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 Tofersen (amyotrophic lateral sclerosis (ALS))

of 19 December 2024

Contents

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 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 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 tofersen on 1 July 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 27 June 2024.

Tofersen for the treatment of amyotrophic lateral sclerosis (ALS) 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 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 1 October 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 G24-17) 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 tofersen.

[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 Tofersen (Qalsody) in accordance with the product information

Qalsody is indicated for the treatment of adults with amyotrophic lateral sclerosis (ALS), associated with a mutation in the superoxide dismutase 1 (SOD1) gene.

Therapeutic indication of the resolution (resolution of 19 December 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 tofersen is assessed as follows:

Adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene

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 III VALOR study. This is a multicentre, randomised, controlled, double-blind study to investigate the safety and efficacy of tofersen compared to placebo.

Patients ≥ 18 years of age with amyotrophic lateral sclerosis (ALS) and confirmed SOD1 mutation were enrolled.

There was a 2:1 randomisation to treatment with tofersen (N = 72) or placebo (N = 36), each applied intrathecally. Stratification was based on the presence of prognostic criteria for rapid disease progression (based on predefined SOD1 mutation forms and ALSFRS-R dynamics prior to randomisation) and on the use of edaravone or riluzole at baseline. With the simultaneous application of both active ingredients, it was stratified based on edaravone.

Patients who had already received a stable dose of riluzole for at least 30 days before the start of the study or edaravone (not approved in Germany) for at least 60 days (2 treatment cycles) before the start of the study should continue their respective pretreatment as is in both study arms.

The study comprises a 4-week screening phase, a 28-week treatment phase including a 4-week titration phase (3 loading doses at intervals of 2 weeks each and 5 maintenance doses at intervals of 4 weeks each) and a follow-up phase of up to 4 weeks.

The final data cut-off from 16 July 2021 is available for the VALOR RCT.

Following the treatment phase, patients could optionally enter an unblinded single-arm extension study 233AS102 (OLE (open-label extension) study), in which all patients receive tofersen.

Integrated analysis based on the VALOR RCT and the OLE

In the dossier, the pharmaceutical company presented the results of an integrated analysis based on data from the VALOR RCT and the OLE. The evaluations are based on interim data cut-offs from January 2022 and February 2023; the results of the final data cut-off from August 2024 are not available.
The integrated analysis is a comparison of patients who already received tofersen during the VALOR RCT and continued to receive tofersen during the OLE ("early tofersen initiation") versus patients who received placebo during the VALOR RCT and have been treated with tofersen since the transition to the OLE ("late tofersen initiation"). The initial randomisation and blinding of allocation in the VALOR RCT were maintained. A total of 95 patients from the VALOR RCT were transferred to the OLE study (63 patients from the intervention arm and 32 patients from the comparator arm).

The database on which the integrated analysis is based is subject to major uncertainty. The patients who initially received placebo for (at least) 28 weeks switched to treatment with tofersen at the end of the VALOR RCT. All patients received tofersen for the remaining period of the entire duration of observation, which amounted to a median of 3.4 years. Thus, beyond the duration of the comparative VALOR RCT, there are no data that allow a comparison of tofersen versus placebo or another active ingredient.

The results of the interim data cut-off from February 2023 are not fully available in the dossier. In addition, information on study and patient characteristics is missing, e.g. on the number and reasons for study discontinuations and on the observation periods. The simultaneity of the treatment arms cannot be assessed against the background of the partially delayed transition from the RCT to the OLE study.

With regard to the survival time analyses, there were also longer observation times for patients without a risk of rapid disease progression ("non-mITT population") than for patients with a risk of rapid disease progression ("mITT population") due to different recruitment times within the ITT population. Information on the corresponding median observation periods and on the consideration of these differences in the evaluation of the survival time analyses is not available. With regard to the responder analyses on endpoints in the morbidity and quality of life category, no information is available on the suitability of the imputation methodology using multiple imputation, including the underlying assumptions, and on study discontinuations.

