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 Ixazomib (reassessment after the deadline: multiple myeloma, at least 1 prior therapy, combination with lenalidomide and dexamethasone)

of 21 April 2022

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of 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 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 € 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 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 marketing authorisation 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 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 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 pharmaceutical company submitted a dossier for the early benefit assessment for the active ingredient ixazomib (Ninlaro) to be assessed for the first time on 19 December 2016. For the resolution of 6 July 2017 made by the G-BA in this procedure, a limitation up to 1 November 2021 was pronounced.

In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Ninlaro recommences when the deadline has expired.

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 29 October 2021.

Ixazomib in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy is authorised as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council dated 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 marketing authorisation 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 February 2022 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 made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG 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 assessed the studies relevant for the marketing authorisation considering 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 ixazomib.

[1] General Methods, version 6.0 from 05.11.2020. 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 ixazomib (Ninlaro) according to product information

Ninlaro in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Therapeutic indication of the resolution (resolution of 21 April 2022):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of ixazomib in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy is assessed as follows:

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

Justification:

C16010 study

For the renewed benefit assessment of ixazomib in the present therapeutic indication, the pharmaceutical company submits the results of the C16010 study, which was decisive for issue of the conditional marketing authorisation. This is a randomised, controlled, double-blind, multicentre phase III study comparing ixazomib in combination with lenalidomide and dexamethasone (ixazomib / LenDex) versus lenalidomide and dexamethasone (LenDex).

The study was conducted in 147 study sites across 26 countries in Europe, North America and the Asia-Pacific region between August 2012 and September 2020. For the present benefit assessment, the final data cut-off of 28 September 2020 is used for all patient-relevant endpoints.

The study enrolled a total of 722 patients (360 and 362 patients in the intervention and control arms, respectively) with relapsed and/or refractory multiple myeloma who had received at least one prior therapy. Patients with refractoriness to lenalidomide or proteasome inhibitors were excluded. Enrolled patients were randomised in a 1:1 ratio according to prior therapies (1 vs 2 or 3), prior proteasome inhibitor exposure (yes/no) and International Staging System (ISS) stage after screening (I or II vs III). Treatment was given until disease progression or occurrence of unacceptable toxicity.

The 115 exclusively Chinese patients from the China Continuation Study (CCS) who were additionally enrolled after the second amendment to the study protocol are also not included in the present reassessment after the deadline. For the justification underlying this assessment, reference is made to the benefit assessment procedure on ixazomib (in combination with lenalidomide and dexamethasone) by resolution of 6 July 2017.

The primary endpoint was "progression-free survival" (PFS). In addition, data were presented on the secondary endpoints of overall survival, morbidity (BPI-SF, EQ-5D VAS, EORTC QLQ-C30 and EORTC QLQ-MY20) and quality of life (EORTC QLQ-C30 and EORTC QLQ-MY20), and side effects.

Mortality

The overall survival is defined in the C16010 study as the time from randomisation to death from any cause.

For the endpoint of overall survival, there was no statistically significant difference between the treatment groups considering the total population of the study.

There is an effect modification by the characteristic "prior therapy with bortezomib" for overall survival. Accordingly, there is a statistically significant effect in favour of ixazomib / LenDex for patients without prior bortezomib therapy. However, there was no statistically significant difference between the treatment groups for patients with prior therapy with bortezomib.

The following points are relevant when interpreting the result.

In the first-line therapy of multiple myeloma, bortezomib is given a high priority as a component of combination therapies in current guidelines. Since the combination (ixazomib in combination with lenalidomide and dexamethasone) to be evaluated here contains lenalidomide for the second-line treatment patients who are refractory to lenalidomide, and thus received lenalidomide until progression in the first-line treatment, are excluded in the C16010 study. The subgroup of patients without bortezomib prior therapy in the C16010 study thus includes patients who did not receive bortezomib in the first-line therapy and are not refractory to lenalidomide. The clinical relevance of this subgroup for the present assessment is considered to be rather low, even taking into account the related statements on the reality of care.

