<i>frequency due to MedDRA convention</i>	
	<i>rare</i> ($\geq 1/10,000$; $< 1/1,000$)	<i>very rare</i> ($< 1/10,000$)
Blood and lymphatic system disorders		Altered blood counts (aplastic anaemia, agranulocytosis,

		pancytopenia, neutropenia, leukopenia, thrombocytopenia)
Nervous system disorders	Headache, dizziness	peripheral neuropathy
Gastrointestinal disorders	Abdominal pain, diarrhoea, flatulence, nausea, vomiting, constipation	
Renal and urinary disorders		Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency
Skin and subcutaneous tissue disorders		Alopecia
Musculoskeletal and connective tissue disorders		Myalgia, arthralgia
Immune system disorders		Hypersensitivity reactions such as allergic exanthema, drug fever, bronchospasm, peri- and myocarditis, acute pancreatitis, allergic alveolitis, lupus erythematosus syndrome, pancolitis
Hepatobiliary disorders		Changes in hepatic function parameters (increase in transaminases and parameters of cholestasis), hepatitis, cholestatic hepatitis
Reproductive system disorders		Oligospermia (reversible)

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
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 (5-Aminosalicylic acid / 5-ASA) may also function as a radical scavenger of reactive oxygen compounds. On reaching the intestinal lumen, rectally administered mesalazine has largely local effects on the intestinal mucosa and submucosal tissue.

Clinical efficacy and safety of Salofalk[®] 1 g suppositories was evaluated in a multicentre phase III study, which included 403 patients with endoscopically and histologically confirmed mild to moderately active ulcerative proctitis. The mean disease activity index (DAI) at base line was 6.2 ± 1.5 (range: 3 – 10). Patients were randomised to treatment with one Salofalk[®] 1 g suppository (1 g OD group) or 3 suppositories containing 0.5 g mesalazine (0.5 g TID group per day for 6 weeks. The primary efficacy variable was clinical remission defined as DAI < 4 at the final visit or withdrawal. At the final per protocol analysis, 87.9% of the patients in the 1 g OD group and 90.7% of the 0.5 g TID group were in clinical remission (Intention-to-treat analysis: 1 g OD group: 84.0%; 0.5 g TID group: 84.7%). The mean change in DAI from baseline was -4.7 in both treatment groups. No drug-related serious AEs occurred.

5.2 Pharmacokinetic properties

General considerations of mesalazine:

Absorption:

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

Biotransformation:

Mesalazine is metabolised both pre-systemically by the intestinal mucosa and in 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 %, dependent 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 1g suppositories specific:

Distribution:

Scintigraphic studies with a similar medicinal product, technetium-labelled mesalazine 500mg suppositories showed peak spread of the suppository that had melted due to body temperature after 2 – 3 hours. The spread was limited primarily to the rectum and rectosigmoid junction. It is assumed that Salofalk 1g suppositories act very similar and thus are particularly suitable for treating proctitis (ulcerative colitis of the rectum).

Absorption:

In healthy subjects mean peak plasma concentrations of 5-ASA after a single rectal dose of 1g mesalazine (Salofalk 1 g Suppository) were 192 ± 125 ng/ml (range 19 – 557 ng/ml), those of the main metabolite N-Ac-5-ASA were 402 ± 211 ng/ml (range 57 – 1070 ng/ml). Time to reach the peak plasma concentration of 5-ASA was 7.1 ± 4.9 h (range 0.3 – 24 h).

Elimination:

In healthy subjects, after a single rectal dose of 1g mesalazine (Salofalk 1g Suppository) approx. 14 % of the administered 5-ASA dose were recovered in the urine during 48 hours.

5.3 Preclinical safety data

With the exception of a local tolerance study in dogs, which demonstrated good rectal tolerance, no preclinical studies have been performed with Salofalk 1g Suppositories.

Preclinical data on mesalazine 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

Hard fat

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original container in order to protect contents from light.

Do not store above 25°C.

