Gemeinsamer Bundesausschuss

Justification

on the Resolution of the Federal Joint Committee to Discontinue a Benefit Assessment Procedure according to Section 35a SGB V on Diroximel fumarate (relapsing-remitting multiple sclerosis)

of 6 July 2023

Contents

1. Legal basis 2

2. Key points of the resolution 2

2.1 Procedural sequence to date 2

2.2 Discontinuation of the benefit assessment procedure 5

3. Bureaucratic costs calculation 6

4. Process sequence 6

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

According to Section 2, paragraph 1 AM-NutzenV, medicinal products with new active ingredients are medicinal products containing active ingredients whose effects are not generally known in medical science when they receive marketing authorisation for the first time. A medicinal product with a new active ingredient is considered to be as such for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

2.1 Procedural sequence to date

On 12 January 2021, the Subcommittee on Medicinal Products discussed the fact that the active ingredient diroximel fumarate is subject to the scope of the early benefit assessment.

The active ingredient diroximel fumarate was listed for the first time on 1 January 2022 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 29 December 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 April 2022 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held on 9 May 2022. At the oral hearing, a representative of the pharmaceutical company stated that the European Commission was expected to confirm the initial marketing authorisations for generic dimethyl fumarate and Tecfidera. According to the pharmaceutical company, the European Commission thus does not recognise the dossier protection of Tecfidera, subject to a final decision by the European Court of Justice (ECJ). This would clarify that no dossier protection is currently recognised for Vumerity either. In view of this, Vumerity was no longer considered a medicinal product containing a new active ingredient. Thus, the benefit assessment procedure of diroximel fumarate (Vumerity) according to Section 35a SGB V was to be discontinued ex officio.

According to information obtained by the G-BA from the Federal Institute for Drugs and Medical Devices (BfArM) dated 31 May 2022, the medicinal product Vumerity with the active ingredient diroximel fumarate belongs to the same "global marketing authorisation" within

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the meaning of Article 6 paragraph 1 of Directive 2001/83/EC as the medicinal product Tecfidera containing the active ingredient dimethyl fumarate. According to information from the BfArM, it could not be assumed that the medicinal product Vumerity with the active ingredient diroximel fumarate had its own dossier protection as of May 2022.

With regard to the medicinal product Tecfidera with the active ingredient dimethyl fumarate, it was also not to be assumed that a dossier protection existed as of May 2022. According to the implementing decision C(2014)601 (final)1[1] of the European Commission from 30 January 2014 on the granting of the initial marketing authorisation for the medicinal product Tecfidera with the active ingredient dimethyl fumarate, the Commission had initially stated that the medicinal product Tecfidera and the already approved medicinal product Fumaderm were not part of the same comprehensive marketing authorisation pursuant to Article 6 paragraph 1 of Directive 2001/83/EC and that Tecfidera with the active ingredient dimethyl fumarate was therefore subject to an independent dossier utilisation protection period of eight years. Dimethyl fumarate is part of the composition of the approved medicinal product Fumaderm from the same marketing authorisation holder, which consists of dimethyl fumarate and ethyl fumarate calcium salt, ethyl hydrogen fumarate magnesium salt and ethyl hydrogen fumarate zinc salt (monoethyl fumarate salts - MEF). The Committee for Medicinal Products for Human Use had concluded that dimethyl fumarate and MEF were two separate active ingredients and not one and the same active ingredient, as they did not have the same active component. An independent dossier protection period of eight years was therefore assumed for Tecfidera.

However, in its judgement of 5 May 2021, the General Court of the European Union (EGC: European General Court) declared the implementing decision C(2014)601 (final) of 30 January 2014 inapplicable insofar as the Commission had found in it that Tecfidera was not part of the same comprehensive authorisation as Fumaderm. The General Court has concluded that the Commission was not entitled to assume that Tecfidera was covered by a different comprehensive marketing authorisation than the already authorised Fumaderm, without having asked the CHMP or the BfArM for a further examination of the role of MEF in Tecfidera. The decisive factor for the EGC was that the EMA and the Commission, when adopting the implementing decision of 30 January 2014, had at their disposal data that were suitable to make the hypothesis that MEF played a role in Fumaderm appear implausible. According to the EGC, whether an already authorised fixed combination of active ingredients and a constituent thereof fall under the same comprehensive marketing authorisation depends not only on a qualitative comparison, but also on the therapeutic contribution made by the active ingredient(s) of the medicinal product for which the initial marketing authorisation has been granted. The judgement called into question the criteria for determining whether medicinal products are covered by the same comprehensive marketing authorisation within the meaning of Article 6 paragraph 1, subparagraph 2 of Directive 2001/83.