Against the background of the limitations described, the evaluations based on the integrated analysis are not considered in the present benefit assessment.

VALOR RCT

Mortality

In the VALOR RCT, one death (1.4%) occurred in the intervention arm overall. Due to the low number of events, the median time to death could not be determined.

Morbidity

The pharmaceutical company submitted responder analyses for several endpoints in the morbidity and quality of life category, which indicate the percentage of patients with a deterioration or improvement by at least 15% of the respective scale range. In view of the progressive course of the disease, deterioration of the symptomatology can be assumed in this therapeutic indication.

Motor functioning using the Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R)

The ALSFRS-R is an external assessment tool for assessing motor functioning in patients with ALS and comprises 4 subscales, each with 3 items relating to the aspects of gross motor skills, fine motor skills, bulbar symptoms (impairment of speech, swallowing or salivation) and respiratory function. A lower score indicates greater functional impairment.

The total ALSFRS-R score was collected as the primary endpoint in the study. The validity with regard to the formation of a total ALSFRS-R score could neither be demonstrated in the development study nor in current validation studies. In contrast, with regard to the subscores, validity and reliability are considered sufficient on the basis of the available data.
Due to the limitations described above, the evaluations based on the total score are not considered in this benefit assessment, but only presented additionally.

For the subscores on gross motor skills, fine motor skills and respiratory function, there were no statistically significant differences between the treatment arms in terms of improvement and deterioration. For the improvement in the subscore for bulbar symptoms (impairment of speech, swallowing or salivation), there was a statistically significant disadvantage of tofersen compared to placebo, whereas there was no statistically significant difference in terms of deterioration.
Since a deterioration in motor functioning is to be assumed in the present therapeutic indication with regard to the progressive course of the disease, the evaluations on deterioration in particular are considered relevant for the present benefit assessment in this specific case. The disadvantageous effect in the improvement of the subscore for bulbar symptoms is not used for the assessment of the additional benefit, taking into account the comparison with placebo and the low absolute event numbers.

Time to death or permanent ventilation

For the VALOR RCT, collection of the time to death or permanent ventilation was intended. "Continuous ventilation" was defined as invasive or non-invasive ventilation for ≥ 22 hours per day for ≥ 21 days without interruption; this was collected using a ventilation diary. Ventilation was performed at the discretion of the principal investigator.

In total, permanent ventilation occurred in 3 patients in the intervention arm and 2 in the comparator arm. For the composite endpoint "time to death or permanent ventilation", 4 events occurred in the intervention arm and 2 events in the comparator arm. Due to the low number of events, the median times to each event could not be determined.

There were no statistically significant differences between the treatment arms for the endpoints "time to permanent ventilation" and "time to death or permanent ventilation".

Fatigue - Fatigue Severity Scale (FSS)

The Fatigue Severity Scale (FSS) is a self-assessment tool and is used to collect fatigue symptoms. It comprises 9 questions on the severity of fatigue and its impact on activities (e.g. impairment of daily activities such as work, family or social life) with a reference period of 2 weeks. A total score of 63 points can be attained. Higher values indicate more pronounced fatigue symptomatology.

There were no statistically significant differences between the treatment arms for the improvement and deterioration by ≥ 15% of the scale range each.

General health status - EuroQol Five Dimension Questionnaire - Visual Analogue Scale (EQ-5D VAS)

The visual analogue scale of the EQ-5D is used to assess the general health status.

There were no statistically significant differences between the treatment arms for the improvement and deterioration by ≥ 15% of the scale range each.

Activities of daily living - Work Productivity and Activity Impairment Questionnaire (WPAI) item 6

The WPAI is used to collect impairments to work productivity and activities. Health economic aspects such as the endpoints of absenteeism and presenteeism collected by the WPAI are not considered patient-relevant and are therefore not taken into account in this benefit assessment. However, the impairment of daily activities due to the disease (question 6) addresses a patient-relevant aspect.

There were no statistically significant differences between the treatment arms for the improvement and deterioration by ≥ 15% of the scale range each.