6.5 Nature and contents of container

Container (strip): PVC/polyethylene film

Package sizes: 10, 12, 15, 20, 30, 60, 90

Not all package sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Germany

Tel: +49 (0)761 1514-0

8 MARKETING AUTHORISATION NUMBER(S)

PL 08637/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/05/2010

10 DATE OF REVISION OF THE TEXT

17/05/2010

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Salofalk® 1g Suppositories

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® 1g Suppositories are and what they are used for
2. Before you use Salofalk® 1g Suppositories
3. How to use Salofalk® 1g Suppositories
4. Possible side effects
5. How to store Salofalk® 1g Suppositories
6. Further information

1. WHAT SALOFALK® 1g SUPPOSITORIES ARE AND WHAT THEY ARE USED FOR

Salofalk® 1g Suppositories contain the active substance mesalazine, an anti-inflammatory agent used to treat inflammatory bowel disease.

Salofalk® 1g Suppositories are used for:

- the treatment of mild to moderate acute episodes of an inflammatory disease limited to the rectum (back passage) known by doctors as ulcerative colitis or ulcerative proctitis.

2. BEFORE YOU USE SALOFALK® 1g SUPPOSITORIES

Do not use Salofalk® 1g Suppositories:

- If you are or have been told you are allergic (hypersensitive) to salicylic acid, to salicylates such as Aspirin® or to the other ingredient of Salofalk® 1g Suppositories (it is listed in section 6, Further information).
- If you have a serious liver and/or kidney disease.

Take special care with Salofalk® 1g Suppositories.

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, and you may need to 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 medicines, such as prednisolone)
- **Sulphonyl ureas** (medicines used to control your blood sugar, such as glibenclamide)
- **Methotrexate** (a medicine used to treat leukaemia or immune disorders)
- **Probenecid/sulphinpyrazone** (medicines used to treat gout)
- **Spironolactone/frusemide** (medicines used to treat heart problems)
- **Rifampicin** (an antibiotic used against tuberculosis)
- **Azathioprine or 6-mercaptopurine** (medicines 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® 1g Suppositories 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® 1g Suppositories during pregnancy if your doctor tells you to.

You should also only use Salofalk® 1g Suppositories during breast-feeding if your doctor tells you to, as this medicine 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® 1g Suppositories

The other ingredient in Salofalk® 1g Suppositories is not likely to cause side effects (see 6. FURTHER INFORMATION).

3. HOW TO USE SALOFALK® 1g SUPPOSITORIES

Always take Salofalk® 1g Suppositories 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. Do NOT take by mouth.

Dosage:

Adults and elderly

The usual dose is one Salofalk® 1g suppository once a day, at bedtime.

Children

There is little experience and only limited documentation for an effect in children.

Duration of treatment

Your doctor will decide how long you need to continue the treatment with this medicine. This will depend on your condition.

To obtain the maximum benefit from this medicine, you should use Salofalk® 1g Suppositories regularly and consistently, as directed.

If you think your Salofalk® 1g Suppositories are too strong or too weak, talk to your doctor.

If you use more Salofalk® 1g Suppositories 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® 1g Suppositories on one occasion, just take your next dose as prescribed. Do not use a smaller amount.

If you forget to use Salofalk® 1g Suppositories

Do not take a larger than normal dose of Salofalk® 1g Suppositories next time, but continue treatment at the prescribed dosage.

If you stop using Salofalk® 1g Suppositories

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® 1g Suppositories 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**

If you experience a marked reduction of your general health, especially if accompanied by fever, and/or a sore throat and mouth, stop using these suppositories and contact your doctor immediately. These symptoms can, very rarely, be due to a fall in the number of white cells in your blood (a condition called agranulocytosis), which may make you more prone to developing a serious infection. A blood test can confirm whether your symptoms are due to an effect of this medicine on your blood.

The following side effects have also been reported by patients using mesalazine:

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

- Abdominal pain, diarrhoea, wind (flatulence), nausea and vomiting, constipation
- 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
- 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 an allergic reaction to this medicine within the bowel
- Skin rash or inflammation
- Muscle and joint pain
- Jaundice or abdominal pain
- Hair loss and the development of baldness
- Numbness and tingling in the hands and feet (peripheral neuropathy)
- Reversible decrease in semen production

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® 1g SUPPOSITORIES

Keep out of the reach and sight of children.

Do not use Salofalk® 1g Suppositories after the expiry date which is stated on the strip for the Suppositories and on the carton. The expiry date refers to the last day of that month.

Do not store above 25 °C.

Store in the original container in order to protect contents from light.

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® 1g Suppositories contain

The active substance in Salofalk® 1g Suppositories is mesalazine, and one suppository of Salofalk® 1g Suppositories contains 1 g mesalazine.

