Public Assessment Report

SALOFALK

INFORMASI PRODUK

Nama obat	:	SALOFALK
Bentuk sediaan	:	Tablet salut selaput
Zat aktif	:	Mesalazine 500 mg
Kemasan	:	Dus, 10 blister @ 10 tablet salut enterik
Pendaftar	:	PT. Darya Varia Laboratoria, Tbk., Bogor
Produsen	:	Diproduksi dan dikemas oleh Losan Pharma GmbH, Neuenburg, Jerman Dirilis oleh Dr. Falk Pharma GmbH, Freiburg, Jerman untuk Dr. Falk Pharma GmbH, Freiburg, Jerman
Kategori Registrasi	:	Posologi baru
Indikasi yang diajukan	:	*Ulcerative colitis, for treatment of mild to moderate acute phases and prevention of recurrences*
Posologi yang diajukan	:	(*Catatan:* Bagian yang digarisbawahi adalah posologi baru yang diajukan) *Adults and elderly:* *Depending upon the clinical requirements in individual cases, the following daily doses are recommended.* *For treatment of acute episodes: 1.5 g to 3.0 g mesalazine daily in three divided doses (1 or 2 tablets of Salofalk 500 mg three times daily).* *For the maintenance of remission: 1.5 g mesalazine in three divided doses (1 tablet of 500 mg three times daily).* *Method of Administration: Oral* *General instructions for use:* *Salofalk tablets should be taken in the morning, at midday and in the evening, 1 hour before meals. They should be swallowed whole, not chewed and taken with plenty of fluid.* *Treatment with Salofalk tablets should be administered regularly and consistently, both in the acute inflammatory stage and during maintenance therapy in order to achieve the desired therapeutic effect.* *The duration of use is determined by the physician.*

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 posologi pemberian obat yaitu penambahan dosis pemberian untuk acute treatment dari 1.5 g daily menjadi 1.5 g sampai 3.0 g daily. Mengingat pendaftaran yang diajukan adalah 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
Penambahan dosis pemberian untuk *acute treatment* dari 1.5 g daily menjadi 1.5 g sampai 3.0 g daily didukung oleh 2 studi klinik (SAT-14 UCA dan SAG-15 UCA)

1. Hasil studi klinik fase 3 (SAT-14 UCA) menunjukkan bahwa pada pasien *dengan mild to moderate active ulcerative colitis*, pemberian Salofalk (*Eudragit-L-coated mesalazine*) tablet dosis 3.0 mg per hari memberikan efikasi yang sebanding dengan Pentasa (*Ethylcellulose-coated mesalazine*) tablet dosis 3.0 g per hari, dengan nilai *remission rates* antara kedua kelompok yaitu 75/109 pasien (69%) pada kelompok Salofalk dan 73/106 pasien (69%) pada kelompok Pentasa (*p-value* 0.0007).

Clinical remission rates:

		Eudragit-L	Ethylcellulose	p-value (lower limit of 95%-CI)
PP analysis	n/N_t (%)	75/109 (69%)	73/106 (69%)	0.0007 (-0.12)
ITT analysis	n/N_t (%)	83/131 (63%)	81/126 (64%)	0.0006 (-0.12)

Note: One of the 127 ITT patients in the Ethylcellulose group was not evaluable with respect to clinical remission.

2. Hasil studi klinik fase 3 (SAG-15 UCA) menunjukkan bahwa pada pasien dengan *mild to moderate active colitis,* pemberian mesalazine pellet dan tablet memberikan efikasi yang sebanding dengan nilai *response rate* 67/98 pasien (68%) pada kelompok mesalazine pellet dan 70/100 pasien (70%) pada kelompok mesalazine tablet. Peningkatan dosis menjadi 3.0 g/hari memberikan nilai *response rate* yang sebanding antara kedua kelompok yaitu 51% vs 57%.

Table XIV: Response rate (PP analysis set)

	mesalazine pellets (n = 98)	mesalazine tablets (n = 100)
patients with dosage increase	19 (51 %, n=37)	27 (57 %, n=47)
patients without dosage increase	48 (79%, n=61)	43 (81%, n=53)
total	67 (68%)	70 (70%)

3. Profil keamanan antara kelompok mesalazine dengan kelompok Pentasa sebanding, dengan efek samping yang sering terjadi yaitu *headache, abdominal pain, nausea* dan *viral infections*. Profil keamanan pada kelompok mesalazine pellet dan mesalazine tablet sebanding.

KEPUTUSAN

Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi penambahan posologi baru Salofalk tablet salut enterik 250 mg disetujui sesuai dengan **posologi yang diajukan** sebagai berikut:

Dosage and Administration

Adults and elderly:
Depending upon the clinical requirements in individual cases, the following daily doses are recommended.

