Gemeinsamer Bundesausschuss

Justification

to the Resolution of the Federal Joint Committee (G-BA) 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

Contents

1. Legal basis

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

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to 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. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at their session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at their session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA 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 decide 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

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient fosdenopterin on 15 March 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 11 March 2025.

Fosdenopterin for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 16 June 2025 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA have adopted their resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G25-12) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA have evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of fosdenopterin.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Fosdenopterin (Nulibry) in accordance with the product information

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

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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

See the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of fosdenopterin is assessed as follows:

Patients with molybdenum cofactor deficiency (MoCD) Type A

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

Justification:

The benefit assessment is based on evaluations of the single-arm MCD-501, -201 and -202 studies. *Escherichia coli* derived recombinant cyclic pyranopterin monophosphate (rcPMP) was administered as an intervention in the MCD-501 study, and fosdenopterin was administered in the MCD-201 and MCD-202 studies. Subjects (pre)treated with rcPMP (from the MCD-501 study) had the option of switching over to the prospective MCD-201 study and receiving treatment with fosdenopterin. According to the European Public Assessment Report (EPAR) of the European Medicines Agency (EMA), rcPMP and fosdenopterin (synthetically derived cPMP) can be considered as therapeutically equivalent.

The MCD-501 study is a retrospective data collection from patient records to investigate the safety and efficacy of rcPMP in patients with MoCD treated with rcPMP as part of a "named-patient treatment plan". 19 subjects of all MoCD types, who had been treated with the intervention at the time of data collection, were identified. Evaluations are available for a total of 15 of the 19 patients. The reason for the retrospective surveys missing 4 of the patients initially identified by the pharmaceutical company in the MCD-501 study could not be determined.
A total of 10 patients with MoCD Type A were enrolled in the MCD-501 study, 6 of whom switched over to the MCD-201 study. The evaluations of the 4 patients who were only assessed in the MCD-501 study are relevant for the benefit assessment.
According to the EPAR, all patients enrolled in the study received rcPMP at a maximum dose of 0.18 mg/kg BW[2] daily. This dose is significantly lower than the recommended dose according to the product information (0.4 mg/kg BW daily for preterm infants and 0.55 mg/kg BW daily for term infants under one year of age; titration to a dose of 0.9 mg/kg BW daily by month 3).
Information on the date of the data cut-off presented in the dossier is not available for the MCD-501 study. It is unclear for how long the patients were observed in total. The median treatment duration in the MCD-501 study with rcPMP was 17.5 days[3].

The MCD-201 study is a prospective single-arm phase II study to investigate the safety and efficacy of fosdenopterin in paediatric patients with MoCD Type A who have been pretreated with rcPMP. A total of 8 patients were enrolled in the study (6 of whom had switched over from the MCD-501 study to the MCD-201 study). The duration of the treatment phase with fosdenopterin was 6 months, following which the patients switched over to an indefinite extension phase.

[2] Refers to the free base; the dosage information for the studies was originally based on the hydrobromide salt: 240 µg fosdenopterin hydrobromide corresponding to 0.182 mg fosdenopterin as free base.
[3] Information based on own calculation from EPAR data.

The patients enrolled in the study initially received fosdenopterin at the same dose as rcPMP for two months as part of the treatment phase, followed by a 4-month build-up dosing phase up to a maximum of 0.9 mg/kg BW daily, which was maintained in the extension phase. The build-up dosage regimen and the duration of the titration phase deviated from the requirements in the product information (titration to maintenance dose within 3 months); moreover, according to the EPAR, only 4 of the 8 patients enrolled in the study reached the maintenance dose of 0.9 mg/kg BW daily as specified in the product information.
The median treatment duration with fosdenopterin in the MCD-201 study was 86 months[3].
The median participation in the study (from consent) was 87.2 months. It is unclear whether this includes the duration of observation including the safety follow-up.
The final data cut-off available from 16 September 2022 was used for the benefit assessment.
A primary endpoint was not defined.