The other ingredient is

hard fat.

What Salofalk® 1g Suppositories look like and contents of the pack

Salofalk® 1g Suppositories are light beige coloured, torpedo-shaped suppositories.

Salofalk® 1g Suppositories are available in packs of 10, 12, 15, 20, 30, 60, 90 suppositories.

Not all package sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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This medicinal product is authorised in the Member States of the EEA under the following names:

Austria, Bulgaria, Czech Republic, Cyprus, Finland, Germany, Great Britain, Greece, Hungary, Ireland, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovak Republic, Sweden and Spain: Salofalk®.

Belgium und Luxembourg: Colitofalk®.

Denmark and Lithuania: Colitosal®.

This leaflet was last approved in July 2010.

PL 08637/0018

PA 0573/4/4

Mock-up

GB-IE/06.10

Module 4

Labelling

Salofalk® 1g Suppositories
Mesalazine
Dr. Falk Pharma GmbH

Salofalk® 1g Suppositories
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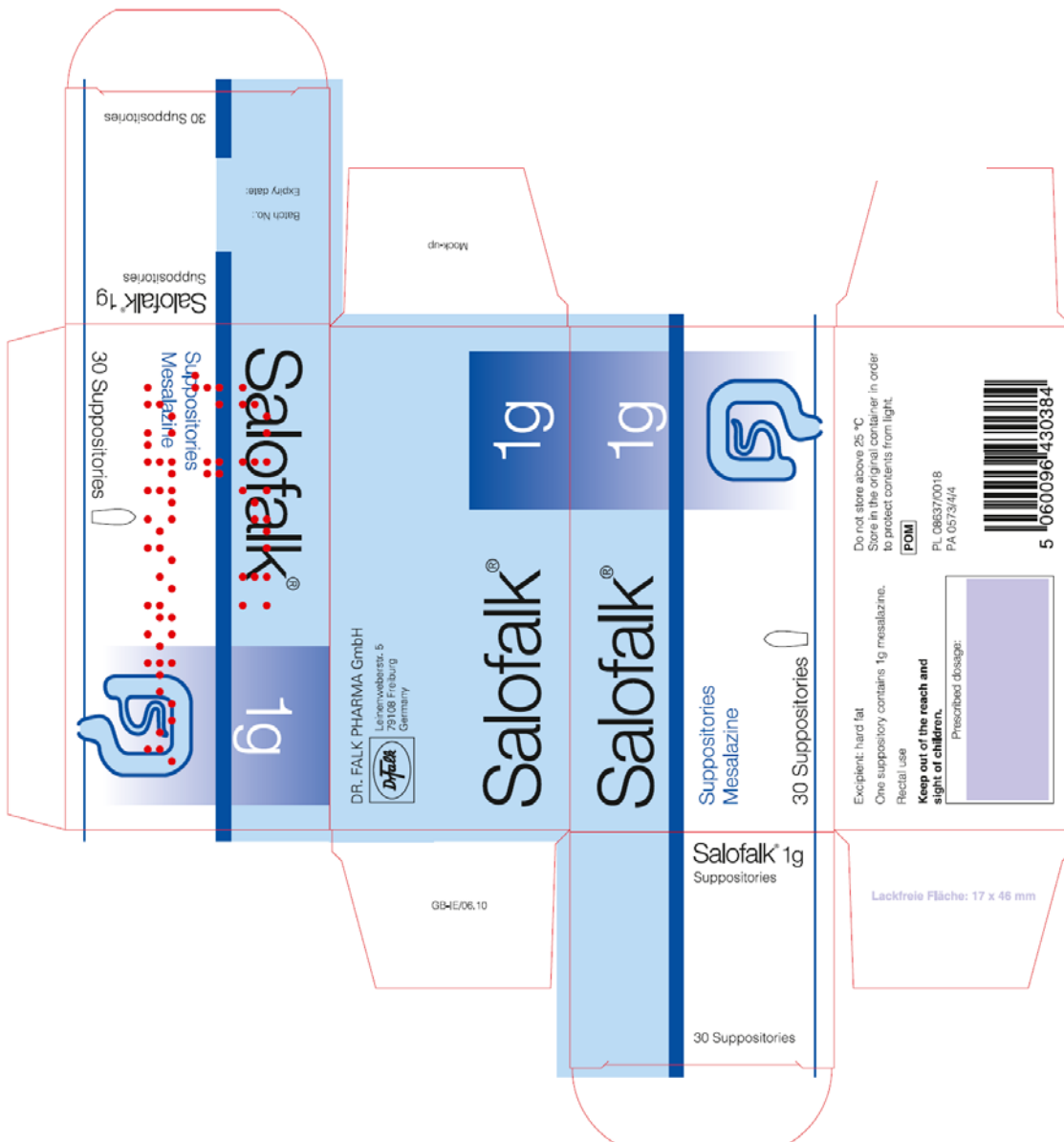
Salofalk® 1g Suppositories
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Salofalk® 1g Suppositories
Mesalazine
Dr. Falk Pharma GmbH



