COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dimethylfumaraat CF 120 mg and 240 mg, gastro-resistant capsule, hard (dimethyl fumarate)

NL/H/5578/001-002/DC

Date: 28 August 2023

This module reflects the scientific discussion for the non-approval of Dimethylfumaraat CF 120 mg and 240 mg, gastro-resistant capsule, hard. The procedure was finalised on 18 January 2023.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have refused a marketing authorisation for Dimethylfumaraat CF 120 mg and 240 mg, gastro-resistant capsule, hard, from Drehm Pharma GmbH.

The indications applied for included the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerose (RRMS).

There were no concerned member states (CMS) involved in this procedure.

The marketing authorisation was applied for pursuant to Article 10(1) of Directive 2001/83/EC, claiming essential similarity between the new product and the innovator product Tecfidera 120 mg and 240 mg gastro-resistant hard capsules from Biogen Netherlands B.V. which has been registered in the EEA via a centralised procedure (EU/1/13/837).

The application was discussed in the board meeting of 5 January 2023. For further details, please refer to the CBG-MEB website, public minutes from the meetings, Openbaar verslag 1019e Collegevergadering.

II. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The marketing authorisation could not be granted due to major objections qualifying as potential serious risk 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):

<u>Overall benefit-risk</u>
The proposed generic products are gastro-resistant hard capsules, modified release dosage forms. Some modified-release oral dosage forms contain active substances and/or excipients that exhibit higher solubility in ethanolic solutions compared to water. Consumption of alcoholic beverages with such products may induce dose dumping (unintended, rapid drug release of the entire amount or a significant fraction of the active substance) which may cause significant risks to patients.

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1, section 6.9), for generic oral formulations, *in vitro* studies of the release in alcohol solutions should be performed. The guideline states: where accelerated active substance release is seen *in vitro* either at high or low alcohol concentrations over a short period of time or at lower alcohol concentrations over a longer period of time, the product should be reformulated. If the alcohol effect cannot be avoided and it is present also in the reference product, the applicant should justify/demonstrate that

it lacks clinical relevance or discuss the possible clinical relevance in comparison to the reference product.

The effect of alcohol on the *in vitro* release of dimethyl fumarate from Tecfidera 240 mg gastro-resistant hard capsules (reference product) and Dimethylfumaraat CF 240 mg hard capsules (test product) has been investigated at various alcohol concentrations in the acidic dissolution medium for routine testing. The reference and test product have been investigated under similar conditions. The results show that:

- the dimethyl fumarate test product is more rapidly release compared to the reference product,
- the dimethyl fumarate test product is also released at lower concentrations of alcohol compared to the reference product.

Furthermore, the lack of clinical relevance of the observed alcohol effect was not demonstrated. In overall, it has not been sufficiently demonstrated that the safety of the test product is equivalent to that of the reference product under all possible conditions. Consequently, the benefit risk of the proposed product is considered negative.

The Board followed the advice of the assessors.

Therefore, the Board concluded that the marketing authorisation for Dimethylfumaraat CF 120 mg and 240 mg, gastro-resistant capsule, hard, cannot be granted. The decentralised procedure was finalised with a negative outcome on 18 January 2023.