Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Fosdenopterin (molybdenum cofactor deficiency Type A)

of 4 September 2025

At their session on 4 September 2025, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient fosdenopterin as follows:

Fosdenopterin

Resolution of: 4 September 2025
Entry into force on: 4 September 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 15 September 2022):

NULIBRY is indicated for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A.

Therapeutic indication of the resolution (resolution of 4 September 2025):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Fosdenopterin is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The G-BA determine the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Patients with molybdenum cofactor deficiency (MoCD) Type A

Extent of the additional benefit and significance of the evidence of fosdenopterin:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

Patients with molybdenum cofactor deficiency (MoCD) Type A

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	n.a.	The data are not assessable.

[1] Data from the dossier assessment of the G-BA (published on 16. June 2025), and from the amendment to the dossier assessment from 15 August 2025, unless otherwise indicated.

Health-related quality of life	∅	No data available.
Side effects	n.a.	The data are not assessable.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

MCD-501 study: retrospective data collection for the investigation of rcPMP[2], based on patient records; N = 4; median treatment duration of 0.58 months

MCD-201 study: prospective single-arm phase II study to investigate fosdenopterin in patients with MoCD Type A who were pretreated with rcPMP; N = 8; median treatment duration of 86 months

MCD-202 study: prospective single-arm phase II/III study to investigate fosdenopterin in patients with MoCD Type A; N = 3; median treatment duration of 17.1 months

Mortality

Endpoint	**Fosdenopterin**		
	MCD-501 N = 4	**MCD-201** N = 8	**MCD-202** N = 3
Overall survival[a]			
Median duration of observation for overall survival, months (min; max)	n.d.[b]	n.d.[b]	n.d.[b]
Deaths, n (%)	2 (50.0)	0	0
Censoring, n (%) Alive at last contact Alive at data cut-off	2 (50.0) 2 (50.0) 0	8 (100) n.d.[c] n.d.[c]	3 (100) n.d.[c] n.d.[c]
Median survival time, months [95% CI]	n.d.	n.a.	n.a.

2 Recombinant Escherichia coli-derived cyclic pyranopterin monophosphate

Morbidity

Endpoint	Fosdenopterin					
	MCD-501 N = 4		MCD-201 N = 8		MCD-202 N = 3	
	N	Subjects with event, n (%)	N	Subjects with event, n (%)	N	Subjects with event, n (%)
Food intake						
Baseline Oral Non-oral Missing	4	n.d.	8	 5 (62.5) 3 (37.5) 0 (0)	3	 2 (66.7) 1 (33.3) 0 (0)
Month 12 Oral Non-oral Missing	4	n.d.	8	 5 (62.5) 3 (37.5) 0 (0)	3	 2 (66.7) 0 (0) 1 (33.3)
Month 48 Oral Non-oral Missing	4	n.d.	8	 4 (50.0) 3 (37.5) 1 (12.5)	3	-
Motor function using GMFCS-E&R[d]						
Baseline Level I Level II Level III Level IV Level V Missing	4	n.d.	8	 3 (37.5) 0 (0) 0 (0) 0 (0) 3 (37.5) 2 (25.0)	3	n.a.
Month 48 Level I Level II Level III Level IV Level V Missing	4	n.d.	7	 3 (37.5) 0 (0) 0 (0) 0 (0) 4 (50.0) 1 (12.5)	3	n.a.
Endpoint	**Fosdenopterin**					
	MCD-501 N = 4		**MCD-201** N = 8		**MCD-202** N = 3	
	N	MV (SD)	N	MV (SD)	N	MV (SD)
Growth parameters						
Body height (z score)						
Baseline	4	n.d.	8	-0.51 (2.24)[e]	3	n.d.
Month 48	4	n.d.	7	-0.73 (2.88)	3	n.d.

Body weight (z score)						
Baseline	4	n.d.	8	0.06 (2.06)[e]	3	n.d.
Month 48	4	n.d.	7	-0.24 (1.61)	3	n.d.

Quality of life

No data available.

Side effects

Endpoint MedDRA system organ classes/ AEs of special interest	**Fosdenopterin**		
	MCD-501[f,g] N = 4	**MCD-201** N = 8	**MCD-202**[h] N = 3
	Subjects with event, n (%)	Subjects with event, n (%)	Subjects with event, n (%)
Total adverse events (presented additionally)			
	n.d.	8 (100)	3 (100)
Serious adverse events (SAE)[i]			
	n.d.	7 (87.5)	3 (100)
Severe adverse events[i]			
	n.d.[j]	5 (62.5)	3 (100)
Therapy discontinuation due to adverse events[k]			
	n.d.[l]	0	0
SAE according to MedDRA system organ class (with an incidence ≥ 10%)			
Gastrointestinal disorders	n.d.	1 (12.5)	n.d.
General disorders and administration site conditions	n.d.	5 (62.5)	n.d.
Infections and infestations	n.d.	6 (75.0)	n.d.
Injury, poisoning and procedural complications	n.d.	2 (25.0)	n.d.
Metabolism and nutrition disorders	n.d.	2 (25.0)	n.d.
Musculoskeletal and connective tissue disorders	n.d.	1 (12.5)	n.d.
Nervous system disorders	n.d.	2 (25.0)	n.d.
Product issues	n.d.	1 (12.5)	n.d.
Respiratory, thoracic and mediastinal disorders	n.d.	2 (25.0)	n.d.

