Justification

Gemeinsamer Bundesausschuss

to the resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Lanadelumab

of 1 August 2019

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 a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999, 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 medicinal benefit in relation to the appropriate comparator therapy need not 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 evaluation of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V in conjunction with the Chapter 5, Sections 5 et seq. of the Rules of Procedure, G-BA (VerfO) has not been carried out. Only the extent of the additional benefit has to be demonstrated.

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 retail prices including VAT exceeds €50 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, subsection 1–6 VerfO, in particular regarding the additional medicinal 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of 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, in the case of orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided by the G-BA is evaluated exclusively on the basis of the approval studies.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate given to the IQWiG in its 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 in such a way that, in the case of orphan drugs, IQWiG is only commissioned to carry out a benefit assessment in case of a previously defined comparator therapy when the sales volume of the drug concerned has exceeded the legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (*cf* Section 35a, paragraph 1, sentence 12 SGB V. 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 shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the Internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient lanadelumab in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the

G-BA (VerfO) is 1 February 2019. 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, number 1 VerfO on 31 January 2019.

Lanadelumab for the treatment of hereditary angiooedema is authorised as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999.

According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be already proven by the marketing authorisation. The extent of the additional benefit is 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 2 May 2019 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. An oral hearing was also 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 G19-04) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for 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 through 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of lanadelumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of lanadelumab (Takhzyro®) in accordance with the product information

Takhzyro is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.

2.1.2 Extent of the additional benefit

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

Lanadelumab provides a considerable additional benefit for patients 12 years of age and older with recurrent attacks of hereditary angiooedema (HAE).

1 General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

Justification:

For the assessment of the extent of the additional benefit, the pharmaceutical company submits the studies DX-2930-03 (HELP study), DX-2930-04 (HELP extension study) and DX-2930-02, which are based on marketing authorisation.

The randomised, double-blind, placebo-controlled Phase III HELP study is used for the benefit assessment. The randomised, double-blind, placebo-controlled Phase Ib study DX-2930-02 is not considered because of non-approval compliant doses of lanadelumab. The open-label Phase III extension study DX-2930-04 (HELP Study Extension) is not included in the benefit assessment on the basis of the non-approved lanadelumab dosing scheme and the lack of a control group because no statements on the additional benefit of lanadelumab beyond the significance of the results of the directly comparative HELP study are to be expected.

The RCT HELP study included patients with HAE type I or II aged 12 years and older with at least one confirmed HAE attack within four weeks during the admission phase. HAE patients who used a long-term prophylaxis to prevent HAE attacks (C1-INH, attenuated androgens, anti-fibrinolytics) underwent a washout period of at least two weeks prior to the study because taking a long-term prophylaxis until ≤ 2 weeks prior to the inclusion of the study was an exclusion criterion. The washout period was followed by a four- to eight-week intake phase, during which the rate of HAE attacks before the start of treatment was recorded. Patients who met the inclusion criteria in the admission phase continued with a 26-week treatment phase. A total of 126 patients were randomised to the placebo arm or the three intervention arms (lanadelumab) with different doses (300 mg every 2 weeks, 300 mg every 4 weeks, or 150 mg every 4 weeks). After completion of the treatment phase, the study participants were included in the HELP extension study; otherwise, the end of study was accompanied by a safety visit after a further 8 weeks. The primary efficacy endpoint was the number of confirmed HAE attacks during the treatment phase.

The study was conducted in six countries (US, Germany, Italy, Great Britain, Canada, and Jordan) between March 2016 and April 2017.

According to the product information, lanadelumab is administered at a dose of 300 mg every two weeks. In patients who are free from attack under treatment, a dose reduction to 300 mg every 4 weeks may be considered, especially in patients with low body weight. For the benefit assessment only the study arms with the corresponding dosages compliant with marketing authorisation are relevant; the study arm with the dosage of 150 mg every 4 weeks is not considered.