Quality of life

36-item Short Form 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. A physical component summary (PCS) score and a mental component summary (MCS) score are formed from the 8 domains. For the domain and summary scores, higher scores mean a higher health-related quality of life.

There were no statistically significant differences between the treatment arms for the deterioration and improvement by ≥ 15% of the scale range in the physical and mental component summary scores.

Side effects

All adverse events (AEs) that occurred after the first administration of the study medication until the end of the VALOR RCT (week 28) or until the premature study discontinuation were collected.

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 tofersen for the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene results of the randomised, double-blind VALOR study comparing tofersen versus placebo are available.

Results of the integrated analysis presented by the pharmaceutical company based on data from the VALOR RCT and the single-arm open-label extension study 233AS102 are not considered here as they do not allow a comparison of tofersen versus placebo or another active ingredient and have methodological limitations.

In the VALOR study, one death occurred among patients treated with tofersen. In the mortality category, there are no relevant differences for the benefit assessment.

In the morbidity category, there were no statistically significant differences for the subscores of the ALSFRS-R for gross motor skills, fine motor skills and respiratory function in relation to an improvement or deterioration by 15% of the scale range. In the ALSFRS-R subscore for bulbar symptoms (impairment of speech, swallowing or salivation), there was a statistically significant disadvantage of tofersen compared to placebo in terms of improvement, whereas there was no statistically significant difference for deterioration. Since a deterioration in motor functioning is to be assumed in the present therapeutic indication with regard to the progressive course of the disease, the evaluations on deterioration in particular are considered relevant for the present benefit assessment in this specific case. The disadvantageous effect in the improvement of the subscore for bulbar symptoms is not used for the assessment of the additional benefit, taking into account the comparison with placebo and the low absolute event numbers.

For the endpoints of time to death or permanent ventilation, fatigue, general health status and activities of daily living, there were no statistically significant differences for improvement and deterioration.

With regard to quality of life, the available data show no statistically significant differences in terms of improvement and deterioration 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 tofersen for the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene as non-quantifiable 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) since the scientific data does not allow quantification.

Significance of the evidence

The present benefit assessment is based on evaluations of the VALOR RCT. The risk of bias of the study is unclear. This is due to incomplete information on baseline characteristics with indications of a possible uneven distribution and missing information on protocol violations. Furthermore, there are limitations with regard to stratification according to the presence of ALSFRS-R and SOD1 gene status-based prognostic criteria for rapid disease progression, which according to the information provided by the pharmaceutical company was unsuitable for balancing the study arms with regard to disease progression.

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

2.1.3 Summary of the assessment

This is a benefit assessment of the active ingredient tofersen, which is approved for the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene.

The benefit assessment is based on the results of the double-blind randomised controlled trial VALOR, in which tofersen was compared with placebo over a treatment period of 28 weeks (including 4 weeks of titration).

With regard to mortality, there was no relevant difference for the benefit assessment.

In the morbidity category, there were no relevant differences for the benefit assessment in the ALSFRS-R subscores for gross motor skills, fine motor skills and respiratory function. In the subscore for bulbar symptoms, there was a statistically significant disadvantage of tofersen compared to placebo in terms of improvement by 15% of the scale range; there was no statistically significant difference in terms of deterioration. Since a deterioration in motor functioning is to be assumed in the present therapeutic indication with regard to the progressive course of the disease, the evaluations on deterioration in particular are considered relevant for the present benefit assessment in this specific case. The disadvantageous effect in the improvement of the subscore for bulbar symptoms is not used for the assessment of the additional benefit, taking into account the comparison with placebo and the low absolute event numbers.

For the endpoints of time to death or permanent ventilation, fatigue, general health status and activities of daily living, there were no relevant differences for the benefit assessment.

With regard to quality of life, there were no relevant differences for the benefit assessment in the physical and mental summary scores of the SF-36.

Also with regard to side effects, there were no relevant differences for the benefit assessment for the severe or serious adverse events and therapy discontinuation due to adverse events.

