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)
Vamorolone (Duchenne muscular dystrophy, ≥ 4 years)

of 4 July 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 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 vamorolone on 15 January 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 January 2024.

Vamorolone for the treatment of Duchenne muscular dystrophy (DMD) in patients 4 years and older 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 15 April 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 G12-01) 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 approval 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 vamorolone.

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 Vamorolone (Agamree) in accordance with the product information

AGAMREE is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older.

Therapeutic indication of the resolution (resolution of 4 July 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 vamorolone is assessed as follows:

For patients 4 years and older with Duchenne muscular dystrophy, there is a hint for a non-quantifiable additional benefit, since the scientific data does not allow a quantification.

Justification:

For the assessment of the extent of the additional benefit: of vamorolone for patients aged 4 years and older with Duchenne muscular dystrophy (DMD), the pharmaceutical company presented the results of the label-enabling VB15-004 (VISION-DMD) study and an indirect comparison of the long-term data of VISION-DMD with the FOR-DMD study.

The VISION-DMD study is a randomised, double-blind, placebo and active-controlled phase IIb study comparing two doses of vamorolone (2.0 mg/kg/day and 6.0 mg/kg/day) with prednisone (0.75 mg/kg/day) or placebo.

121 male patients aged ≥ 4 years and < 7 years and weighting > 13.0 kg and ≤ 39.9 kg at the screening visit were enrolled in the study. In addition, the participants had to be able to walk independently and without assistance and complete the endpoint "time to stand from supine" (TTSTAND) without assistance in < 10 seconds.

The first and comparative treatment phase lasted 24 weeks. The dose of prednisone and placebo was then reduced in a four-week transition phase before the patients in all treatment groups received one of the two doses of vamorolone once daily for 20 weeks in the second treatment phase.

The study was conducted between June 2018 and August 2021 in eleven countries (including Europe).

In its statement, the pharmaceutical company argued that glucocorticoid therapy with a standardised dose did not correspond to the regular treatment of all DMD patients. In the written statement procedure, two clinical experts point out that treatment with glucocorticoids is offered from the age of 4-5 years, but that some parents decide against such

treatment. The Society for Neuropaediatrics states in the written statement procedure that a comparison with placebo would not correspond to the current therapy standard.
Since regular treatment with glucocorticoids can therefore be assumed for the majority of patients in the present therapeutic indication, the comparison of the intervention group vamorolone with a dosage strength of 6 mg/kg/day (according to the product information) versus the control group prednisone 0.75 mg/kg/day at the end of treatment phase 1 (week 24) is considered in the benefit assessment.

The FOR-DMD study is a randomised controlled trial in which three corticosteroid dosage regimens were investigated in corticosteroid-naive patients aged 4-7 years with DMD. For the indirect comparison with the VISION-DMD study, the groups prednisone 0.75 mg/kg/day and deflazacort 0.9 mg/kg/day were considered. The indirect comparison is not used in the benefit assessment because, among other things, the selection of confounders is not described, information on the operationalisation of the endpoints is missing and insufficient information on the quality of the indirect comparison (e.g. information on the overlap of the propensity scores) is available.

Mortality

In the VISION-DMD study, no deaths occurred during treatment phase 1 (week 24).

Morbidity

Time-to-stand test (TTSTAND)
The TTSTAND endpoint measures the time (in seconds) it takes a patient to get from a supine position on the floor to an upright standing position ("time to stand").

The endpoint is considered patient-relevant in this therapeutic indication.
Two operationalisations are available for the TTSTAND: "time to stand" (TTSTAND), specified in seconds and "stand-up velocity" (TTSTAND velocity), specified as rises/seconds.

Due to limitations, the "stand-up velocity", recorded as "TTSTAND velocity", including the responder analyses conducted post hoc, is not taken into account for the benefit assessment. Fluctuations in the "time to stand" (TTSTAND) in the upper measuring range, for example, are not adequately reflected by the "stand-up velocity". In addition, the variability in the response time of the test subject when measuring low "time to stand" values has a significant effect on the stand-up velocity. The duration of the rise processes, recorded as "TTSTAND", in seconds can be determined linearly over the entire measuring range. In addition, the duration (in seconds) required by the patient to rise from the supine position is of more clinical relevance than the velocity for assessing the change in function in this therapeutic indication.

Therefore, the pre-specified analyses of the "time to stand" are expressed in seconds in the present benefit assessment.