Uncertainties of the study:

The randomised controlled trial HELP used for the benefit assessment is a study with a low risk of bias.
However, it should be noted that lanadelumab is indicated for “routine prevention of recurrent HAE attacks”, yet patients with HAE who had to use long-term prophylaxis to prevent HAE attacks two weeks prior to inclusion were excluded from participation in the study. All patients who were suitable for the study but required long-term prophylaxis had to discontinue long-term prophylaxis in a washout period. While patients with a previous long-term prophylaxis in the intervention arm again received a long-term prophylaxis (with lanadelumab), this was not the case for the affected patients randomised into the placebo group. Approximately half (53.7%) of the patients in the placebo arm of the HELP study received long-term prophylaxis with a C1 inhibitor prior to inclusion in the study and discontinued prophylaxis treatment during the washout period. It can be assumed that during the HELP study, these patients did not receive prophylaxis for their HAE disease in line with the currently respected standard of care. The use of C1 inhibitors as concomitant medication during the study was permitted as acute therapy for HAE attacks.

Mortality

No deaths occurred in the HELP study.

Morbidity

HAE attacks

During the study, patients were required to report HAE attacks within a defined period of time. Moreover, HAE attacks were recorded by regular patient consultation. The severity of the attack was also recorded on the basis of the information provided by the patient or, if this was not possible, on the basis of information provided by relatives. The HAE attacks recorded were confirmed by the study personnel in accordance with the HAARP (HAE attack assessment and reporting procedures) criteria.

The occurrence of HAE attacks is a patient-relevant endpoint. Because the disease burden of the seizures results from their frequency, severity, and localisation, the following analyses are used for the benefit assessment.

Number of HAE attacks

The total number of confirmed HAE attacks during the treatment phase (Day 0 to Day 182) is shown as the attack rate per month along with the number of confirmed moderate to severe HAE attacks, the number of confirmed laryngeal attacks, and the number of confirmed HAE attacks leading to an emergency or hospital stay.
The mean monthly attack rate was 0.3 and 0.6 in the two lanadelumab arms (300 mg every 2 weeks and every 4 weeks, respectively) and 2.5 in the placebo arm. With respect to moderate to severe HAE attacks, the mean monthly attack rate was 0.2 and 0.4 in the two lanadelumab arms (300 mg every 2 weeks and 4 weeks, respectively) and 1.4 in the placebo arm.
For the number of HAE attacks, there are statistically significant differences in favour of lanadelumab treatment in both dosage arms (300 mg every 2 weeks or every 4 weeks) compared with placebo treatment (rate ratio [95% CI]): 0.1 [01 to 0.2]; $p < 0.001$ or 0.3 [0.2 to 0.4]; $p< 0.001$) and the number of moderate to severe HAE attacks (rate ratio [95% CI]): 0.2 [0.1 to 0.3]; $p < 0.001$ or 0.3 [0.2 to 0.5]; $p< 0.001$).

Serious HAE attacks in the sense of laryngeal attacks or HAE attacks that led to an emergency room stay or a hospital admission hardly occurred at all within the study. For both endpoints, no statistically significant difference between lanadelumab and placebo could be demonstrated.

Time to the first HAE attack

Time to the first confirmed HAE attack

The analysis of the endpoint “median time to first confirmed HAE attack” included 40 attacks in the placebo arm and 35 attacks in the lanadelumab arms. Patients who had no HAE attack during the study period were censored. HAE attacks were recorded as events. Information on the median observation time was not identified.
The median time to first attack was 59 days and 28 days in the lanadelumab arms (300 mg every 2 weeks and every 4 weeks) and 8 days in the control arm.
There are statistically significant differences in favour of lanadelumab treatment in both dosage arms (300 mg every 2 weeks and every 4 weeks, respectively) compared with placebo treatment (HR [95% CI]): 0.3 [0.1 to 0.5]; $p < 0.001$ or 0.4 [0.2 to 0.7]; $p < 0.001$).