The risk of bias of the VALOR study is assessed as unclear due to uncertainties regarding a possible unequal distribution of baseline characteristics, missing information on protocol violations and limitations with regard to stratification according to ALSFRS-R and SOD1 gene status-based criteria for rapid disease progression.

In the overall assessment, a hint for a non-quantifiable additional benefit of tofersen for the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene 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 estimate of patient numbers presented by the pharmaceutical company in the dossier is subject to uncertainty overall, particularly with regard to the database for determining the prevalence of ALS in Germany.
The resolution is therefore based on the estimate of patient numbers in IQWiG's assessment (G24-17), taking into account the information provided by the pharmaceutical company in the dossier.

In the first step, IQWiG's assessment procedure is based on determining the prevalence of ALS in Germany using an Orphanet publication[2] (lower limit) and a prevalence estimate based on German registry data for the Swabia region[3] (upper limit).
Analogous to the procedure of the pharmaceutical company in the dossier, the next step is to derive the percentage of sporadic or familial ALS cases, on the basis of which the respective percentage of SOD1-associated diseases is then determined using a meta-analysis[4] with reference to European populations and a cohort study from Germany[5].

Limitations of this approach arise due to uncertainties with regard to the determined percentages of SOD1 mutations, as the literature also reports higher SOD1 percentages in familial and sporadic ALS cases.

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 Qalsody (active ingredient: tofersen) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 1 November 2024):

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

Treatment with tofersen should only be initiated and monitored by doctors experienced in the therapy of amyotrophic lateral sclerosis.

This medicinal product was approved under “exceptional circumstances”. This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The European Medicines Agency will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

[2] Orphanet Report Series. Prevalence and incidence of rare diseases: Bibliographic data. 2023.
[3] Rosenbohm A, Peter RS, Erhardt S et al. Epidemiology of amyotrophic lateral sclerosis in Southern Germany. J Neurol 2017; 264(4): 749-757. https://doi.org/10.1007/s00415-017-8413-3.
[4] Zou ZY, Zhou ZR, Che CH et al. Genetic epidemiology of amyotrophic lateral sclerosis: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2017; 88(7): 540-549. https://doi.org/10.1136/jnnp-2016-315018.
[5] Ruf WP, Boros M, Freischmidt A et al. Spectrum and frequency of genetic variants in sporadic amyotrophic lateral sclerosis. Brain Commun 2023; 5(3): fcad152. https://doi.org/10.1093/braincomms/fcad152.

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 December 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				
Tofersen	Continuously, every 28 days	13	1	13

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					
Tofersen	100 mg	100 mg	1 x 100 mg	13	13 x 100 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 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						
Tofersen 100 mg	1	SFI	€ 28,931.47	€ 2.00	€ 1,648.99	€ 27,280.48
Abbreviations: SFI = solution for injection						

LAUER-TAXE® last revised: 1 December 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.

Additionally required SHI services for the application of the medicinal product to be assessed result from the lumbar puncture as part of the intrathecal application according to the product information. At the time of the resolution, however, there is no fee structure item in the Uniform Value Scale for an intrathecal therapeutic application, which is why the resulting costs are non-quantifiable.

Type of service	Costs per treatment	Number of treatments/ patient/ year	Costs per patient per year
Lumbar puncture	non-quantifiable	13	non-quantifiable

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.

<u>Concomitant active ingredient</u>

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 with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene

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 tofersen (Qalsody); Qalsody™ 100 mg; last revised: July 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 27 June 2024, the pharmaceutical company submitted a dossier for the benefit assessment of tofersen 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 1 October 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 22 October 2024.

The oral hearing was held on 11 November 2024.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 29 November 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 10 December 2024, and the draft resolution was approved.

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

Chronological course of consultation

Session	**Date**	**Subject of consultation**
Subcommittee Medicinal products	24 September 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	6 November 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 November 2024	Conduct of the oral hearing
Working group Section 35a	20 November 2024 4 December 2024	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 Medicinal products	10 December 2024	Concluding discussion of the draft resolution
Plenum	19 December 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 December 2024

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

Prof. Hecken