*Public Assessment Report*

**SALOFALK**

## INFORMASI PRODUK

| | | |
|---|---|---|
| Nama obat | : | SALOFALK |
| Bentuk sediaan | : | Suppositoria |
| Zat aktif | : | Mesalazine 500 mg |
| Kemasan | : | Dus, 6 strip @ 5 suppositoria |
| Pendaftar | : | PT. Darya Varia Laboratoria, Tbk., Bogor |
| Produsen | : | Diproduksi dan dikemas oleh Vifor A.G., Ettingen, Swiss<br>Dirilis oleh Dr. Falk Pharma GmbH, Freiburg, Jerman untuk<br>Dr. Falk Pharma GmbH, Freiburg, Jerman |
| Kategori Registrasi | : | Indikasi dan posologi baru |
| Indikasi yang diajukan | : | *Treatment of acute episodes of ulcerative colitis that is limited to the rectum* |
| Posologi yang diajukan | : | *Adults and elderly:*<br>*One Salofalk suppository three times daily (equivalent to 1500 mg mesalazine daily) inserted into the rectum, according to the individual clinical requirement.*<br><br>*The dosage should be adjusted to suit the progress of the condition. Do not discontinue treatment suddenly.*<br><br>*Method of administration:*<br>*Rectal* |

## PENGANTAR

Salofalk merupakan obat dengan zat aktif mesalazine dengan mekanisme anti-inflamasi yang belum diketahui, namun hasil studi *in-vitro* mengindikasikan bahwa inhibisi lipooksigenase memegang peranan penting. Mesalazine juga memberikan efek pada konsentrasi prostaglandin dalam mukosa intestinal. Mesalazine (5-aminosalicylic acid/5-ASA) dapat berfungsi sebagai pengumpul radikal dari senyawa oksigen reaktif.

Saat ini Salofalk mengajukan perubahan indikasi dan posologi baru dengan rincian sebagai berikut:

- Indikasi:
  - dari mild & moderate attacks and maintenance treatment ulcerative colitis menjadi treatment of acute episodes of ulcerative colitis.
  - dari penggunaan pada bagian rectum, sigmoid colon and descending colon menjadi hanya terbatas pada rectum.
- Posologi:
  - Penambahan dosis pemberian untuk acute treatment dari 1 g daily (500 mg bid) menjadi 1.5 g daily (500 mg tid)

Mengingat pendaftaran yang diajukan adalah indikasi dan posologi baru, saat ini evaluasi difokuskan pada data uji klinik untuk pembuktian efikasi dan keamanan obat lebih lanjut.

## ASPEK KHASIAT DAN KEAMANAN

### Studi Nonklinik

Tidak ada studi non klinik yang diserahkan.

**Studi Klinik**
Evaluasi dilakukan pada 1 studi klinik fase 3 (Study SAS-6-UCA)

1. Hasil studi klinik fase 3 menunjukkan bahwa pemberian mesalazine 1 g OD memberikan efikasi yang sebanding dengan mesalazine 0,5 g TD dengan nilai *clinical remission rates* (DAI<4) berturut-turut 160/182 (87.9%) vs. 156/172 (90,7%) pada pasien *acute ulcerative proctitis dengan mildly to moderately active disease.*

| | | Number (%) of patients with clinical remission at the final/withdrawal examination | | Difference between proportions* [95%-CI] | Shifted asymptotic $\chi^2$-test for comparing two rates** |
|---|---|---|---|---|---|
| | | 1 g mesalazine OD | 0.5 g mesalazine TID | | |
| 1st interim analysis | PP | 60 (82.2%) n = 73 | 64 (88.9%) n = 72 | -6.7% [-18.1%, 4.7%] | 0.0819*** |
| | ITT | 65 (79.3%) n = 82 | 66 (80.5%) n = 82 | -1.2% [-13.5%, 11.1%] | 0.0150*** |
| 2nd interim analysis | PP | 121 (86.4%) n = 140 | 117 (90.0%) n = 130 | -3.6% [-11.2%, 4.1%] | 2.692**** |
| | ITT | 131 (83.4%) n = 157 | 129 (83.2%) n = 155 | 0.2% [-8.1%, 8.5%] | 3.436**** |
| Final analysis | PP | 160 (87.9%) n = 182 | 156 (90.7%) n = 172 | -2.8% [-9.2%, 3.6%] | 3.463**** |
| | ITT | 168 (84.0%) n = 200 | 172 (84.7%) n = 203 | -0.7% [-7.8%, 6.4%] | 3.790**** |

* Difference between proportions [1 g mesalazine OD – 0.5 g mesalazine TID]; asymptotic CI;
** 'Effect' = difference between proportions [1 g mesalazine OD – 0.5 g mesalazine TID] + 0.15);
*** observed p-value (one-sided);
**** inverse normal.