Absence of HAE attacks

Absence of attacks is defined as the proportion of study participants who did not experience a confirmed HAE attack during the treatment phase (Day 0 to Day 182).
The endpoint absence of attacks is a different operationalisation of the endpoint “time to first confirmed HAE attack” (see above). The operationalisation of the endpoint “absence of attacks” as the number of patients who had no HAE attack during the study period therefore refers to the same data basis.
In the lanadelumab arms (300 mg every 2 weeks or every 4 weeks), 12 (44.4%) or 9 (31%) patients achieved absence of attacks; in the control arm, only 1 patient achieved absence of attacks.
There are statistically significant differences in favour of lanadelumab treatment in both dosage arms (300 mg every 2 weeks and every 4 weeks, respectively) compared with placebo treatment (RR [95% CI]): 18.2 [2.5 to 132.2]; p < 0.001 or 12.7 [1.7 to 95.0]; p = 0.001).

EQ-5D-VAS

The general health status was assessed using the visual analogue scale (VAS) from the EQ-5D questionnaire. Differences in the mean changes in the VAS of EQ-5D from Day 0 to Day 182 as well as differences in the proportions of patients who achieved a change of at least 7.5 between 10 points on a VAS scale are shown.
There is no statistically significant difference between lanadelumab and placebo

Quality of life

AE-QoL

In the HELP study, quality of life was assessed using the disease-specific Angioedema Quality of Life Questionnaire (AE-QoL). AE-QoL is a tool for assessing symptom specific quality of life impairment in adults with recurrent angiooedema. The questionnaire contains a total of 17 questions in the domains function, fatigue/mood, anxiety/shame, and nutrition, which are answered using a five-point Likert scale (from 1 (never) to 5 (very often)). For the total value of the AE-QoL, there are possible scores in the range from 0 to 100. An improvement in the health-related quality of life is shown by a reduction in the AE-QoL score.

In the two lanadelumab arms (300 mg every 2 weeks and every 4 weeks, respectively), the AE-QoL score decreased from Day 0 to Day 182 by an average of 20.9 and 18 points, respectively, while the mean reduction in the placebo arm was 3.8 points.

There are statistically significant differences in favour of lanadelumab treatment in both dosage arms (300 mg every 2 weeks and every 4 weeks, respectively) compared with placebo treatment (mean difference [95% CI]): −16.6 [−28.5 to −4.6]; p =0.0025 or −12.7 [−24.5 to −0.8]; p = 0.0315). In the treatment arm lanadelumab at a dose of 300 mg every 2 weeks, Hedges’ g exceeds the irrelevance threshold of 0.2, whereby the effect reaches a clinically relevant level. However, in the treatment arm 300 mg every 4 weeks, the lower limit of the confidence interval of Hedges’ g is not outside the irrelevance threshold.

Based on the responder analyses with a MCID of 6 points in the total value, the proportion of patients with a response in the lanadelumab intervention arms is 80.8% and 63%, respectively and thus significantly above the proportion of 36.8% in the placebo arm (RR [95% CI]): 2.2 [1.4 to 3.5]; p =0.0008 or 1.7 [1.0 to 2.8]; p = 0.0383).

A statistically significant and (according to Hedges’ g) clinically relevant advantage over placebo for lanadelumab is also shown in the function domain for both intervention arms. The reduction in the number of points from Day 0 to Day 182 amounts to an average of 35.4 and 24.3 points respectively compared with 4.7 points in the placebo arm (mean difference [95% CI]): −30.6 [−45.1 to 16.0]; p < 0.0001 or −18.9 [−33.2 to −4.5]; p = 0.0046).
The results in the nutrition domain (i.e. a reduction of 15.9 points on average from Day 0 to

Day 182 compared with a reduction of 2 points) are also statistically significant for the treatment arm lanadelumab 300 mg every 2 weeks (mean difference [95% CI]): −18.5 [−33.0 to −4.1]; p = 0.0059). According to Hedges' g, there is a clinically relevant difference for the treatment arm lanadelumab 300 mg every 2 weeks in the nutrition domain.

For the domains AE-QoL fatigue/mood and anxiety/shame, there is no statistically significant difference between the treatment groups.