The MCD-202 study is a prospective single-arm phase II/III study to investigate the efficacy and safety of fosdenopterin in paediatric patients up to 5 years of age with MoCD Type A. One exclusion criterion of the study related to the severity grade of the existing damage to the brain: Patients with cortical or subcortical cystic encephalomalacia, clinically significant intracranial haemorrhage or other abnormalities in brain images were not enrolled in the study. A total of 3 patients were enrolled in the study.
The patients received treatment with fosdenopterin in accordance with the requirements in the product information (titration within 3 months to a maintenance dose of 0.9 mg/kg BW daily). The treatment phase with fosdenopterin lasted 12 months, followed by a 24-month long-term treatment phase, after which further treatment was possible.
The median treatment duration with fosdenopterin in the MCD-202 study was 17.1 months[3].
The final data cut-off available from 16 September 2022 was used for the benefit assessment.
Overall survival was assessed as the primary endpoint.

Comparison between the intervention studies
The three studies MCD-501, MCD-201 and MCD-202 differ fundamentally in terms of study design, inclusion criteria and dosage.
While the MCD-501 study was a retrospective collection in which the available data was extracted from patient records, the MCD-201 and MCD-202 studies had clear guidelines for the administration of the intervention and a prospective collection.
An MoCD diagnosis and treatment with rcPMP were required for enrolment in the MCD-501 study. Patients in the MCD-201 study had to have received pretreatment with rcPMP for enrolment in the study; a total of 6 of the 10 subjects in the MCD-501 study switched over to the MCD-201 study. The remaining 4 subjects were presented as patients of the MCD-501 study. It is therefore assumed that the subjects in the MCD-201 study were older than those in the MCD-501 study. In the MCD-201 study, the patients had a median age of 51.9 months at first administration of fosdenopterin (min; max: 8; 75). Due to this later start of treatment compared to MCD-501, an immortal time bias cannot be ruled out for the patients in the MCD-201 study.
Initially, only neonates were to participate in the MCD-202 study, but the inclusion criteria were expanded to include infants and toddlers, so that ultimately 2 neonates and 1 toddler with a late diagnosis were enrolled in the study. An exclusion criterion of the MCD-202 study was the severity grade of the existing brain damage, which did not exist in the MCD-501 and MCD-201 studies. A comparison of the severity grade of the brain damage at baseline is not possible as no data is available.
The maximum dose used in the MCD-501 study (0.18 mg/kg BW/day) corresponds to the starting dose in the MCD-201 study. The maximum dose in the MCD-201 study was 0.9 mg/kg BW/day. In the MCD-202 study, the starting dose was 0.55 mg/kg BW/day (preterm infants:

0.4 mg/kg BW/day) and was also uptitrated to 0.9 mg/kg BW/day. Thus, the dosage regimens used in the studies differ.
There are further differences between the studies in the collection and operationalisation of endpoints as well as in the frequency of the collections.
These differences preclude joint evaluation of the three studies.

On the evaluations based on the intervention studies: Violation of the ITT principle
Not all patients enrolled in the studies were included in the primary analyses of the intervention studies: A total of 19 patients of all MoCD Types were identified for the MCD-501 study, of which 10 with MoCD Type A were enrolled in the study. 6 of these 10 patients switched over to the MCD-201 study. Overall, 2 of the 4 subjects who did not switch over to MCD-201 discontinued the MCD-501 study due to a poor prognosis and one of the 3 subjects discontinued the MCD-202 study on doctor's recommendation due to a poor neurological prognosis. These subjects were censored in the analyses of overall survival. Informative censoring cannot be ruled out. The intention-to-treat (ITT) principle is not fulfilled as not all of the subjects enrolled in the intervention studies were therefore taken into account in these evaluations.

On the indirect comparison with a natural history cohort
In the dossier, the pharmaceutical company presented an indirect comparison without a bridge comparator on the efficacy of fosdenopterin versus "standard of care" based on a pooling of individual patient data from the three interventional studies (MCD-501, MCD-201 and MCD-202) and a natural history cohort (MCD-502 and MCD-503).

The MCD-502 study is a multicentre study with retrospective and prospective parts to assess the natural course of disease in subjects with MoCD or isolated sulphite oxidase (SOX) deficiency. In the retrospective part of the study, the patients' data were extracted from the patient records from birth to enrolment in the study or death. Inclusion and exclusion criteria were defined for enrolment in the study. Patients who were still alive were followed up in the prospective part. The evaluations of the MCD-502 study are therefore based on retrospective and prospective data.