For the endpoint of "time to stand" (TTSTAND), no statistically significant differences between the treatment groups were detected at week 24.

Walking/ running 10 m (TTRW)

For the endpoint "walking/ running 10 m" (TTRW), the time required by the patient to walk or run 10 m is measured.

The endpoint is considered patient-relevant in this therapeutic indication.

There are two operationalisations for the "walking/ running distance of 10 m": "Time to walk/ run 10 m" (time to run or walk: TTRW), given in seconds, and "walking/ running speed over 10 m" (TTRW velocity), given in metres/seconds.

In the present benefit assessment, the analyses on the " time to walk/run 10 m" (TTRW) are preferred (*see comments on the TTSTAND endpoint*). The "10 m run/walk velocity" (TTRW velocity) including the responder analyses calculated post hoc are not shown due to the limitations mentioned.

The pharmaceutical company subsequently submitted analyses on the "Time to run/walk 10 m " (TTRW) for the ITT population in the written statement procedure.

There are no statistically significant differences between the treatment groups.

Climbing 4 stairs(TTCLIMB)

The endpoint "time to climb 4 stairs" (TTCLIMB) measures the time the patient needs to climb four stairs.

The endpoint is considered patient-relevant in this therapeutic indication.

Two operationalisations are available for "time to climb 4 stairs": "time for climbing 4 stairs" (time to climb: TTCLIMB), given in seconds, and "velocity to climb 4 stairs" (TTCLIMB velocity), given in stairs/seconds.

In the present benefit assessment, the analyses on the "time to climb 4 stairs" (TTCLIMB) are preferred (*see comments on the TTSTAND endpoint*). The "velocity for climbing 4 stairs" (TTCLIMB velocity) including the post hoc responder analyses are not shown due to the limitations mentioned.

The pharmaceutical company subsequently submitted analyses on the "time for climbing 4 stairs" (TTCLIMB) for the ITT population in the written statement procedure. No descriptive data could be identified for the two survey time points (baseline and week 24). A conclusive assessment of the results is therefore not possible.

There are no statistically significant differences between the treatment groups.

6-minute walking test (6MWT)

The 6-minute walk test (6MWT) is used to examine physical functioning and measures the distance a patient can walk within 6 minutes. The endpoint is considered patient-relevant in this therapeutic indication.

The 6MWT was only performed if the patient's "time run/walk 10 m" (TTRW) was ≤ 25 seconds. According to information provided by the pharmaceutical company in the written statement procedure, this applied to all patients.

In the written statement procedure, the pharmaceutical company submitted data on the reasons for missing values at baseline and week 24 for the 6MWT. According to the data, around 16% of the data is missing at baseline in both study arms. Due to the multiple imputation procedure chosen by the pharmaceutical company, this limitation is not considered to be restrictive for the evaluation.

For the "6MWT" endpoint, no statistically significant differences between the treatment groups were detected at week 24.

Functional performance (NSAA)

Functional performance was assessed using the North Star Ambulatory Assessment (NSAA) clinical rating scale by a clinical expert who assesses the walking ability of male patients with DMD. Limitations in functional performance, especially walking ability, are considered patient-relevant. However, due to uncertainties in the operationalisation (possible double collection of the two items TTSTAND and TTRW included in the NSAA) and limited information on reliability, validity and sensitivity to change, the endpoint is not considered in the benefit assessment.

Physical functioning (PODCI)

The "Paediatric Outcomes Data Collection Instrument (PODCI)" is an instrument for assessing general health, pain and the ability to lead a routine and active lifestyle. The endpoint is considered a patient-relevant endpoint in this case.

However, the PODCI is not considered in the benefit assessment due to insufficient sensitivity to change, the complete survey of the individual subscales depending on the age of the patients, and unclear patient relevance of the "satisfaction" subscale.

Quality of life

No data on quality of life was assessed.

Side effects

During treatment phase 1 (week 24), one severe adverse event (AE) (preferred term "aggression") and one treatment discontinuation due to AE occurred in one patient in the prednisone treatment arm; there were no significant differences between the treatment groups. No serious AEs occurred during this period in the VISION-DMD study.