Side effects

Overall, the proportion of adverse events (AE) was similar in all treatment arms. In the two lanadelumab arms, severe AE occurred in 8 out of 56 patients (14.3%) during the treatment phase; in the placebo arm, severe AE occurred in 4 out of 41 patients (9.8%). However, serious AE occurred in 4 out of 56 patients treated with lanadelumab (4.8%) and in none in the placebo arm. There are no significant differences between the treatment groups with regard to side effects.

Overall assessment/conclusion

For the assessment of the extent of the additional benefit of lanadelumab for patients aged 12 years and older with recurrent attacks of hereditary angiooedema (HAE), the overall results on mortality, morbidity, quality of life, and side effects from the randomised, double-blind, placebo-controlled Phase III study HELP are available. Within the HELP study, the use of long-term prophylaxis (with C1 inhibitors) was not permitted; the use of C1 inhibitors was only permitted as acute therapy for HAE attacks. The patients in the control arm of the study who received long-term prophylaxis before the start of study (about half of the patients) had to discontinue it before inclusion in the study. It can be assumed that during the HELP study, these patients did not receive prophylaxis for their HAE disease in line with the currently respected standard of care.

No deaths occurred in the HELP study.

The endpoints of the morbidity category were the number of HAE attacks, the time to first HAE attack, and the absence of attacks. Data on the EQ-5D-VAS is also available. In both dosage arms, there are statistically significant differences in favour of lanadelumab treatment compared with placebo treatment with respect to the number of HAE attacks and the number of moderate to severe HAE attacks. Laryngeal attacks and HAE attacks leading to emergency or hospital admission during the treatment phase were very rare in the study; there was no statistically significant difference between treatment arms.
For the endpoints "time to first HAE attack" and "absence of attacks", there are also statistically significant differences in favour of lanadelumab. It must be taken into account that both endpoints represent different operationalisations of the same database.

For the endpoint EQ-5D VAS, no statistically significant difference between the treatment arms was determined.

The AE-QoL was surveyed in the health-related quality of life category. For the overall score as well as for the responder analysis and the function and nutrition domains (only in the treatment arm lanadelumab 300 mg every 2 weeks), statistically significant differences in favour of lanadelumab compared with placebo were observed. In accordance with Hedge's g, the statistically significant differences in the AE-QoL total score and in the nutrition domain (only in the treatment arm lanadelumab 300 mg every 2 weeks) as well as in the domain function (in the treatment arms lanadelumab 300 mg every 2 weeks and every 4 weeks) reach a clinically relevant level.

In the category side effects, there were no statistically significant differences determined between the treatment arms with lanadelumab and placebo.

Based on the criteria in Section 5, Paragraph 7 of the AM-NutzenV, the G-BA arrived at the following result taking the disease's degree of severity, the written statements, and the oral hearing for patients 12 years of age and older with recurrent attacks of hereditary angiooedema and determined a considerable additional benefit for the treatment with lanadelumab.

2.1.3 Summary of the assessment

For the assessment of the extent of the additional benefit of lanadelumab for patients 12 years and older with recurrent attacks of hereditary angiooedema (HAE), the pharmaceutical company submitted the pivotal studies DX-2930-03 (HELP study), DX-2930-04 (HELP extension study) and DX-2930-02. The randomised, double-blind, placebo-controlled Phase III HELP study is used for the benefit assessment.

From the HELP study also only the study arms with dosage schemes compliant with marketing authorisation (300 mg lanadelumab every 2 weeks or every 4 weeks) were used. Within the HELP study, the use of long-term prophylaxis (with C1 inhibitors) was not permitted; the use of C1 inhibitors was only permitted as acute therapy for HAE attacks. The patients in the control arm of the study who received long-term prophylaxis before the start of study (about half of the patients) had to discontinue it before inclusion in the study. It can be assumed that during the HELP study, these patients did not receive prophylaxis for their HAE disease in line with the currently respected standard of care. No deaths occurred in the HELP study. In the area of morbidity, in both dosage arms, there are statistically significant differences in favour of lanadelumab treatment compared with placebo treatment with respect to the number of HAE attacks and the number of moderate to severe HAE attacks. Laryngeal attacks and HAE attacks leading to emergency or hospital admission during the treatment phase were very rare in the study; there was no statistically significant difference between treatment arms.
For the endpoints "time to first HAE attack" and "absence of attack", there are also statistically significant differences in favour of lanadelumab. For the endpoint EQ-5D VAS, no statistically significant difference between the treatment arms was determined.

