Public Assessment Report

Scientific discussion

Dimethyl fumarate 30 mg and 120 mg Teva, gastro-resistant tablets

(dimethyl fumarate)

NL/H/2844/001-002/DC

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This module reflects the scientific discussion for the non-approval of Dimethyl fumarate 30 mg and 120 mg Teva, gastro-resistant tablets. The procedure was finalised on 1 July 2014.

A list of literature references is given on page 9.

List of abbreviations

ALAT	Alanine Aminotransferase
ASAT	Aspartate Aminotransferase
ASMF	Active Substance Master File
DAC	Deutscher Arzneimittel Codex
DDI	Drug-drug Interaction
DMF	Dimethyl Fumarate
EC	European Commission
FAE	Fumaric Acid Ester
MEB	Medicines Evaluation Board of the Netherlands
MEF	Monoethyl Hydrogen Fumarate
MMF	Monomethyl Fumarate
MTX	Methotrexate
PASI	Psoriasis Area and Severity Index
Ph.Eur.	European Pharmacopoeia
PML	Progressive Multifocal Leukencefalopathy
RH	Relative Humidity
TSE	Transmissible Spongiform Encephalopathies
SmPC	Summary of Product Characteristics

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands has refused granting a marketing authorisation for Dimethyl fumarate 30 mg and 120 mg Teva, gastro-resistant tablets from Teva Pharma B.V.

The applicant applied for the indication psoriasis. The marketing authorisation was applied pursuant to Article 10a of Directive 2001/83/EC, a well-established use application through a decentralised procedure with the Netherlands as Reference Member State. The applicant withdrew the application in the Concerned Member States after the first round of assessment, before the restart of the procedure.

II. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The marketing authorization could not be granted due to potential serious risks to public health as defined in the Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC — March 2006 (2006/C 133/ 05).

The potential serious risk to public health precluding a recommendation of marketing authorisation pertained to the following principal deficiency:

The benefit/risk balance for these products cannot be established. Insufficient data on the mono-product containing dimethyl fumarate only to demonstrate well-established use according to Article 10a Directive 2001/83 have been provided by the applicant. Therefore, the legal basis of Article 10a is not considered justified. Furthermore, data are lacking to bridge literature to the medicinal products applied for.
Safety concerns exist due the recently identified risk of Progressive Multifocal Leukencefalopathy (PML). Also the quality dossier is not acceptable, as some issues arisen during the assessment have not been resolved.

For this decision the MEB has taken into account the European Commission Decision on Tecfidera 120 mg gastro-resistant capsules, stating that monoethyl hydrogen fumarate (MEF) and dimethyl fumarate (DMF) are both active and are not the same active substance since they do not share the same therapeutic moiety. Like Dimethyl fumarate Teva, Tecfidera is a medicinal product that contains DMF only. Tecfidera was approved in January 2014 for the indication multiple sclerosis. The decision was laid down in EC decision C(2014)601.

As DMF and MEF are not considered the same active substance, literature on products containing DMF + MEF cannot be used to show well-established use of DMF. Given the fact that the current application was based on the established use of Fumaderm, which consists of DMF and three other salts (Ca-methylethanol fumarate (Ca-MEF), Mg-methylethanol fumarate (Mg-MEF) and Zn-methylethanol fumarate (Zn-MEF)), well established use of DMF only could not be shown.

This means that the established use of Fumaderm is not relevant to substantiate the well-established use of this application for Dimethyl fumarate Teva.

The assessment of the quality, non-clinical and clinical parts of the dossier is briefly described below, in section III.

III. QUALITY, NON-CLINICAL AND CLINICAL ASSESSMENT

III.1 Quality aspects

Drug substance
The active substance dimethyl fumarate is an established substance described in the Deutscher Arzneimittel Codex (DAC). It is the dimethyl ester of fumaric acid and is the trans (or E) isomer. Dimethyl maleate is the cis (or Z) isomer. Only one morphic form is produced.
The ASMF-procedure is used for the active substance.

The substance has been adequately characterized and acceptable specifications have been adopted for the starting material and solvents. The drug substance specification is in line with the Deutscher Arzneimittel Codex and general Ph.Eur. requirements. Two additional tests should however be included. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (up to 18 months) and 40°C/75% RH (up to 6 months). Based on these data a re-test period of 30 months is considered acceptable. Additional stability data were however required in order to fully establish the re-test period.

Drug product
The development of the product was based on the established product Fumaderm. The main studies performed concerned the development of a suitable gastro-resistant coating.
Additional studies are required to compare the dissolution profiles of the two strengths and dissolution studies mimicking food-effect should be performed.

Manufacturing process validation data on the product has been presented for three smallest commercial-scale batches. The information provided on the manufacturing process, which is non-standard, is insufficient. The specifications for the excipients are acceptable although functionality-related characteristics of several excipients need to be further discussed. TSE certificates have been provided.