A total of 37 patients (full analysis set, FAS) with MoCD Type A were enrolled and used as a comparator population for the indirect comparison. 20 patients were retrospectively enrolled in the study and had already died at the time of the prospective survey. Of the 17 patients still alive (46%), 14 (38%) were enrolled in the 12-month prospective data collection (prospective FAS, PFAS). A total of 13 subjects (35%) completed this prospective follow-up. One subject died before completion of the prospective data collection. The study was to be terminated when the last subject had completed the last study visit in the prospective part.

The primary endpoint was survival up to month 12 after birth for patients with MoCD Type A (FAS, retrospective and prospective survey).
For the prospective cohort, survival was assessed by annual telephone contact until the time of death or until the end of the study. However, enrolment in this cohort of the study did not take place prospectively at birth, but at an unspecified point in time in the course of the disease. The median duration of observation for the prospective part was 370 days in total.

In the MCD-503 study, additional survival data were retrospectively collected from patients from the MCD-501 and MCD-502 studies who were still alive at the end of the study. A total of 6 patients who had previously participated in the MCD-502 study were followed up as part of the MCD-503 study. The fact that no living subjects from the MCD-501 study could be identified cannot be verified on the basis of the available documents, as at least 6 subjects who had previously participated in the MCD-501 study were still alive according to the study

documents of the MCD-201 study. The data from the MCD-503 study were integrated into the analyses of the MCD-502 study.

In total, the indirect comparison included evaluations of 15 patients from the MCD-501, -201 and -202 studies on the intervention side and 37 patients from the MCD-502 and -503 studies on the comparator side.

The evaluations based on the indirect comparison without bridge comparator were not used for the quantification of the additional benefit in the present benefit assessment for the following reasons:

Limitations with regard to the similarity of the study populations
With regard to disease-related patient characteristics, sufficient similarity of the study populations to be compared cannot be assumed with certainty on the basis of the information provided. For example, 10 of the 15 patients (66.7%) in the intervention studies had seizures at baseline, whereas the percentage of patients with seizures in the comparator study (MCD-502) was 92% (34 of 37 subjects, without clear indication of the reference time point).

Overall, it cannot therefore be assumed that there is sufficient structural equality within the pooled populations and between the populations to be compared with regard to important disease-related characteristics.

Violation of the ITT principle
Moreover, there are further methodological limitations. As explained above, the evaluation strategy for overall survival for the intervention studies of the pharmaceutical company does not fulfil the intention-to-treat (ITT) principle, as not all subjects included in the intervention studies were taken into account in the analyses. Informative censoring cannot be ruled out.
In contrast, the patients in the natural history cohort MCD-502 (and MCD-503) were observed until their death or the end of the study; premature study discontinuation due to deteriorated health status would not have been possible. On the comparator side, the survival status without censoring (except "alive" at the data cut-off) was thus available for the MCD-502 study at any time during the course of the disease (ITT-like).

Immortal time bias
A further limitation arose with regard to the operationalisation of overall survival, defined as the period between the date of birth and the date of death or the last alive date known:
On the intervention side, the evaluations include patients from the MCD-501 and -201 studies who were enrolled after pretreatment with rcPMP. Patients up to the age of 5 years could be enrolled in the MCD-202 study; one patient in this study was already 33.4 months old at the start of treatment.
Thus, it is a selection of patients in the pooled intervention arm who must have survived until the respective enrolment in the study. As a result, patients who had potentially suffered an early death (prior to possible enrolment in the study) were not included in the postnatal survival time analysis on the intervention side. In contrast, on the comparator side, a death event was possible at any time from birth and was collected as such.
This leads to a potential immortal time bias with regard to overall survival from the time of birth. Comparability of the respective analyses of overall survival from birth is therefore not given due to the lack of structural equality of the study populations.

Moreover, no observation periods could be identified for the intervention studies, thus also significantly limiting the comparability of the analyses.

Confounder
Furthermore, no systematic review according to relevant factors was carried out as part of the identification of confounders for the indirect comparison. The pharmaceutical company only carries out an adjustment using matching based on the genotype (MOCS1 gene) as the only

characteristic manifestation. Matching for this characteristic manifestation could be carried out for 9 out of 15 subjects (60%) from the intervention studies. In addition, uncertainties remain with regard to the clinical relevance of the selected matching factor.

