Gemeinsamer Bundesausschuss

Justification

of 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
Omaveloxolone (Friedreich's ataxia, ≥ 16 years)

of 19 September 2024

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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 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 German Social Code, Book Five (SGB V). 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 its 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 its 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 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

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient omaveloxolone on 15 March 2024 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 15 March 2024.

Omaveloxolone for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older 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.

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 evaluate 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 17 June 2024 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 has adopted its 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 G24-06) 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 has 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 omaveloxolone.

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

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Omaveloxolone (Skyclarys) in accordance with the product information

Skyclarys is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.

Therapeutic indication of the resolution (resolution of 19 September 2024):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

Adults and adolescents aged 16 years and older with Friedreich's ataxia

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

Justification:

For the benefit assessment, the pharmaceutical company submitted evaluations from the phase II MOXIe study.

Part 2 of the MOXIe study is a multicentre, randomised, controlled, double-blind study phase to investigate the safety and efficacy of omaveloxolone compared to placebo.

Patients aged ≥ 16 and ≤ 40 years with genetically confirmed Friedreich's ataxia and a modified Friedreich's Ataxia Rating Scale (mFARS) score ≥ 20 and ≤ 80 were enrolled.

There was a 1:1 randomisation to treatment with 150 mg omaveloxolone or placebo, stratified according to the presence of foot deformity in the form of pes cavus. The treatment was administered over a period of 48 weeks, followed by a 4-week safety follow-up.

The evaluations relating to the total number of randomised patients (= ITT population) in part 2 of the MOXIe study are considered relevant for the benefit assessment: A total of 51 patients were assigned to the omaveloxolone arm and 52 patients to the placebo arm.

In the dossier, the pharmaceutical company also presented supportive evaluations on an indirect comparison of omaveloxolone and "best supportive care" (without a bridge comparator) based on data from the open-label extension phase of the MOXIe study and a natural history cohort from the Friedreich Ataxia Clinical Outcome Measures Study (FA-COMS).

Due to methodological limitations with regard to confounder identification and an unclear structural equality between the respective study populations, as well as against the background of a potential selection bias due to the high percentage of study dropouts in part 2 of the MOXIe study, the evaluations based on the indirect comparison are not considered here.

Mortality

Deaths were surveyed as part of the safety assessment. No deaths occurred.

Morbidity

Physical functioning using the modified Friedreich Ataxia Rating Scale (mFARS)

The modified Friedreich Ataxia Rating Scale (mFARS) is used to survey physical functioning in patients with Friedreich's ataxia and comprises four domains (bulbar function, upper limb coordination, lower limb coordination and upright stability). A higher score indicates a more severe physical impairment.

The evaluations of the validated 93-point version of the mFARS subsequently submitted in the written statement procedure are considered relevant for the benefit assessment. There is insufficient information on the validity of the 99-point version.

In addition to the evaluations of the mean change, the dossier also presented data on responder analyses based on the definition of clinical improvement or deterioration by a decrease of ≤ 1.9 or an increase of ≥ 1.9 points on the mFARS. The selected relevance threshold cannot be interpreted on the basis of the literature and also does not correspond to the relevance threshold of 15% of the scale range considered appropriate for the benefit assessment.

The evaluations of the mean change in mFARS at week 48 compared to baseline showed a statistically significant difference in favour of omaveloxolone compared to placebo. The 95% confidence interval of the Hedges' g effect size is not completely outside the irrelevance range from - 0.2 to 0.2, so that it cannot be concluded that the effect is clinically relevant.

General health status using Patient Global Impression of Change (PGI-C)

The PGI-C is used for patient-reported assessment of the change in health status compared to the start of treatment. The question on the change in health status since the start of treatment is answered using a 7-point scale of "very much improved" (= 1), "much improved" (= 2), "minimally improved" (= 3), "no change" (= 4), "minimally worse" (= 5), "much worse" (= 6) and "very much worse" (= 7).

Evaluations of responder analyses based on the definition of an improvement (< 4 points) or deterioration (> 4 points) in the PGI-C are available.

There were no statistically significant differences between omaveloxolone and placebo for either deterioration or improvement at week 48.

Clinical Global Impression using Clinical Global Impression of Change (CGI-C)

The CGI-C is an external assessment scale for surveying changes in the clinical global impression compared to the start of treatment by the investigators. The question on the change in the clinical global impression since the start of treatment is answered using a 7-point scale of "very much improved" (= 1), "much improved" (= 2), "minimally improved" (= 3), "no change" (= 4), "minimally worse" (= 5), "much worse" (= 6) and "very much worse" (= 7).