There are remaining issues regarding the product specification and validation. Additional data need to be provided.

Sufficient stability data is lacking, which is considered a potential serious risks to public health. These data are required for determining the shelf-life of the drug product, but also for the acceptability of the specification, container closure system, manufacturing process and pharmaceutical development.

III.2 Non-clinical aspects

The applicant submitted an overview based on literature review and did not provide additional studies. Taking into account the ground for refusal (*i.e.* insufficient data have been provided on the mono-product containing dimethyl fumarate only to demonstrate well-established use according to Article 10a Directive 2001/83), the non-clinical documentation provided is considered insufficient.

Environmental Risk Assessment (ERA)
Since Dimethyl fumarate Teva is intended as a substitute for products that are available on the market, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.3 Clinical aspects

III.3.1 Pharmacokinetics

Based on the published data, dimethyl fumarate is beyond detection in the plasma as it is rapidly hydrolysed to the assumed active metabolite monomethyl fumarate (MMF) by

esterases in the small intestine. As shown by *in vitro* data, the metabolism of DMF to MMF is pH dependent and takes place in the small intestine due to the alkaline environment as in acidic environment conversion does not take place. Although it is generally assumed that DMF is completely hydrolyzed to MMF, there are some data indicating that DMF might not be completely hydrolyzed in the small intestine. Further, food appeared to influence the bioavailability of MMF, although definite conclusions cannot be drawn.

Overall, the available data on the pharmacokinetics of dimethyl fumarate is considered very limited and not well-understood. The results in the published literature cannot be extrapolated to the proposed product due to the following reasons:

- All of the published studies provided used formulations which are different from the proposed product: (a) Fumaderm (considered by the applicant as the reference product) is a mixture of dimethyl fumarate and three salts of fumarate, and (b) magistral preparations which can differ in quality.
- The formulation is a single-unit, enteric-coated formulation. Release characteristics are dependent on the formulation itself, *i.e.* formulation specific, which cannot be bridged by literature data. Furthermore, gastric emptying may be prolonged and highly erratic, especially under fed conditions, the consequences of which are largely unpredictable.
- There are no data available on the risk of unexpected release (*e.g*. dose dumping).
- The metabolic pathway is not clear and proper drug-drug interaction (DDI) studies in accordance with the current DDI-guideline are lacking.

It was therefore concluded that the pharmacokinetic data in the literature cannot be bridged to the proposed medicinal products. Pharmacokinetic studies should be performed to provide data to enable proper pharmacokinetics assessment. This was identified as a potential serious risk to public health.

III.3.2 Efficacy

Most reports on the clinical effects of DMF and/or the mixture of DMF + MEF in the treatment of psoriasis concern observational, uncontrolled studies. Only a few randomized controlled studies have been published.

Studies with DMF

In the literature, abstracts are available summarizing the results of two randomised controlled studies with Tecfidera gastro-resistant capsules containing 120 mg of DMF. This product was approved in January 2014 for the indication multiple sclerosis.

One abstract reports the results of a double-blind, randomized, placebo-controlled Phase III trial in subjects with moderate-severe psoriasis. Mean Psoriasis Area and Severity Index (PASI) score was 18 at baseline, indicating moderate-severe psoriasis. A total of 105 subjects were uptitrated to 720 mg DMF daily, and 70 received placebo. The PASI 75 responder rate after 16 weeks was 39% in active treatment, versus 1% in the placebo arm (PASI 50 was 65% versus 14%, respectively). About 7% of the subjects dropped-out in the active arm because of gastro-intestinal intolerability, versus none in placebo.

The other abstract briefly points out that a randomized, parallel, placebo-controlled Phase 2 dose finding study has been performed with Tecfidera 120 mg, where 144 patients were randomized to DMF 120 mg/360, mg/720 mg or placebo for 12 weeks. It was noted that improvement of psoriasis was observed at 2 weeks and that this was dose related. No details are provided regarding responder rates.

These short abstracts seem to support the proof of concept of DMF, and in the Phase III study, the response may be considered clinically relevant. However, the results are difficult to interpret as many details were not specified, *e.g.* regarding randomisation procedure and total number of drop-out. The Phase II study is relevant, but the details are too limited to

draw any conclusion on efficacy. Moreover, it is unclear to what extent the Teva product could be bridged to the study drug Tecfidera 120 mg.

Controlled studies with diverse FAE combination products; evidence for bridging
Reference is made to studies of Fumaderm® or other products containing 120 mg DMF + MEF (monoethyl fumarates). According to the applicant, adding MEF ester monomers do not provide a relevant effect on top of DMF alone, and DMF is to be considered the main active ingredient.