Body height, body weight, body mass index (BMI)

Anthropometric parameters were surveyed as safety endpoints in the study. The recommended long-term use of glucocorticoids restricts the development of patients. The administration of glucocorticoids can also lead to severe weight gain and growth retardation or growth arrest[2]. The endpoints of body height and body weight are considered patient-

2 Biggar WD, Skalsky A, McDonald CM.: Comparing Deflazacort and Prednisone in Duchenne Muscular Dystrophy. J Neuromuscul Dis. 2022;9(4

relevant in this indication. Data adjusted for age and sex (z-scores) are preferred over absolute values.

The endpoint of BMI (z-score) is a composite endpoint consisting of the endpoints of body height and body weight, both of which are presented in the benefit assessment. The endpoint of BMI (z-score) is therefore not additionally considered in the benefit assessment.

Age and gender-adjusted z-scores were calculated for the endpoints of body height and body weight. The z scores reflect the number of standard deviations (SD) of a value from the normal mean scores, standardised by age and sex. The data were presented as SD values above or below the age-specific reference (≙ 0). The reference tables of the "Centers for Disease Control and Prevention" (CDC) were used.

At week 24, there was a statistically significant difference in favour of vamorolone 6.0 mg/kg/day compared to prednisone 0.75 mg/kg/day for the endpoint of body height (z-scores).

For the endpoint of body weight (z-score), there was a statistically significant difference to the disadvantage of vamorolone 6.0 mg/kg/day compared to prednisone 0.75 mg/kg/day.

For the endpoint of body height and body weight, there are differences or, in some cases, imbalances between the treatment arms at baseline. Comparator data for both endpoints are only available for a relatively short period of 24 weeks. Therefore, it cannot be concluded that the significant differences for the endpoints of body height and body weight are clinically relevant effects.

Overall assessment/ conclusion

The present benefit assessment is based on the results of the randomised, double-blind, placebo and active-controlled phase IIb VB15-004 study (VISION-DMD), which investigated the administration of two doses of vamorolone versus prednisone or placebo. For the benefit assessment, the comparison of vamorolone in the approved dosage with the prednisone control group at the end of treatment phase 1 (week 24) is taken into account. Results from the categories of mortality, morbidity and side effects are available.

No statements can be made on the extent of the additional benefit for the mortality category as no deaths occurred in the study.
In the endpoint category of morbidity, there were no significant differences between the treatment groups for the endpoints of time-to-stand test (TTSTAND), time to /run/walk 10 m (TTRW), time to climb 4 stairs (TTCLIMB) and 6-minute walk test (6MWT). Likewise, no statements on the extent of additional benefit can therefore be derived for the morbidity category.
In the side effects category, there were no significant differences between the treatment groups for the severe AEs and therapy discontinuations due to AEs. Serious AEs did not occur.
For the anthropometric parameters collected as safety endpoints, there was a statistically significant difference to the disadvantage of vamorolone for the endpoint of body height (z-

scores) and a statistically significant difference to the disadvantage of vamorolone for the endpoint of body weight (z-score). Taking into account imbalances in the baseline values and the availability of comparator data for the endpoints of body height and body weight over a relatively short period of 24 weeks, it cannot be concluded that these are clinically relevant effects. Likewise, no statements on the extent of additional benefit can therefore be derived for the side effects category.

The risk of bias of the VB15-004 study is considered unclear.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Agamree" with the active ingredient vamorolone. Vamorolone is approved as an orphan drug for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older.
The present benefit assessment is based on the results of the randomised, double-blind, placebo and active-controlled phase IIb VB15-004 study (VISION-DMD), which investigated the administration of two doses of vamorolone versus prednisone or placebo, as well as an indirect comparison of the long-term data of VISION-DMD with the FOR-DMD study. The indirect comparison with the FOR-DMD study, which investigated three corticosteroid dosage regimens, was not included in the benefit assessment due to missing information on confounders and operationalisation of the endpoints, among other reasons.
For the benefit assessment, the comparison of vamorolone in the approved dosage with the prednisone control group at the end of treatment phase 1 (week 24) is taken into account. Results from the categories of mortality, morbidity and side effects are available.

