Fumarates

Instructions for use

Dimethyl fumarate (DMF) is a pro-drug for oral administration; the active in vivo moiety is monomethylfumarate[1]. For the treatment of psoriasis a drug containing DMF is registered in Europe (Skilarence®) and a mixture of DMF and three salts of ethylhydrogenfumarates (Fumaderm®) is registered in Germany only.

Further reference is for the DMF drug with European label.

Table 1: Instructions for use (dimethyl fumarate)

<u>Pre-treatment</u>

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- History and clinical examination
- Reliable contraception
- Laboratory parameters (see **Table 2**)

<u>During treatment</u>

- Objective assessment of the disease (such as PASI/BSA/PGA)
- HRQoL (such as DLQI/Skindex-29 or -17)
- Clinical examination
- Reliable contraception
- Laboratory parameters (see **Table 2**)

<u>Post-treatment</u>

- None

[1] due to personal-financial conflict of interest 2 abstentions

Recommendations for lab controls

Table 2: Recommended laboratory controls (dimethyl fumarate)

	Period in months	
Parameter	**Pre-treatment**	**Every 3 months**
Blood count*	x	x
Liver enzymes	x	x
Serum creatinine	x	x
Urine status	x	x
Pregnancy test (urine or blood)	x	
Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure.		

* If leukocytes are < 3000/µl DMF therapy must be stopped. If lymphocytes are < 1000/µl and >700/µl monthly monitoring is required. If lymphocytes remain below 700/µl at two consecutive visits DMF treatment must be stopped. Analysis should include platelets and eosinophils.

The recommendations are based on clinical experience. No evidence is available.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Gastrointestinal complaints, mainly diarrhoea and increased stool frequency (which occur in up to 60 % of patients) and flush symptoms are the most frequent ADR during treatment with DMF.

Leucocytopenia, lymphocytopenia, and eosinophilia can be observed during therapy with DMF. An increase in eosinophils is temporary and is usually observed between weeks four and ten of treatment. Occasionally, proteinuria occurs during DMF therapy, but disappears after dose reduction or cessation of treatment.

Overview of important side effects

Very frequent	Diarrhoea, flush, mild leukopenia and lymphopenia (approx. 50% of patients)

Frequent	Abdominal cramps, flatulence, severe lymphocytopenia (approx. 3% of patients), transient eosinophilia
Occasional	Nausea, dizziness, headache, fatigue, proteinuria, increase in serum creatinine, increase in liver enzymes
Rare	Allergic skin reaction
Very rare	None

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Gastrointestinal tolerance may be improved by taking the tablets after a meal. The administration of acetylsalicylic acid can help to decrease flush symptoms.

The dose of DMF can be adjusted to the individual effective dose ranging from the minimum available dose 30 mg/day to the maximum dose as per label 720 mg/day. In general, it is recommended to follow the dose titration schedule until clinical response and subsequently adjust the dose individually.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Absolute contraindications

- Severe disease of the gastrointestinal tract including liver and/or the kidneys
- Pregnancy or breastfeeding (lack of clinical experience)

Relative contraindications

- Haematological disease

Drug interactions

There are no known drug interactions with DMF.

Because fumarates may impair renal function, drugs with known nephrotoxic potential should not be used concomitantly.

Overdose/measures in case of overdose

None

References

1. Mrowietz U, Morrison PJ, Suhrkamp I, Kumanova M, Clement B. The Pharmacokinetics of Fumaric Acid Esters Reveal Their In Vivo Effects. *Trends in pharmacological sciences*. Jan 2018;39(1):1-12. doi:10.1016/j.tips.2017.11.002