The investigator's assessment of the change in the health status is not considered to be patient-relevant. In principle, the self-assessment of the concerned subject regarding their health status is favoured over an external assessment in the benefit assessment.

Activities of Daily Living (ADL)

The patient-reported questionnaire "Activities of Daily Living (ADL)" was used in the study to assess limitations in everyday activities.

Using 9 disease-specific items on a scale from 0 (no limitation) to 4 points (unable to perform the activity), patients provide information on limitations in activities, functions and activities of daily living (speech, swallowing, eating food and handling utensils, dressing, personal hygiene, falls, walking, quality of sitting position and bladder function). The total score is the sum of the item values and can range from 0 to 36 points.

The pharmaceutical company presented evaluations of responder analyses with a definition of clinically relevant improvement by a change of ≤ 0.4 points per year as well as analyses of the change at week 48 compared to baseline.

The relevance threshold selected for the responder analyses cannot be interpreted on the basis of the literature and does not correspond to the relevance threshold of 15% of the scale range considered appropriate for the benefit assessment. The evaluations of the change at week 48 compared to the baseline are therefore taken into account here.

There was no statistically significant difference between the treatment arms in these analyses.

Fine motor skills of the upper extremities using the 9-Hole Peg Test (9-HPT)

The 9-Hole Peg Test (9-HPT) is used to survey the fine motor function of the arms and hands. The time a patient takes to remove 9 pegs individually from a container, insert them into holes in a board and put them back into the container is measured. Longer test times reflect a greater impairment of the function of the upper extremities.

Fine motor function is fundamentally patient-relevant in this therapeutic indication. Data on the execution speed (reciprocal value = pegs/second) is presented in the dossier. Evaluations of the time in seconds required to complete the task, which are considered relevant for a meaningful and comprehensible interpretation of the assessment of change in fine motor skills of the upper limbs, are not available.

Functionality of the lower extremities using the Timed 25 Foot Walk Test (T25-FWT)

The Timed 25 Foot Walk Test (T25-FWT) is used to assess walking ability. The time a patient takes to cover a distance of 25 feet (7.6 metres) is measured. Longer test times reflect a greater impairment of walking ability.

The walking ability is fundamentally patient-relevant in this therapeutic indication. The dossier shows data on walking speed. Evaluations of the time in seconds required to complete the task, which are considered relevant for a meaningful and comprehensible interpretation of the assessment of change in walking ability, are not available.

Quality of life

Short Form (36)-health survey (SF-36)

SF-36 is a generic instrument for measuring health-related quality of life, consisting of eight domains and a total of 36 questions. In addition, the 8 domains are summarised into a physical component summary (PCS) score and a mental component summary (MCS) score. For the domain and summary scores, higher values mean a better health-related quality of life.

For the benefit assessment, evaluations of responder analyses with a definition of deterioration as a change from baseline to week 48 of ≤ -9.4 points in the physical component summary score and ≤ -9.6 points in the mental component summary score (corresponding to 15% of the scale range in each case) are presented.

There were no statistically significant differences between the treatment arms for the physical and mental component summary scores of the SF-36.

Side effects

All adverse events (AEs) that occurred after the first administration of the study medication up to 30 days after the last administration of the study medication were taken into account. The severity grading was categorised according to the impairment or complications caused by adverse events.

There were no statistically significant differences between the treatment arms for the overall rates of severe adverse events, serious adverse events (SAEs) and adverse events that led to discontinuation of the study medication. Adverse events of special interest were not pre-specified.

Overall assessment

For the benefit assessment of omaveloxolone for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older, results of the randomised, double-blind MOXIe study part 2 are available, in which omaveloxolone was compared with placebo.

There were no deaths in either treatment arm of the study.

In the morbidity category, there was a statistically significant advantage of omaveloxolone compared to placebo in the endpoint of physical functioning. Based on Hedges' g, it cannot be concluded in this regard that the effect is clinically relevant.

There was no statistically significant difference for the endpoints of general health status and activities of daily living.

With regard to quality of life, the available data show no statistically significant differences in either the physical or mental component summary score of the SF-36.

Regarding side effects, there were also no statistically significant differences in the overall rates of severe and serious adverse events and treatment discontinuation due to adverse events. Adverse events of special interest were not pre-specified.

In summary, no statements on the extent of the additional benefit can be made based on the available data.