Both the European Commission as well as Biogen Netherlands BV and the European Medicines Agency have appealed against the EGC's judgement of 5 May 2021 to the European Court of Justice (ECJ). In the European Commission's implementing decision C(2022)3251 (final)[2] of 13 May 2022 on the extension of the marketing authorisation for the medicinal product Tecfidera with the active ingredient dimethyl fumarate "for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS)", the Commission rejected an extension of the marketing protection for a further year in accordance with Article 14 paragraph 11 of Regulation (EC) No. 726/2004. The European

[1] https://ec.europa.eu/health/documents/community-register/2014/20140130125880/dec_125880_en.pdf
[2] https://ec.europa.eu/health/documents/community-register/2022/20220513154921/dec_154921_en.pdf

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Commission has also indicated that the resolution C(2014)601 (final) should be amended accordingly.

Since unclear legal situation in May 2022 led to considerable uncertainties regarding the existence of dossier protection to the advantage of the medicinal product Vumerity with the active ingredient diroximel fumarate, the G-BA temporarily suspended the adoption of a resolution on the benefit assessment pursuant to Section 35a, paragraph 3, sentence 1 SGB V for the medicinal product Vumerity with the active ingredient diroximel fumarate in the therapeutic indication for the treatment of adult patients with relapsing-remitting multiple sclerosis by resolution of 16 June 2022 until the final decision of the ECJ in the following appeal proceedings:

- Case C-438/21 P: Appeal brought on 14 July 2021 by the European Commission against the judgement of the General Court of the European Union (EGC) - Seventh Chamber, Extended Composition - delivered on 5 May 2021 in Case T-611/18 Pharmaceutical Works Polpharma vs EMA,

- Case C-439/21 P: Appeal brought on 14 July 2021 by Biogen Netherlands BV against the judgement of the General Court of the European Union (EGC) - Seventh Chamber, Extended Composition - delivered on 5 May 2021 in Case T-611/18 Pharmaceutical Works Polpharma vs EMA,

- Case C-440/21 P: Appeal brought on 15 July 2021 by the European Medicines Agency against the judgement of the General Court of the European Union (EGC) - Seventh Chamber, Extended Composition - delivered on 5 May 2021 in Case T-611/18 Pharmaceutical Works Polpharma vs EMA.

In its judgement of 16 March 2023, the ECJ held that the Commission had not committed a manifest error of assessment in deciding that Tecfidera was not covered by the same comprehensive marketing authorisation as Fumaderm according to Article 6, paragraph 1, subparagraph 2 of Directive 2001/83. Consequently, the European Commission's implementing decision C(2014) 601 final of 30 January 2014, which stated that monoethyl fumarate salts (MEF) and dimethyl fumarate (DMF), which are constituents of Fumaderm, are two active ingredients with different therapeutically active components and that Tecfidera and Fumaderm differ in terms of active ingredient composition, is fully valid.

The ECJ pointed out in particular that it cannot be concluded from the wording of Article 6, paragraph 1, subparagraph 2 of Directive 2001/83 and the systematic context of this provision that the concept of a comprehensive marketing authorisation would apply to medicinal products with different qualitative compositions within the meaning of marginal no. 86 of the judgement. Under marginal no. 86, the court had shown that an extension of the marketing authorisation within the meaning of Section 1, letter a of Annex I to Regulation No. 1234/2008 and thus a change in the marketing authorisation is given if there is a "substitution of a chemical active ingredient by another salt/ester complex or another salt/ester derivative with the same active component with insignificantly different efficacy and safety characteristics". In order to determine whether medicinal products are covered by the same comprehensive marketing authorisation, it is sufficient to compare them in qualitative terms and not to examine, in addition, what therapeutic contribution is made by the active ingredient(s) of the medicinal product for which the initial marketing authorisation has been granted.

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Pursuant to the European Commission's implementing decision C(2023)3067 (final)[3] of 2 May 2023 amending the marketing authorisation granted by resolution C(2014)601 (final) for the medicinal product Tecfidera containing the active ingredient dimethyl fumarate, it has been determined that - in the light of the final judgement of the ECJ of 16 March 2023 - the marketing protection pursuant to Article 14 paragraph 11 of Regulation (EC) No. 726/2004 may be extended for a further year. Thus, the marketing protection for the medicinal product Tecfidera ends on 2 February 2025.

Since the medicinal product Tecfidera with the active ingredient dimethyl fumarate belongs to the same "global marketing authorisation" within the meaning of Article 6 paragraph 1 of Directive 2001/83/EC as the medicinal product Vumerity with the active ingredient diroximel fumarate, it follows that a valid dossier protection must currently also be taken into account for the medicinal product Vumerity (diroximel fumarate).