Skin and subcutaneous tissue disorders	n.d.	1 (12.5)	n.d.
Surgical and medical procedures	n.d.	1 (12.5)	n.d.
Vascular disorders	n.d.	2 (25.0)	n.d.
Severe adverse events according to MedDRA system organ class (with an incidence ≥ 10%)			
Gastrointestinal disorders	n.d.	2 (25.0)	n.d.
General disorders and administration site conditions	n.d.	4 (50.0)	n.d.
Infections and infestations	n.d.	4 (50.0)	n.d.
Injury, poisoning and procedural complications	n.d.	1 (12.5)	n.d.
Investigations	n.d.	1 (12.5)	n.d.
Metabolism and nutrition disorders	n.d.	1 (12.5)	n.d.
Musculoskeletal and connective tissue disorders	n.d.	1 (12.5)	n.d.
Nervous system disorders	n.d.	1 (12.5)	n.d.
Product issues	n.d.	1 (12.5)	n.d.
Respiratory, thoracic and mediastinal disorders	n.d.	2 (25.0)	n.d.
Skin and subcutaneous tissue disorders	n.d.	1 (12.5)	n.d.
Vascular disorders	n.d.	2 (25.0)	n.d.

a. Primary endpoint of the MCD-202 study (no primary endpoints were defined in the MCD-501 and -201 studies)
b. No data available for the respective median duration of observation. The median treatment duration was 0.58 months (min; max: 0.20; 14.8) in the MCD-501 study, 86.0 months (min; max: 29.3; 94.7) in the MCD-201 study and 17.1 months (min; max: 0.3; 72.2) in the MCD-202 study.
c. No data available on censoring reasons for the data cut-off from 16.09.2022. The information on patient disposition shows that one subject each discontinued the MCD-201 and -202 studies prematurely, fosdenopterin was commercially available (MCD-201) or the subject had to discontinue the study due to a doctor's decision (MCD-202). It is assumed that the other 7 or 2 subjects were censored at the data cut-off.
d. Level I means: walks without restrictions; Level V means: is transported in a manual wheelchair.
e. The baseline values for body height (z score) and body weight (z score) were extracted from the statistical outputs (data cut-off: 16.09.2022). They differ from the values reported in Module 4 and in the EPAR (data cut-off: 31.10.2020).
f. No data available on AEs of the MCD-501 study for N = 4.
g. In the MCD-501 study, signs and symptoms associated with the underlying disease were not categorised as AEs. These include seizures, psychomotor retardation, ectopic lenses, dysmorphic signs, hypertension, hypotension, spastic quadriplegia, opisthotonus, enophthalmos, myoclonus, deficient nutrition, microcephaly, nystagmus, cerebral blindness and stroke-like episodes.
h. No aggregated data available on the AEs of the MCD-202 study for the data cut-off of 16.09.2022; these were calculated by ourselves.
i. The study's own criteria were used for severity grading.
j. In the MCD-501 study, only the severity grade of SAEs were extracted from the patient records.
k. MCD-201 and MCD-202: Study participants received the study medication until withdrawal of informed consent, unacceptable toxicity, or other medical reasons at the discretion of the investigator, whichever

occurred first. These possible therapy discontinuation reasons that may occur prior to potential discontinuation due to AEs thus represent a competing event, which is why the reliability of data and interpretability of the results is limited. Since the data for the MCD-501 study were extracted from patient records, it is unclear whether similar criteria for study discontinuation were present in the "named patient treatment plan".

l. In the MCD-501 study, discontinuations of study medication due to AEs were only extracted for SAEs.

Abbreviations used:
n.d. = no data available; CI = confidence interval; MV = mean value: N = number of patients evaluated; n = number of patients with (at least one) event; n.a. = not applicable; SD = standard deviation

2. Number of patients or demarcation of patient groups eligible for treatment

Patients with molybdenum cofactor deficiency (MoCD) Type A

Approx. 2 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Nulibry (active ingredient: fosdenopterin) at the following publicly accessible link (last access: 1 July 2025):

https://www.ema.europa.eu/en/documents/product-information/nulibry-epar-product-information_en.pdf

Treatment with fosdenopterin should only be initiated and monitored in a hospital by specialists who are experienced in the treatment of patients with congenital metabolic disorders.

Fosdenopterin may only be used if the patient has a confirmed genetic diagnosis or a suspected diagnosis of MoCD Type A. Patients with a suspected diagnosis of MoCD Type A must undergo a genetic test to confirm the diagnosis of MoCD Type A. Fosdenopterin must be discontinued if the diagnosis of MoCD Type A cannot be confirmed by genetic testing.

This medicinal product was approved under "special conditions". This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The EMA will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for patients and caregivers, who are expected to use Nulibry at home. In particular, the training material contains instructions for use and an infusion diary.

4. Treatment costs

Annual treatment costs:

Patients with molybdenum cofactor deficiency (MoCD) Type A

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Fosdenopterin	€ 574,612.20 - € 4,596,897.60

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2025)

Costs for additionally required SHI services: not applicable

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Patients with molybdenum cofactor deficiency (MoCD) Type A

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

6. Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product Nulibry is a medicinal product placed on the market from 1 January 2025.

No information was provided on the number of study participants involved in the clinical studies of the medicinal product in the therapeutic indication under assessment, which were conducted or commissioned by the pharmaceutical company at study sites within the scope of SGB V and/or on the total number of study participants.

Due to the absence of information, it is therefore not possible to determine that the percentage of study participants reached or exceeded the relevance threshold of at least 5 per cent.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant extent within the scope of SGB V.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 4 September 2025.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 4 September 2025

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

Prof. Hecken