In the overall assessment, the evaluations presented by the pharmaceutical company on the basis of the indirect comparison show methodological limitations, particularly with regard to the similarity of the comparator populations, the violation of the ITT principle, a potential immortal time bias and confounder identification.

Against this background, the evaluations based on the indirect comparison of fosdenopterin with the natural history were not used to quantify the additional benefit.

Results of the MCD-501, -201 and -202 studies

Mortality

In the three studies, deaths were collected as part of the safety assessment.

With regard to the evaluations of overall survival, it should be noted overall that there was no survival follow-up in the MCD-201 and MCD-202 studies. The safety follow-up took place within 7 days of therapy discontinuation in the MCD-201 study and within 28 days in the MCD-202 study. In particular with regard to the MCD-201 study, an immortal time bias cannot be ruled out, as only patients who had received pretreatment with rcPMP and had not died during this period were enrolled in this study.

In the MCD-501 study (assessment-relevant sub-population N = 4), the median treatment time with rcPMP was 17.5 days (min; max: 6; 451). 2 deaths occurred. The other 2 patients discontinued the study prematurely due to a poor prognosis. It is unclear whether these subjects are still alive.
In the MCD-201 study (N = 8), the median treatment time with fosdenopterin at the present data cut-off from 16 September 2022 was 86.0 months (min; max: 29.3; 94.7). No deaths were recorded. Of the patients in the MCD-201 study, one patient discontinued the study prematurely because fosdenopterin was commercially available.
In the MCD-202 study (N = 3), the median treatment time with fosdenopterin at the present data cut-off from 16 September 2022 was 17.1 months (min; max: 0.3; 72.2). No deaths were recorded until then. One patient discontinued the study after 9 days at the doctor's discretion due to a poor neurological prognosis. Whether this subject is still alive cannot be determined from the data due to the short follow-up period.

Based on the single-arm data on mortality, no statement can be made on the extent of the additional benefit of fosdenopterin.

Morbidity

In the dossier, the results of the last assessment were presented for the efficacy endpoints of all three studies. The presentation of the results of the last assessment is viewed critically. Since the last surveys of the patients presumably took place at different times, the results of both shorter and longer observation periods are summarised. It is therefore unclear to which point in time the result relates and whether it represents a short-term or long-term effect. Therefore, in deviation from the pharmaceutical company's approach, the descriptive results of the individual studies at month 12 and 48 are used here.

Food intake

In the dossier, the endpoint was presented as a dichotomous variable with the "oral" and "non-oral" categories. Evaluations of food intake at the last assessment and the time to permanent non-oral feeding were presented.

In the MCD-501 study, there were no a priori defined survey time points; instead, the available data were extracted from the patient records. Therefore, it cannot be assumed that the surveys took place at the same time as in the MCD-201 and MCD-202 clinical studies. A time-to-event analysis is considered inappropriate due to the different survey time points and the different time intervals between the surveys.

The evaluations of food intake at month 12 and 48 are therefore used here.

There are no corresponding results for the MCD-501 study. In the MCD-201 study, 5 patients were able to take food orally at baseline, while 3 patients required non-oral food intake. At month 12, food intake was also oral in 5 patients and non-oral in 3. At month 48, 4 patients took the food orally, 3 non-orally and no data was available for one patient. In the MCD-202 study, 2 patients took the food orally and one patient took it non-orally at baseline. At month 12, 2 patients continued to take the food orally and no results were available for one patient.

Motor function using the Gross Motor Function Classification System - Expanded and Revised version (GMFCS-E&R)

The GMFCS-E&R is an instrument for assessing the gross sensory motor functions of children with cerebral palsy on the basis of their self-initiated movement.

No GMFCS-R&R results are available for the MCD-501 study. The return rate for the MCD-501 study was < 70% at baseline and the other survey time points. In the MCD-202 study, the GMFCS-E&R was only collected 12 months of age and older; a baseline survey was not planned. Therefore, the results of the MCD-202 study are not used here.