For the interpretation of the subgroup results, it is also taken into account that no equidirectional effects are observed across several endpoints in either of the two subgroups.

In addition, there is no statistically significant interaction for overall survival for the subgroup "proteasome inhibitor (PI) prior therapy" (yes versus no). In a comparison of the two subgroup analyses on "PI prior therapy" and "bortezomib prior therapy", discrepant data on the number and percentage of people in the "PI prior therapy" subgroup can also be seen.

For these reasons, the observed effect modification due to the characteristic "bortezomib prior therapy" is not considered sufficient to derive corresponding separate statements on the additional benefit in the overall assessment.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint of the C16010 study. PFS was defined as the time from randomisation to the time of the first documented disease progression (definition according to the International Myeloma Working Group, IMWG) or death of the patient, regardless of the cause of death - whichever occurred earlier. The PFS was then assessed by an independent review committee (IRC). The analysis of progression-free survival was performed for the ITT population using the data cut-off of 12 July 2015.

There is no statistically significant difference between the treatment arms.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" is assessed according to IMWG criteria and thus not in a symptom-related manner but rather by means of laboratory parametric, imaging, and haematological procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

Pain (BPI-SF)

Self-assessment of pain was recorded using the Brief Pain Inventory-Short Form (BPI-SF) and was collected until progression or death or discontinuation from the study.

The recording of pain intensity (items 3-6) and impairment due to pain (items 9A - 9G) via the BPI-SF is considered patient-relevant.

The pharmaceutical company submits, among others, the MMRM analyses for the mean change in pain intensity (separately for all 4 individual items) and pain interference (items 9A - 9G).

These continuous analyses (MMRM) for mean change are also used for the present reassessment in analogy to the first assessment. The corresponding evaluations up to cycle 8 are included, since up to this point the return rate does not fall below approx. 70%.

There are no statistically significant differences between the treatment groups in the 4 items of the pain intensity domain or in the score across the 7 items of the pain interference domain (9A-9G).

Symptomatology (EORTC QLQ-C30/ EORTC QLQ-MY20)

Disease symptomatology was assessed in the C16010 study using the cancer-specific questionnaire EORTC QLQ-C30 and the myeloma-specific additional module EORTC QLQ-MY20 until the onset of disease progression.

The pharmaceutical company submitted responder analyses for the percentage of patients with a change of ≥ 10 points for the time to first deterioration and for the so-called "time to confirmed permanent deterioration".

The so-called "time to confirmed permanent deterioration" was defined as the time from randomisation to deterioration by at least the response threshold without a subsequent improvement back to a value above the response threshold. The observation period of the endpoints on disease symptomatology covers only a small percentage of the total observation time due to the discontinuation of the observation with disease progression. A sufficiently long observation in relation to study duration and overall survival is not given. In addition, the return rate for all endpoints of disease symptomatology at cycle 8 is at least 70% in both treatment groups for the last time. For these reasons, the amendment states that it is not considered appropriate to speak of a "permanent deterioration" in this situation, as it is rather a "deterioration confirmed several times" over the shortened observation period. Furthermore, although there are no significant differences in the median observation times for the endpoints of disease symptomatology between the treatment arms, there may be an average of 1 to 2 more observations in the intervention arm, depending on the endpoint, due to the survey time points. As a result, deterioration confirmed several times across all follow-up scores is potentially harder to achieve in the longer observed intervention arm, which can lead to a risk of bias in favour of the intervention group. In addition, the survival time analyses on deterioration confirmed several times are considered to potentially have a high risk of bias due to the decreasing return rate, as an ever decreasing number of people with measurement data are included in the evaluation. Nevertheless, both operationalisations ("time to first deterioration" and the "time to deterioration confirmed several times") are considered patient-relevant, the time-to-event analysis for the first deterioration is used against the background of the uncertainties described for the deterioration confirmed several times, as this is considered to have a lower risk of bias than the analysis for the deterioration confirmed several times.