2.2 Discontinuation of the benefit assessment procedure

Following a renewed examination of the factual and legal situation, the G-BA came to the conclusion, as a result of the ECJ judgement of 16 March 2023, that the benefit assessment procedure pursuant to Section 35a SGB V for the medicinal product Vumerity with the active ingredient diroximelfumarate in the therapeutic indication for the treatment of adult patients with relapsing-remitting multiple sclerosis is to be discontinued despite the valid dossier protection, as diroximel fumarate is the same active ingredient as dimethyl fumarate.

By letter of 31 May 2022, the BfArM stated that diroximel fumarate and dimethyl fumarate are both esters of fumaric acid which, as so-called prodrugs, are converted pre-systemically in their respective active form to monomethyl fumarate. Diroximel fumarate and dimethyl fumarate were to be classified as the "same active ingredient" under Article 10 paragraph 2b of Directive 2001/83/EC, because the EPAR published on Vumerity did not provide any evidence from a clinical point of view that the two esters of fumaric acid could be expected to differ "significantly in their properties with regard to safety and/or efficacy".

The G-BA is not bound by the EMA's decision that a new active ingredient is present when it comes to the question of whether it is a "new active ingredient" pursuant to Section 35a SGB V. Chapter 4 Section 16 VerfO defines the prerequisites under which active ingredients are considered to be one and the same active ingredient. Thus, according to paragraph 3, 1st indent, different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active ingredient are in principle considered to be one and the same active ingredient. Despite the existence of these prerequisites, the G-BA can assume a "new active ingredient" within the meaning of Section 35a SGB V if this can be justified with regard to the function and specific purpose of the early benefit assessment ("in principle"). When assessing the active ingredients with regard to their structural comparability according to the definition presented, the G-BA originally used the already approved active ingredient dimethyl fumarate as a comparison. Based on the ECJ's comments in the judgement of 16 March 2023, the G-BA carried out a re-examination. However, it concluded that both dimethyl fumarate and diroximel fumarate have the same active metabolite and both active ingredients are esters of fumaric acid and that, in view of the specific purpose of the early benefit assessment, there

[3] https://ec.europa.eu/health/documents/community-register/2023/20230502159131/dec_159131_en.pdf

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are no reasons for a different assessment. The G-BA now assumes that both active ingredients are the same active ingredient.

However, for the new medicinal product Vumerity with the active ingredient diroximel fumarate, there is no new therapeutic indication within the meaning of Chapter 5 Section 2, paragraph 2, sentence 2 VerfO compared to the already approved therapeutic indications for medicinal products with the active ingredient. A benefit assessment procedure has already been carried out for the medicinal product Tecifdera with the active ingredient dimethyl fumarate in this indication. Pursuant to Section 7, paragraph 4, sentence 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), this resolution on the benefit assessment of 16 October 2014, last amended by resolution of 7 January 2016[4], is the basis for agreements pursuant to Section 130b SGB V on reimbursement amounts for all medicinal products with the same active ingredient and for the determination of requirements for the appropriateness, quality and cost-effectiveness of the prescription as well as for the recognition as a special feature in practice or for the assignment of medicinal products without additional benefit to a reference price group pursuant to Section 35 SGB V.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 29 December 2021, the pharmaceutical company submitted a dossier for the benefit assessment of diroximel fumarate to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 3 January 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient diroximel fumarate.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 March 2022, and the written statement procedure was initiated with publication on the G-BA website on 01 April 2022. The deadline for submitting statements was 22 April 2022.

The oral hearing was held on 9 May 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

[4] https://www.g-ba.de/downloads/91-1385-111/2016-01-07_Geltende-Fassung_Dimethylfumarat_D-100.pdf

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At its session on 8 June 2022, the Subcommittee on Medicinal Products discussed the temporary suspension of a resolution on the benefit assessment according to Section 35a, paragraph 3, sentence 1 SGB V and consented to the draft resolution.

At its session on 16 June 2022, the plenum decided on the temporary suspension of a resolution on the benefit assessment according to Section 35a, paragraph 3, sentence 1 SGB V.

At its session on 27 June 2023, the Subcommittee on Medicinal Products discussed the discontinuation of the benefit assessment procedure according to Section 35a SGB V and consented to the draft resolution.

At its session on 6 July 2023, the plenum decided to discontinue the benefit assessment procedure according to Section 35a SGB V.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 January 2021	Consultation on the dossier obligation according to Section 35a SGB V
Subcommittee Medicinal products	8 June 2022	Consultation on the temporary suspension of a resolution on the benefit assessment according to Section 35a SGB V
Plenum	16 June 2022	Resolution on the temporary suspension of a resolution on the benefit assessment according to Section 35a SGB V
Working group Section 35a	21 June 2023	Consultancy on the discontinuation of the procedure according to Section 35a SGB V
Subcommittee Medicinal products	27 June 2023	Consultancy on the discontinuation of the procedure according to Section 35a SGB V
Plenum	6 July 2023	Resolution on the discontinuation of the procedure according to Section 35a SGB V

Berlin, 6 July 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken

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