In the MCD-201 study, 3 patients had level I (no limitations) and 3 patients had level V (severe limitations) in the GMFCS-E&R at baseline; the data of 2 patients were missing. At month 48, 3 patients had level I and 4 patients had level V; no data were available for one patient.

Body height and body weight

Anthropometric parameters were assessed as patient-relevant morbidity parameters, especially in children with characteristic, disease-related growth failures. Data adjusted for age and sex were preferred to absolute values.

For the MCD-501 and MCD-202 studies, no evaluations (MCD-501) or no suitable evaluations (MCD-202) of the growth parameters were available. In the MCD-201 study, the z score for body height averaged -0.51 at baseline and -0.73 at month 48. The average z score for body weight was 0.06 at baseline and -0.24 at month 48.

Early childhood development functions using Bayley Scales of Infant and Toddler Development, Third Edition (Bayley III) and Wechsler Preschool and Primary Scale of Intelligence (WPPSI)

The Bayley III is a standardised, norm-compliant assessment of developmental functions in infants and toddlers up to the age of 42 months. The endpoint is considered to be patient-relevant.

However, no results are available for the assessment-relevant sub-population (N = 4) of the MCD-501 study. The return rate for the MCD-201 study was too low and the Bayley III was only collected from day 28 in the MCD-202 study. Due to the lack of baseline surveys, it is not possible to show changes over time. The return rate is also too low with regard to the

evaluations of the WPSSI. In the overall assessment, the evaluations of Bayley III and the WPPSI cannot be used here.

Sit unassisted

The ability to sit without support is generally considered to be patient-relevant in the present therapeutic indication.
However, the evaluations presented in the dossier cannot be used for the present benefit assessment due to the low return rate.

Seizures

Epileptic seizures are generally considered to be patient-relevant in the present therapeutic indication.

In the dossier, the pharmaceutical company presented evaluations of epileptic seizures, including on the basis of seizure diaries to be completed by parents and electroencephalography (EEG) findings. Patients were categorised according to their seizure history ("absent", "disappeared", "controlled", "present").

The studies show differences in the surveys of seizures. Overall, the survey methods (EEG, seizure diary), on which the categorisation and evaluations are based, remains unclear.

Against the background of the limitations described with regard to operationalisation, the endpoint of seizures is not used here.

Neurological examinations

In the studies, spontaneous movements, muscle tone (trunk and extremities), deep tendon reflexes and primitive reflexes were collected. No information is available on how the neurological examinations were carried out in the studies, who were responsible for carrying them out and which tools were used. Instructions for testing and assessing movements, reflexes and tone were not available. Therefore, the overall comparability between the implementation and assessment of examinations is unclear.

Against the background of the limitations described with regard to operationalisation, the endpoint of neurological examination is not used here.

Biomarkers and neuroimaging

The evaluations of laboratory parameters and imaging examination procedures presented in the dossier are considered to be non-patient-relevant.

Overall, no statement can be made on the extent of the additional benefit of fosdenopterin, based on the single-arm data on the endpoints in the morbidity category.

Quality of life

No results on quality of life are available.

Side effects

No evaluations are available for the assessment-relevant sub-population of the MCD-501 study (N = 4).

In the MCD-201 study, all adverse events (AEs) which occurred after the first intake of fosdenopterin within 7 days of discontinuation of the study were collected; in the MCD-202 study, all AEs which occurred after the first intake of fosdenopterin until 28 days after the last administration of the study medication were collected.

For both studies, there are no evaluations that do not take disease-related events or events of the underlying disease into account. Therefore, it cannot be ruled out that the safety data also partly reflect efficacy aspects. The study's own criteria were defined for assessment of the severity grade.

The median treatment duration of the MCD-201 study was 86 months (min; max: 29.3; 94.7). AEs had occurred in all 8 patients up to the present data cut-off from 16 September 2022. Of these, 5 had a severe AE and 7 had a serious adverse event (SAE). There was no therapy discontinuation due to AEs.

The median treatment duration of the MCD-202 study was 17.1 months (min; max: 0.3; 72.2). Severe AEs and SAEs had occurred in all 3 patients up to the present data cut-off from 16 September 2022. There was no therapy discontinuation due to AEs.

Based on the single-arm data on safety, no statement can be made on the extent of the additional benefit of fosdenopterin.