No statements can be made on the extent of the additional benefit for the mortality category as no deaths occurred in the study.
In the endpoint category of morbidity, there were no significant differences between the treatment groups for the endpoints of time-to-stand test (TTSTAND), time to /run/walk 10 m (TTRW), time to climb 4 stairs (TTCLIMB) and 6-minute walk test (6MWT). Likewise, no statements on the extent of additional benefit can therefore be derived for the morbidity category.
In the side effects category, there were no significant differences between the treatment groups for the severe AEs and therapy discontinuations due to AEs. Serious AEs did not occur. For the anthropometric parameters collected as safety endpoints, there was a statistically significant difference to the disadvantage of vamorolone for the endpoint of body height (z-scores) and a statistically significant difference to the disadvantage of vamorolone for the endpoint of body weight (z-score). Taking into account imbalances in the baseline values and the availability of comparator data for the endpoints of body height and body weight over a relatively short period of 24 weeks, it cannot be concluded that these are clinically relevant effects. Likewise, no statements on the extent of additional benefit can accordingly be derived for the side effects category.

Therefore, the overall assessment shows a non-quantifiable additional benefit for patients aged 4 years and older with Duchenne muscular dystrophy 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 patient numbers stated in the pharmaceutical company's dossier are subject to a high degree of uncertainty. It is unclear whether the two meta-analyses used to calculate the prevalence, which use comparable studies from 1977 to 2005 from Europe and North Africa, can be applied to the current population in Germany. In addition, the meta-analyses used show a high degree of scattering between the individual estimates. The G-BA therefore takes into account the patient numbers from the IQWiG assessment, taking into account other sources and applying a lower limit from the incidence data from Orphanet (www.orpha.net) and an upper limit from the incidence data from König et al. from 2019[3].

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 Agamree (active ingredient: vamorolone) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 9 February 2024):

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

Treatment with vamorolone should only be initiated and monitored by doctors experienced in treating Duchenne muscular dystrophy.

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 June 2024).

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.

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.

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

3 König K, Pechmann A, Thiele S et al. De-duplicating patient records from three independent data sources reveals the incidence of rare neuromuscular disorders in Germany. Orphanet J Rare Dis 2019; 14(1): 152.

the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The active ingredient vamorolone is approved for patients 4 years and older according to the product information. The recommended dose is 6 mg vamorolone per kilogram of body weight once daily for patients with a body weight of up to 40 kg. For patients weighing over 40 kg, the recommended dose is 240 mg vamorolone (equivalent to 6 ml) once daily. Depending on individual tolerability, the daily dose can be titrated down to 4 mg/kg/day or 2 mg/kg/day.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics of the Microcensus[4] 2017 and 2021 were used as a basis (average body weight of a four-year-old boy: 18.8 kg; average body weight of an adult male: 85.8 kg). The lower consumption limit was based on a dosage range of 2 mg/kg/day and 6 mg/kg/day for a four-year-old boy, and the upper limit was based on a dosage range of 2 mg/kg/day and 240 mg once daily for an adult male.

Treatment period:

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

Consumption:

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					
Patients aged 4 years/ body weight up to 40 kg					
Vamorolone	36 mg = 0.9 ml - 108 mg = 2.7 ml	1 x 0.9 ml - 1 x 2.7 ml	1 x 0.9 ml - 1 x 2.7 ml	365.0	365 x 0.9 ml - 365 x 2.7 ml
Patients with a body weight over 40 kg					

4 Federal Health Reporting. Average body measurements of the population (2017 and 2021: aged 1 year and older and 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
Vamorolone	80 mg = 2 ml - 240 mg = 6 ml	1 x 2 ml - 1 x 6 ml	1 x 2 ml - 1 x 6 ml	365.0	365 x 2 ml - 365 x 6 ml

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:

Patients aged 4 years and older with Duchenne muscular dystrophy

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					
Vamorolone 40 mg	100 ml SAE	€ 6,799.01	€ 2.00	€ 385.00	€ 6,412.01
Abbreviations: SAE: oral suspension					

LAUER-TAXE® last revised: 15 June 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 information 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:

Patients aged 4 years and older with Duchenne muscular dystrophy

- 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 vamorolone (AGAMREE); AGAMREE® 40 mg/ml oral suspension; last revised: December 2023

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 January 2024, the pharmaceutical company submitted a dossier for the benefit assessment of vamorolone 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 15 April 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 6 May 2024.

The oral hearing was held on 27 May 2024.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 17 June 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 25 June 2024, and the proposed resolution was approved.

At its session on 4 July 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 April 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	14 May 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 May 2024	Conduct of the oral hearing
Working group Section 35a	4 June 2024 18 June 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	25 June 2024	Concluding discussion of the draft resolution
Plenum	4 July 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 4 July 2024

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

Prof. Hecken