Module 5

Scientific discussion during initial procedure

I RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Salofalk 1g Suppositories, in the treatment of acute mild to moderate ulcerative colitis that is limited to the rectum (ulcerative proctitis), is approvable.

II EXECUTIVE SUMMARY

Problem statement

Salofalk 1g Suppository is a new product strength designed to be administered once daily in the treatment of the inflammatory bowel condition, acute ulcerative proctitis.

With UK as the Reference Member State (RMS) in this Decentralised Procedure, Dr. Falk Pharma is applying for the Marketing Authorisations for Salofalk 1g suppositories in the following as Concerned Member States (CMS): AT, BE, BG, CY, CZ, DE, DK, EL, ES, FI, HU, IE, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI and SK.

About the product

Salofalk 1g suppositories contain the active ingredient mesalazine which has been used for many years in the treatment of ulcerative colitis. Being a topically acting agent, it exerts its therapeutic effect on the inflamed mucosa (epithelial cells and macrophages in the lamina propria) from the luminal side of the bowel. Hence, mucosal, rather than systemic, drug levels relate to the therapeutic action of mesalazine (though systemic absorption may be of relevance in terms of safety profile).

General comments on the submitted dossier

This application is made under Article 8(3) of the Directive 2001/83/EC and a full dossier has been submitted. The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory framework.

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

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

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or

‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

Statements have been provided confirming that the submitted studies were conducted according to the principles of GCP and conformed with the requirements of the Declaration of Helsinki.

III SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance

The chemical-pharmaceutical documentation and Expert Report in relation to Salofalk 1g suppositories are of sufficient quality in view of the present European regulatory requirements. The active substance, mesalazine, is the subject of a monograph in the European Pharmacopoeia. The drug substance specification for the drug substance is acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed and the results support the proposed re-test period.

Drug Product

The development of the product has been described, the choice of the excipient is justified and its functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis results show that the finished product meets the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The stability data support the proposed shelf-life of 3 years when the storage precautions “Store in the original container in order to protect contents from light” and “Do not store above 25°C” are applied.

Non clinical aspects

The pharmacological, pharmacokinetic and toxicological properties of mesalazine are well known. As mesalazine is a well known active substance an overview based on a literature review, original non-clinical studies and a local tolerance study is appropriate to support this application. Salofalk 1g Suppositories were not considered to be irritant in a 4 week study.

The non-clinical overview has been written by a toxicologist with suitable experience. It is dated June 2008. The overview cites 66 references from the published literature which are dated from 1972 to 2007. The non-clinical overview is adequate.

There are no objections to approval of Salofalk 1g Suppositories from a non-clinical point of view.

Clinical aspects

The applicant conducted two clinical studies to support this application:

- A three-way bioequivalence study comparing Salofalk 1g Suppositories with two Salofalk 0.5 g suppositories and one Pentasa 1 g suppository.

Mesalazine is an agent which acts locally from within the bowel lumen, hence, any systemic absorption is unwanted and irrelevant to therapeutic activity, though possibly of relevance in terms of safety profile. Bioequivalence was not shown between the proposed Salofalk 1g Suppositories and the reference products (the licensed products Salofalk 2 x 500mg suppositories and Pentasa 1g suppository), however, given the small and highly variable absorption from the rectal route, these findings are not surprising and the efficacy and safety study (see below) demonstrates the therapeutic efficacy of Salofalk 1g Suppositories.