The basis for bridging is one small-scaled, double-blind parallel trial in psoriasis patients by Nieboer et al (1990), where treatment with 120 mg of DMF alone was compared to a combination of 120 mg DMF + 95 mg MEF (3 mg Mg-, 5 mg Zn- and 87 mg Ca-salts, conform the composition of the current Fumaderm product). Twenty-two patients received DMF alone, and 23 the combination. Whether or how the subjects were randomized is unclear. Maximal dose was 4 tablets a day. It was reported that efficacy was sooner achieved with the combination than DMF alone, but detailed data to support this statement are lacking. In the end of the study, after 4 months, a similar clinical improvement was achieved in both groups. More than 50% improvement from baseline was achieved in 10/22 (45%) of the DMF-treated subjects, versus 12/23 (52%) of the DMF + MEF combination group. In both groups, 4 subjects achieved full clearance of skin symptoms. Drop out rate was numerically lower for DMF alone (18% versus 35%). Adverse events were flushing (86% and 87%), diarrhea (55% and 61%), nausea/gastric discomfort (50% and 61%) and leukopenia (14% and 13%), for the DMF and the combination tablet, respectively. Remarkably, increases of ALAT/ASAT were only noted for the combination (86%).

No firm conclusions can be drawn from this explorative study regarding non-inferiority between DMF to DMF + MEF combination. No placebo control was included, making it difficult to estimate assay sensitivity, and to compare with natural course. This is especially relevant as disease state of the subjects at baseline or the level of co-medication is not specified.

Another comparative study is available by Kolbach et al. (1992). This is an open-label observational study including 129 patients with moderate-severe psoriasis treated with DMF alone, versus 67 patients treated with a combination of DMF + MEF. The choice of treatment depended on insurance company of the patient. The maximal allowed net DMF-dose was twice as high for the combination product as for the mono-component product. Perhaps therefore the combination was superior to monotherapy: after 24 months, 55% of the patients still continued treatment with the combination, versus 15% of the DMF alone group. The leading reasons for discontinuation were lack of efficacy in the DMF group (36%), versus Adverse Events in the combination group. Considering the differences in dose levels, and the open-label non-randomised design, this study does not provide evidence of bridging. At best, this study provides some supportive evidence for the dose recommendation.

Additional controlled studies with diverse FAE combination products
Placebo-controlled studies
Data of two placebo controlled studies with the combination product were provided. In the study by Altmeyer et al. (1994), 100 subjects with moderate-severe psoriasis, irresponsive to local treatment, were randomized to a combination of DMF + MEF (120-95 mg) or placebo control. The dose was to be individually titrated till maximal 6 tablets a day. After 16 weeks, 72.3% of the subjects in active treatment arm versus 18% in the placebo group responded at least moderately ($p<0.0001$). The exact number of good response-remission has not been reported in the applicant's clinical overview. Treatment was terminated prematurely in 38.8% of the active treatment group, versus 58% in the placebo group. This study is considered supportive of the proof of concept of the DMF combination product.

In the study by Nugteren-Huying, 39 subjects were randomized to a combination of DMF + MEF, placebo or octafumarate. Only the mean PASI scores were reported, which significantly dropped from baseline (mean 21) group by 70% in the DMF-MEF at Week 16,

whereas it remained unchanged in the other groups. This study is rather considered as exploratory, considering the small sample size.

Active-controlled studies
One randomized controlled trial is available, where a magistral DMF + MEF combination product (120 mg + 95 mg) was compared to methotrexate (maximal 15 mg once weekly), in 60 patients with severe psoriasis (Fallah Arani et al. 2011). No placebo was included. The primary endpoint was difference in PASI after 12 weeks of treatment. In the primary analyses, 25 subjects of the MTX group and 26 of the fumarate group were included. Two patients in the FAE group left the study because of diarrhea, and 4 patients in the MTX group withdrew because of adverse events. After 12 weeks, mean PASI decreased from 18.1 to 10.5 in those randomised to FAE and from 14.5 to 6.7 in those receiving MTX (baseline-adjusted absolute difference 1.4 (-2.0 to 4.7; p = 0.417)). PASI-75% was achieved by 5 (19%) patients on FAE and by 6 (24%) on MTX.

A 15 mg dose for MTX is considered appropriate for treatment of psoriasis. The study is, however, not considered sufficiently powered to establish formally non-inferiority or superiority of either treatment. The lack of placebo hampers assessment of assay sensitivity.

Other, non-randomised studies
Of interest is a retrospective analysis of clinical reports of 984 psoriasis patients treated with Fumaderm® in German clinics (FUTURE database, Reich et al. 2009). Mean treatment duration was 44 months. The percentage of patients documented as markedly improved (*i.e.* PASI 75) or clear was 67% after six months, 78% after 24 months, and 82% after 36 months of therapy. Retrospective analyses are however hampered by patients selection, and the responder rates may be overestimated as drop-out are not taking into account.