In the overall assessment of the available results on the patient-relevant endpoints, the G-BA therefore classifies the extent of the additional benefit of omaveloxolone for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older on the basis of the

criteria in Section 5, paragraph 8 in conjunction with Section 5, paragraph 7, sentence 1, numbers 1 to 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as non-quantifiable because the scientific data basis does not allow quantification.

Significance of the evidence

The MOXIe study part 2 on which the benefit assessment is based has a high risk of bias. This is due to an uneven distribution of baseline characteristics and differences between the treatment arms with regard to the number of premature study discontinuations. An unintended limitation of blinding may also result from the frequent occurrence of specific adverse events in the omaveloxolone arm.

In the overall analysis, the significance of the evidence is classified as a hint.

2.1.3 Summary of the assessment

This is the benefit assessment of the active ingredient omaveloxolone, which is approved for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.

The results of the double-blind randomised MOXIe study part 2, in which omaveloxolone was compared with placebo over a treatment period of 48 weeks, are available for the benefit assessment.

There were no deaths with regard to the endpoint category of mortality.

In the morbidity category, there was a statistically significant advantage of omaveloxolone in the endpoint of physical functioning, but Hedges' g does not indicate that the effect is clinically relevant. There were no statistically significant differences for the endpoints of general health status and activities of daily living.

With regard to quality of life, there were no statistically significant differences between the treatment arms for the physical and mental component summary scores of the SF-36.

There were also no statistically significant differences in the area of side effects for the endpoints of severe or serious adverse events and therapy discontinuation due to adverse events.

Due to the unequal distribution in the baseline characteristics and the differences between the treatment arms in the number of premature study discontinuations as well as against the background of the potentially limited blinding due to the frequent occurrence of specific side effects in the omaveloxolone arm, the risk of bias of the MOXIe study part 2 is assessed as high.

In the overall assessment, a hint for a non-quantifiable additional benefit of omaveloxolone for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older was identified because the scientific data basis 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 provided by the pharmaceutical company in the dossier.

These are based, among other things, on the determination of federal state-specific prevalence rates using a publication[2], which takes into account data from anonymised patient lists of the self-help organisation Deutsche Heredo-Ataxie-Gesellschaft e. V. (DHAG), as well as on information from the Federal Statistical Office on the population status to determine the percentage of patients aged ≥ 16 years.

Limitations of this approach result from uncertainties regarding the data basis on which the prevalence rates are based with regard to the unclear completeness of the patient lists and the limited timeliness. Further limitations result from the lack of consideration of a range and the assumption of the percentage of patients aged ≥ 16 years based on the total population.

Overall, the data on the number of patients is subject to uncertainties.

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 Skyclarys (active ingredient: omaveloxolone) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 1 August 2024):

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

Treatment with omaveloxolone should only be initiated and monitored by doctors experienced in treating patients with Friedreich's ataxia.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 August 2024).

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				
Omaveloxolone	1 x daily	365.0	1	365.0

2 Vankan P. Prevalence gradients of Friedreich's Ataxia and R1b haplotype in Europe co-localize, suggesting a common Palaeolithic origin in the Franco-Cantabrian ice age refuge. J Neurochem 2013; 126: 11-20. https://doi.org/10.1111/jnc.12215

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 co-morbidities) are not taken into account when calculating the annual treatment costs.

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					
Omaveloxolone	150 mg	150 mg	3 x 50 mg	365.0	1,095 x 50 mg

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 fixed reimbursement rates 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						
Omaveloxolone	270	HC	€ 85,366.38	€ 2.00	€ 4,872.00	€ 80,492.38
Abbreviations: HC = hard capsules						

LAUER-TAXE® last revised: 1 August 2024

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 designates 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 has 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 has 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 has 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:

Adults and adolescents aged 16 years and older with Friedreich's ataxia

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

References:
Product information for omaveloxolone (Skyclarys); Skyclarys™ 50 mg; last revised: February 2024

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 15 March 2024, the pharmaceutical company submitted a dossier for the benefit assessment of omaveloxolone 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 17 June 2024 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 8 July 2024.

The oral hearing was held on 22 July 2024.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 7 August 2024.

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 27 August 2024, and the proposed resolution was approved.

At its session on 19 September 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 June 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	17 July 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	22 July 2024	Conduct of the oral hearing

Working group Section 35a	31 July 2024 14 August 2024	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	27 August 2024	Concluding discussion of the draft resolution
Plenum	19 September 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 September 2024

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

Prof. Hecken