This relative bioavailability study does, however, provide useful information and reassurance about the likely safety of the proposed product. Peak levels are equivalent to those seen with Pentasa and less than levels following two 500mg Salofalk suppositories. It should be borne in mind that the 500mg suppositories would normally be provided as single doses thrice daily, rather than two together, therefore, the comparison with Salofalk 500mg is not strictly applicable to the clinical situation. Nevertheless, the Salofalk 1g suppository was well tolerated in this study and the C_{max} achieved is known to be substantially less than following oral therapy, presumably because the distal bowel to which it is applied is a non-absorptive surface. Therefore, this study has raised no safety concerns for this product.

- A pivotal efficacy and safety study comparing the 1g suppository once daily vs. 0.5g suppositories administered three times daily in patients with acute ulcerative proctitis.

From an efficacy perspective, mesalazine is a topical agent which acts on the mucosa from the luminal side of the gut, therefore, mucosal rather than systemic drug levels relate to the therapeutic action of this active. However, as there are currently no validated methods for quantifying mucosal concentrations, it was necessary to establish clinical efficacy.

To prove the therapeutic equivalence of Salofalk 1g Suppositories OD vs. Salofalk 0.5 g suppositories TID in patients with active acute ulcerative proctitis the following study was performed:

Type of study	Design	Objectives of the Study	Test Products, Dosage Regimen, Route of Administration, and Duration of Treatment	Number of Subjects Treated, Demographics
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Efficacy and safety	Single (investigator) blind, multicentre, randomised, active-control, comparative, phase III study.	To prove therapeutic equivalence of mesalazine 1 g sup OD vs mesalazine 0.5 g sup TID in patients with active ulcerative proctitis.	Salofalk 1 g sup OD; Salofalk 0.5 g sup TID Rectal administration. Duration:6 weeks.	403 patients (SP); 1 g group: 200; 0.5 g group: 203. M: 178; F: 225; mean age: 42 y; age range: 18–74 y.
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OD = once daily; sup = suppository; TID = three times daily

In the six week study in patients with mild to moderately active ulcerative proctitis, once daily administration of the proposed Salofalk 1g Suppositories was shown to be non-inferior (and can be considered therapeutically equivalent) to three times daily administration of the currently licensed Salofalk 0.5 g suppository in terms of induction of remission. As well as non-inferiority demonstrated by a DAI $1 < 4$, this was also shown using another definition of remission in accordance with the guideline on the development of new medicinal products for the treatment of ulcerative colitis i.e. DAI $1 < 4$ and stool frequency = 0 and rectal bleeding = 0, which satisfies the latest recommendations (CHMP/EWP/18463/2006).

Both treatment regimens were associated with high remission rates but the majority of patients indicated a preference for a once daily suppository in contrast to having to take more than one a day.

The Clinical Experts have provided a thorough review of the known safety profile of the active, mesalazine, based on data from the various formulations available. It is recognised that, relative to sulfasalazine, mesalazine is better tolerated (many investigators have attributed ADRs to the sulfapyridine component of the former).

Phase I data have shown that the systemic absorption of mesalazine and its metabolite from Salofalk 1g Suppositories OD is considerably less than would be expected from the oral route (based on the published data of Dilger et al. 2007). Furthermore, the systemic absorption from Salofalk 1g Suppositories is not a concern as the pharmacokinetic study has shown that peak plasma concentrations of mesalazine and Ac-5-ASA were less than with Salofalk 2x 0.5g or Pentasa 1g and AUC_{0-24h} and AUC_{0-∞} values fell between the values for the comparators.

Salofalk 1g Suppositories appear to have a comparable safety and tolerability profile to that of the licensed 0.5g product and no major new safety signals have arisen. In conclusion, there are no safety concerns in relation to the proposed Salofalk 1g Suppositories and although there are no long-term data this is considered acceptable given the comparability in terms of efficacy and short-term safety profile to that of the established product; a comparable long-term safety profile can also therefore be expected.

In addition to the above studies, the Clinical Expert provided a satisfactory review of the known pharmacokinetic and clinical properties of mesalazine.

Pharmacovigilance system

The RMS considers that the pharmacovigilance system fulfils the requirements. The Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community, or in a third country.

Risk Management Plan

No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary as the active substance is well known.

Assessment of User Testing

All product literature (SPC, PIL and labelling) is satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

IV BENEFIT RISK ASSESSMENT

The benefit-risk ratio is considered favourable. A Marketing Authorisation should be granted.