Overall assessment

The benefit assessment of fosdenopterin for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A is based on evaluations of the single-arm MCD-501, -201 and 202 studies.
Results on mortality, morbidity, and side effects are available. No comparative statements can be made due to the single-arm study design. In summary, the quantification of the extent of the additional benefit of fosdenopterin is not possible on the basis of the data presented.
In the overall assessment of the available results, the G-BA categorised the extent of the additional benefit of fosdenopterin for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The present benefit assessment is based on single-arm data. The risk of bias is estimated to be high in view of the lack of comparison at study and endpoint level. In addition, the data basis presented for the benefit assessment shows methodological limitations.
The significance of the evidence is classified as a "hint" overall.

2.1.3 Summary of the assessment

This is the benefit assessment of a new therapeutic indication for the active ingredient fosdenopterin. The medicinal product Nulibry was approved as an orphan drug. The present therapeutic indication assessed is as follows: "NULIBRY is indicated for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A."

The benefit assessment is based on the results of the single-arm MCD-501, -201 and -202 studies. No statements on the extent of the additional benefit of fosdenopterin can be derived on the basis of the results presented due to the single-arm design of the studies. Furthermore, the studies show methodological limitations.

In the dossier, the pharmaceutical company also presented an indirect comparison of fosdenopterin with a natural history cohort without a bridge comparator. This is not used for the benefit assessment due to methodological limitations, in particular with regard to the similarity of the comparator populations, the violation of the ITT principle, a potential immortal time bias and confounder identification.

In the overall assessment, a hint for a non-quantifiable additional benefit of fosdenopterin for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A was identified since the scientific data does not allow quantification.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on the information presented by the pharmaceutical company in the dossier. This is based on an estimate of the percentage of patients with MoCD Type A in those born alive. A SHI percentage is not taken into account.

Owing to the pharmaceutical company's approach, patients who were already diagnosed with MoCD Type A before the year under review and are still alive in the year under review were not included in the estimate.

Overall, the information provided by the pharmaceutical company is subject to uncertainties and tends to be an underestimate.

2.3 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.

If deemed appropriate by the doctor, fosdenopterin can also be administered at home by the patient's caregiver in accordance with section 6.6 of the product information.

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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2025).

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Fosdenopterin	Continuously, 1 x daily	365.0	1	365.0

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.
In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population"[4] and/or "Microcensus 2021 – body measurements of the population"[5] were used as a basis (average body weight of a child < 1 year: 7.6 kg; adult: 77.7 kg).

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Fosdenopterin	6.8 mg (= 0.9 mg/kg BW)	6.8 mg	9.5 mg	365.0	365 x 9.5 mg
Fosdenopterin	69.9 mg	69.9 mg	8 x 9.5 mg	365.0	2,920 x 9.5 mg

4 Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de
5 Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	(= 0.9 mg/kg BW)				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size		Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed						
Fosdenopterin	1	PSI	€ 1,811.11	€ 1.77	€ 235.06	€ 1,574.28
Abbreviations: PSI = powder for solution for injection						

LAUER-TAXE® last revised: 15 August 2025

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be

classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from

the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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.

Justification for the findings on designation in the present resolution:

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.

References:
Product information for fosdenopterin (Nulibry); NULIBRY 9.5 mg; last revised: July 2024

2.6 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. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV. Approval studies include all studies submitted to the regulatory authority in the authorisation dossier for the

assessment of the clinical efficacy and safety of the medicinal product in the therapeutic indication to be assessed.

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 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.

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 11 March 2025, the pharmaceutical company submitted a dossier for the benefit assessment of fosdenopterin to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 16 June 2025 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 7 July 2025.

The oral hearing was held on 28 July 2025.

An amendment to the benefit assessment with a supplementary assessment was submitted on 15 August 2025.

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.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 26 August 2025, and the draft resolution was approved.

At their session on 4 September 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	11 June 2025	Information of the benefit assessment of the G-BA
Working group Section 35a	15 July 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	28 July 2025	Conduct of the oral hearing
Working group Section 35a	5 August 2025 19 August 2025	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	26 August 2025	Concluding discussion of the draft resolution
Plenum	4 September 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 4 September 2025

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

Prof. Hecken