2. Profil keamanan antara kelompok mesalazine 1 g dengan kelompok mesalazine 0,5 g sebanding.

**Table 50: Number (%) of AEs/ADRs and number (%) of patients with at least one AE/ADR (safety analysis set)**

| | | 1 g mesalazine OD | | 0.5 g mesalazine TID | |
|---|---|---|---|---|---|
| | | AEs n = 48 | Patients n = 200 | AEs n = 67 | Patients n = 203 |
| Treatment-emergent AE | n (%) | 48 (100.0%) | 38 (19.0%) | 67 (100.0%) | 43 (21.2%) |
| ADR | n (%) | 6 (12.5%) | 5 (2.5%) | 9 (13.4%) | 7 (3.4%) |

Source: Appendix 8.2, Table 3-1.1

**Table 51: Patients with at least one treatment-emergent AE by SOC (safety analysis set)**

| System Organ Classes | | 1 g mesalazine OD n = 200 | 0.5 g mesalazine TID n = 203 |
|---|---|---|---|
| Gastrointestinal disorders | n (%) | 13 (6.5%) | 10 (4.9%) |
| Infections and infestations | n (%) | 5 (2.5%) | 16 (7.9%) |
| Nervous system disorders | n (%) | 5 (2.5%) | 12 (5.9%) |
| Investigations | n (%) | 7 (3.5%) | 7 (3.4%) |
| Musculoskeletal and connective tissue disorders | n (%) | 3 (1.5%) | 2 (1.0%) |
| General disorders and administration site conditions | n (%) | 2 (1.0%) | 2 (1.0%) |
| Blood and lymphatic system disorders | n (%) | 2 (1.0%) | 1 (0.5%) |
| Injury, poisoning and procedural complications | n (%) | 1 (0.5%) | 2 (1.0%) |
| Skin and subcutaneous tissue disorders | n (%) | — | 3 (1.5%) |
| Vascular disorders | n (%) | 2 (1.0%) | 1 (0.5%) |
| Hepatobiliary disorders | n (%) | 1 (0.5%) | 1 (0.5%) |
| Reproductive system and breast disorders | n (%) | 1 (0.5%) | 1 (0.5%) |
| Immune system disorders | n (%) | — | 1 (0.5%) |
| Metabolism and nutrition disorders | n (%) | 1 (0.5%) | — |
| Psychiatric disorders | n (%) | — | 1 (0.5%) |
| Renal and urinary disorders | n (%) | 1 (0.5%) | — |
| Respiratory, thoracic and mediastinal disorders | n (%) | 1 (0.5%) | — |

Source: Appendix 8.2, Table 3-1.2.1

**KEPUTUSAN**
Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi indikasi dan posologi baru Salofalk suppositoria **disetujui dengan perbaikan indikasi** sebagai berikut:

**Indikasi:**
*Treatment of acute episodes of mildly to moderate active ulcerative proctitis.*

**Posologi:**
*Adults and elderly:*
*One Salofalk suppository three times daily (equivalent to 1500 mg mesalazine daily) inserted into the rectum, according to the individual clinical requirement.*

*The dosage should be adjusted to suit the progress of the condition. Do not discontinue treatment suddenly.*

*Method of administration:*
*Rectal*

*Public Assessment Report*

**SALOFALK**

## PRODUCT INFORMATION

| | | |
|---|---|---|
| Drug name | : | SALOFALK |
| Dosage form | : | Suppository |
| Active substance | : | Mesalazine 500 mg |
| Packaging | : | Box, 6 strips @ 5 suppositories |
| Registration holder | : | PT. Darya Varia Laboratoria, Tbk., Bogor |
| Manufacturer | : | Manufactured & packaged by Vifor A.G., Ettingen, Switzerland<br>Released by Dr. Falk Pharma GmbH, Freiburg, Germany for Dr. Falk Pharma GmbH, Freiburg, Germany |
| Registration category | : | New indication and posology |
| Proposed indication | : | *Treatment of acute episodes of ulcerative colitis that is limited to the rectum* |
| Proposed posology | : | *Adults and elderly:*<br>*One Salofalk suppository three times daily (equivalent to 1500 mg mesalazine daily) inserted into the rectum, according to the individual clinical requirement.*<br><br>*The dosage should be adjusted to suit the progress of the condition. Do not discontinue treatment suddenly.*<br><br>*Method of administration:*<br>*Rectal* |

## INTRODUCTION

Salofalk is a drug with the active substance mesalazine with an unknown anti-inflammatory mechanism, but the results of in-vitro studies indicate that lipoxygenase inhibition plays an important role. Mesalazine also has an effect on prostaglandin concentrations in the intestinal mucosa. Mesalazine (5-aminosalicylic acid/5-ASA) can work as a radical collector from reactive oxygen compounds.