In the health-related quality of life category, the AE-QoL shows statistically significant differences in favour of lanadelumab versus placebo for the overall score as well as for the responder analysis and the function and nutrition domains (only in the treatment arm lanadelumab 300mg every 2 weeks). These are classified as clinically relevant in accordance with Hedges' g.

In the category side effects, there were no statistically significant differences determined between the treatment arms with lanadelumab and placebo.

Based on the criteria in Section 5, Paragraph 7 of the AM-NutzenV, the G-BA arrived at the following result taking the disease's degree of severity, the written statements, and the oral hearing for patients 12 years of age and older with recurrent attacks of hereditary angiooedema and determined a considerable additional benefit for the treatment with lanadelumab.

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. These are based on the data from the pharmaceutical company's dossier.

However, the information is subject to uncertainties. The calculation of the lower limit of the number of patients with HAE in Germany is based on an estimated HAE prevalence rate for Greece (which is low compared with other countries) because according to the pharmaceutical company, no data are available for Germany. The extent to which the data can be transferred to the German care context is therefore questionable. Further uncertainties arise for the upper limit of patients with HAE in Germany. This is based on an expert survey as well as on the limitation of the number of patients determined to the proportion of patients who, according to

the expert survey, are currently being treated with long-term prophylaxis. Because this excludes patients who do not currently receive long-term prophylaxis but are suitable for routine prophylaxis, a possible underestimation of the number of patients can be assumed.

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 Takhzyro® (active ingredient: lanadelumab) at the following publicly accessible link (last access: 28 May 2019):

https://www.ema.europa.eu/documents/product-information/takhzyro-epar-product-information_de.pdf

Lanadelumab treatment should be initiated and monitored by physicians with experience in treating patients with hereditary angiooedema (HAE).

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 July 2019).

To facilitate comparability, the pharmaceutical costs were approximated both on the basis of the pharmacy sales price level and also the price less statutory rebates in accordance with Sections 130 and 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 pharmaceutical costs were then calculated on the basis of the costs per pack less the statutory rebates.

For the cost representation only the dosages of the general case are considered. Patient-individualised dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

The recommended dose of lanadelumab is 300 mg every 2 weeks. In patients who are free from attack under treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low body weight.

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				
Lanadelumab	continuous, every 2 - 4 weeks	13 - 26	13 - 26	13 - 26

Usage and consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Lanadelumab	300 mg	300 mg	1 × 300 mg	13 - 26	13 - 26 × 300 mg

Costs:

Costs of the medicinal product:

Designation of the therapy	Package 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					
Lanadelumab	6 injection solutions	€ 104,236.92	€ 1.77	€ 5,949.72	€ 98285.43

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 July 2019

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 medical treatment or the prescription of other services when using the medicinal product to be assessed 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 usual expenditure in the course of the treatment are not shown.

Since there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed in accordance with the product information, no costs were incurred for additionally required SHI services had to be taken into consideration.

3. Bureaucratic costs

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 31 January 2019, the pharmaceutical company submitted a dossier for the benefit assessment of lanadelumab to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 2 May 2019 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 23 May 2019.

The oral hearing was held on 11 June 2019.

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 statements received and the oral hearing were discussed at the session of the subcommittee on 23 July 2019, and the proposed resolution was approved.

At its session on 1 August 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 April 2019	Knowledge of the benefit assessment of the G-BA
Working group Section 35a	4 June 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 June 2019	Conduct of the oral hearing
Working group Section 35a	19 June 2019 2 July 2019 16 July 2019	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 statement procedure
Subcommittee Medicinal products	23 July 2019	Concluding discussion of the proposed resolution
Plenum	1 August 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 August 2019

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

Prof Hecken