For treatment of acute episodes: 1.5 g to 3.0 g mesalazine daily in three divided doses (1 or 2 tablets of Salofalk 500 mg three times daily).

For the maintenance of remission: 1.5 g mesalazine in three divided doses (1 tablet of 500 mg three times daily).

Method of Administration: Oral

General instructions for use:
Salofalk tablets should be taken in the morning, at midday and in the evening, 1 hour before meals. They should be swallowed whole, not chewed and taken with plenty of fluid.

Treatment with Salofalk tablets should be administered regularly and consistently, both in the acute inflammatory stage and during maintenance therapy in order to achieve the desired therapeutic effect.

The duration of use is determined by the physician.

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PRODUCT INFORMATION

Drug name	:	SALOFALK
Dosage form	:	Enteric coated tablet
Active substance	:	Mesalazine 500 mg
Packaging	:	Box, 10 blisters @ 10 enteric coated tablets
Registration holder	:	PT. Darya Varia Laboratoria, Tbk., Bogor
Manufacturer	:	Manufactured & packaged by Losan Pharma GmbH, Neuenburg, Germany Released by Dr. Falk Pharma GmbH, Freiburg, Germany for Dr. Falk Pharma GmbH, Freiburg, Germany
Registration category	:	New posology
Proposed indication	:	*Ulcerative colitis, for treatment of mild to moderate acute phases and prevention of recurrences*
Proposed posology	:	(*Note:* The underlined part is the proposed new posology) *Adults and elderly:* *Depending upon the clinical requirements in individual cases, the following daily doses are recommended.* *For treatment of acute episodes: 1.5 g to 3.0 g mesalazine daily in three divided doses (1 or 2 tablets of Salofalk 500 mg three times daily).* *For the maintenance of remission: 1.5 g mesalazine in three divided doses (1 tablet of 500 mg three times daily).* *Method of Administration: Oral* *General instructions for use:* *Salofalk tablets should be taken in the morning, at midday and in the evening, 1 hour before meals. They should be swallowed whole, not chewed and taken with plenty of fluid.* *Treatment with Salofalk tablets should be administered regularly and consistently, both in the acute inflammatory stage and during maintenance therapy in order to achieve the desired therapeutic effect.* *The duration of use is determined by the physician.*

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 changes for posology of drug administration with increase the dose for acute treatment from 1.5 g daily to 1.5 g to 3.0 g daily. 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
Increasing the dose for acute treatment from 1.5 g daily to 1.5 g to 3.0 g daily is supported by 2 clinical studies (SAT-14 UCA and SAG-15 UCA)

1. The results of the phase 3 clinical study (SAT-14 UCA) show that in patients with mild to moderate active ulcerative colitis, administration of Salofalk (Eudragit-L-coated mesalazine) tablets at a dose of 3.0 mg per day provides comparable efficacy to Pentasa (Ethylcellulose-coated mesalazine) tablet dose of 3.0 g per day, with remission rates between the two groups, namely 75/109 patients (69%) in the Salofalk group and 73/106 patients (69%) in the Pentasa group (p-value 0.0007).

Clinical remission rates:

		Eudragit-L	Ethylcellulose	p-value (lower limit of 95%-CI)
PP analysis	n/N_t (%)	75/109 (69%)	73/106 (69%)	0.0007 (-0.12)
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Note: One of the 127 ITT patients in the Ethylcellulose group was not evaluable with respect to clinical remission.

2. The results of the phase 3 clinical study (SAG-15 UCA) showed that in patients with mild to moderate active colitis, administration of mesalazine pellets and tablets provided comparable efficacy with a response rate of 67/98 patients (68%) in the mesalazine pellet and group. 70/100 patients (70%) in the mesalazine tablet group. Increasing the dose to 3.0 g/day provided a comparable response rate between the two groups, namely 51% vs 57%.

Table XIV: Response rate (PP analysis set)

	mesalazine pellets (n = 98)	mesalazine tablets (n = 100)
patients with dosage increase	19 (51 %, n=37)	27 (57 %, n=47)
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total	67 (68%)	70 (70%)

3. The safety profile between the mesalazine group and the Pentasa group is comparable, with side effects that often occur is headache, abdominal pain, nausea and viral infections. The safety profiles in the mesalazine pellet and mesalazine tablet groups were comparable.

DECISION
Considering the efficacy and safety data mentioned above, it was decided the registration of new posology of Salofalk enteric coated tablets 500 mg **approved in accordance with the proposed posology** as follows:

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Adults and elderly:
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