Currently Salofalk is propose change for new indication and posology with the following details:

- Indication:
  - from mild & moderate attacks and maintenance treatment of ulcerative colitis to treatment of acute episodes of ulcerative colitis.
  - from use in the rectum, sigmoid colon and descending colon to being limited to the rectum.
- Posology:
  - Increased dose for acute treatment from 1 g daily (500 mg bid) to 1.5 g daily (500 mg tid)

Considering that the proposed registration is a new indication and posology, thus the evaluation is focused on clinical trial data to further prove the efficacy and safety of the drug.

## EFFICACY AND SAFETY ASPECT

### Nonclinical study

No non-clinical studies were submitted

**Clinical study**
Evaluation was carried out in one of phase 3 clinical study (Study SAS-6-UCA)

1. The results of the phase 3 clinical study showed that administration of mesalazine 1 g OD provided comparable efficacy to mesalazine 0.5 g TD with clinical remission rates (DAI<4) respectively 160/182 (87.9%) vs. 156/172 (90.7%) in acute ulcerative proctitis patients with mild to moderately active disease.

| | | Number (%) of patients with clinical remission at the final/withdrawal examination | | Difference between proportions* [95%-CI] | Shifted asymptotic $\chi^2$-test for comparing two rates** |
|---|---|---|---|---|---|
| | | 1 g mesalazine OD | 0.5 g mesalazine TID | | |
| 1st interim analysis | PP | 60 (82.2%) n = 73 | 64 (88.9%) n = 72 | -6.7% [-18.1%, 4.7%] | 0.0819*** |
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* Difference between proportions [1 g mesalazine OD – 0.5 g mesalazine TID]; asymptotic CI;
** 'Effect' = difference between proportions [1 g mesalazine OD – 0.5 g mesalazine TID] + 0.15);
*** observed p-value (one-sided);
**** inverse normal.

2. The safety profile between the 1 g mesalazine group and the 0.5 g mesalazine group is comparable.

**Table 50: Number (%) of AEs/ADRs and number (%) of patients with at least one AE/ADR (safety analysis set)**

| | | 1 g mesalazine OD | | 0.5 g mesalazine TID | |
|---|---|---|---|---|---|
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Source: Appendix 8.2, Table 3-1.1

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| Investigations | n (%) | 7 (3.5%) | 7 (3.4%) |
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| General disorders and administration site conditions | n (%) | 2 (1.0%) | 2 (1.0%) |
| Blood and lymphatic system disorders | n (%) | 2 (1.0%) | 1 (0.5%) |
| Injury, poisoning and procedural complications | n (%) | 1 (0.5%) | 2 (1.0%) |
| Skin and subcutaneous tissue disorders | n (%) | — | 3 (1.5%) |
| Vascular disorders | n (%) | 2 (1.0%) | 1 (0.5%) |
| Hepatobiliary disorders | n (%) | 1 (0.5%) | 1 (0.5%) |
| Reproductive system and breast disorders | n (%) | 1 (0.5%) | 1 (0.5%) |
| Immune system disorders | n (%) | — | 1 (0.5%) |
| Metabolism and nutrition disorders | n (%) | 1 (0.5%) | — |
| Psychiatric disorders | n (%) | — | 1 (0.5%) |
| Renal and urinary disorders | n (%) | 1 (0.5%) | — |
| Respiratory, thoracic and mediastinal disorders | n (%) | 1 (0.5%) | — |

Source: Appendix 8.2, Table 3-1.2.1

**DECISION**
Considering the efficacy and safety data mentioned above, it was decided to registration of new indication and posology of Salofalk suppository **approved with revision on indication** as follows:

**Indication:**
*Treatment of acute episodes of mildly to moderate active ulcerative proctitis.*

**Posology:**
*Adults and elderly:*
*One Salofalk suppository three times daily (equivalent to 1500 mg mesalazine daily) inserted into the rectum, according to the individual clinical requirement.*

*The dosage should be adjusted to suit the progress of the condition. Do not discontinue treatment suddenly.*

*Method of administration:*
*Rectal*