Therapeutic indication
The following indications were applied for:

- *Dimethyl fumarate 30 mg gastro-resistant tablets* - initiation of treatment of moderate to severe forms of psoriasis vulgaris, if purely external treatment is insufficient before treatment with the 120 mg strength, to improve tolerability.
- *Dimethyl fumarate 120 mg gastro-resistant tablets* - treatment of moderate to severe forms of psoriasis vulgaris, if purely external treatment is insufficient. Prior adjustment of tolerability with the 30 mg gastro-resistant tablets is necessary.

The separate indications for the 30 and 120 mg tablet were not supported. The MEB raised a comment that the indication should shortly reflect the target condition and should not include a titration schedule or other dosing aspects. These are addressed in section 4.2 of the SmPC.
Considering the risk of PML, other systemic treatment options may be considered first. The indication should therefore be limited to patients in whom PUVA and other systemic therapies are not considered appropriate. The MEB stated in the first round of assessment that the indication should be replaced by: *Treatment of moderate to severe forms of psoriasis vulgaris, if purely external topical treatment is insufficient and other systemic treatment options are not considered appropriate.*

The MEB noted that further rewording could be necessary, depending on whether the potential serious risks to public health regarding the place of fumarates in the treatment arsenal of psoriasis considering the risk of PML would be addressed. The benefit/risk balance of Dimethyl fumarate Teva could however not be established.

III.4 Safety

Safety data were mainly obtained from several observational studies in about 1000 subjects. In addition, data are available of the German Fumaderm registry of 960 patients.

Flushes, diarrhea, and gastro-intestinal intolerance were very commonly reported (40-70%), and a common cause of treatment interruption. According to the presented literature gastrointestinal disturbance can occur in up to 70% of patients receiving treatment with fumaric acid esters. This number is high but seems to result in discontinuation of therapy in less than 10% of patients. Flushing occurs in 30% of the patients especially at the beginning of the therapy.
Slow titration and an enteric-coated tablet are proposed as preventive measures. This is supported, although it has not been established in randomized trials to what extent these measures actually prevent gastro-intestinal adverse events.

Transient eosinophilia has been reported in up to 50% of patients. The clinical consequences are unclear. In the literature, DMF used as a preservative in fabrics for the prevention of mould has been associated with local allergic reactions. Whether contact allergy or other allergic reactions would also occur with tablets is unknown.

Increments of liver enzymes were commonly reported in studies. Nephrotoxicity was observed in animal studies. Incidental cases of acute renal failure or proteinuria have been reported in patients treated with fumaric acid esters. Hepatic and renal functions have to be routinely monitored during treatment.

The risk of haematological changes and renal adverse events is subject for concern. According to the applicant, DMF has not been associated with infections, despite a drop of lymphocytes. Leukopenia and lymphocytes reductions were frequently reported. Relevant advice should be given in the SmPC, *i.e.* pre-treatment monitoring, followed by monitoring at regular intervals. It is agreed that constant monitoring of lymphocytes, leukopenia, hepatic enzymes and renal damage is required, and this may lower the risks.
Often dose reductions were sufficient to control lymphocytopenia. However, recently two cases of progressive multifocal leukencefalopathy (PML) were reported, associated with fumaric acid therapy in psoriasis. This risk needs to be reported in the SmPC and included in the Risk Management Plan. An alert card should be provided to all patients, to promote early intervention. Furthermore, because of the now established risk of PML, the place of DMF in the treatment arsenal of psoriasis needs further discussion.

Literature references

Altmeyer PJ, Matthes U, Pawlak F et al. Antipsoriatic effect of fumaric acid derivatives. Results of a multicenter double-blind study in 100 patients. J Am Acad Dermatol. 1994 Jun; 30(6):977-81

Fallah Arani S, Neumann H, Hop WC, Thio HB. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled clinical trial. Br J Dermatol. 2011 Apr; 164(4): 855-61

Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: results and adverse effects of 2 years of treatment. J Am Acad Dermatol. 1992 Nov; 27(5 Pt 1): 769-71.

Nieboer C, de Hoop D, Langendijk PN et al. Fumaric acid therapy in psoriasis: a double-blind comparison between fumaric acid compound therapy and monotherapy with dimethylfumaric acid ester. Dermatologica. 1990; 181(1): 33-7.

Nugteren-Huying WM, van der Schroeff JG et al. Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. J Am Acad Dermatol. 1990 Feb; 22 (2 Pt 1): 311-2

Reich K, Thaci D, Mrowietz U, Kamps A, Neureither M, Luger T. Efficacy and safety of fumaric acid esters in the long-term treatment of psoriasis—a retrospective study (FUTURE). J Dtsch Dermatol Ges. 2009 Jul; 7(7): 603-11