In the analysis of the "time to first deterioration" by ≥ 10 points, a statistically significant difference in favour of ixazomib/LenDex over Len/Dex was only shown for the domain "appetite loss". Based on this alone, no advantage can be derived in the overall consideration of the results for the symptomatology.

Thus, there are no relevant differences between the treatment arms with regard to symptomatology.

General health status (EQ-5D VAS)

Health status will be assessed in the C16010 study using the EQ-5D visual analogue scale (VAS) beyond disease progression until death or until the end of the study.

The pharmaceutical company submitted post hoc responder analyses for the "time to first deterioration" and the "time to deterioration confirmed several times", each defined as a decrease in score of ≥ 15 points compared to the baseline value.

The results on "time to deterioration confirmed several times" are classified as potentially having a high risk of bias due to the uncertainties described under the explanations on symptomatology and additionally due to the strongly decreasing return rate in the course of the study, despite the planned survey until the end of the study, which cannot be explained by death alone. Therefore, the analyses on the "time to first deterioration" is also used for the endpoint of health status.

For this evaluation, no statistically significant difference could be identified between the treatment arms.

Quality of life

Health-related quality of life was assessed in the C16010 study using the functional scales and the global health status scale of the cancer-specific questionnaire EORTC QLQ-C30 and the myeloma-specific additional module EORTC QLQ-MY20 until the onset of disease progression.

The pharmaceutical company submits evaluations for the "time to first deterioration" and for the "time to deterioration confirmed several times" by ≥ 10 points.

Also, for the endpoints of health-related quality of life, the analyses of the "time to first deterioration" are also used in accordance with the above statements on symptomatology.

In the analyses of the "time to 1st deterioration" by ≥ 10 points, there was a statistically significant difference to the disadvantage of ixazomib / LenDex over Len/Dex for the domain "Global health status / Global quality of life" and a statistically significant difference to the advantage of ixazomib / LenDex over Len/Dex for the domain "Future perspective". Thus, there is both a positive and a negative effect.

No relevant difference was found in the overall results for health-related quality of life.

Side effects

Adverse events (AEs) in total

In the C16010 study, almost all randomised patients experienced at least one adverse event. The results were only presented additionally.

Serious adverse events (SAEs), severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs

For the endpoints of serious adverse events (SAE), severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs, there is no statistically significant differences between the treatment arms.

For the endpoint of severe AEs, there was an advantage for renal and urinary disorders (SOC) and a disadvantage for skin and subcutaneous tissue disorders (SOC) for ixazomib / LenDex compared to LenDex. In the SOC of gastrointestinal disorders, ixazomib / LenDex showed a disadvantage for both severe AEs (CTCAE grade ≥ 3) and SAEs compared to LenDex.

Conclusion on side effects

In the overall assessment of the results on side effects, there are no relevant difference for the benefit assessment between the treatment arms.

Overall assessment / conclusion

For the assessment of the additional benefit of ixazomib in combination with lenalidomide and dexamethasone (ixazomib / LenDex) for the treatment of multiple myeloma in adult patients who have received at least one prior therapy, results are available from the randomised, controlled, double-blind, multicentre phase III C16010 study on the endpoint categories of mortality, morbidity, health-related quality of life and side effects compared to lenalidomide and dexamethasone (LenDex).

For the endpoint overall survival, no statistically significant difference was detected between the treatment groups.

For the endpoints of the category of morbidity, there were no relevant differences between a treatment with ixazomib in combination with lenalidomide and dexamethasone and a treatment with lenalidomide in combination with dexamethasone in the overall analysis of the results with regard to symptomatology (assessed by EORTC QLQ-C30 and EORTC QLQ-MY20), general health status (assessed by EQ-5D VAS) and pain (BPI-SF).

There were also no relevant differences in the overall results for health-related quality of life (assessed using the EORTC QLQ-C30 and EORTC QLQ-MY20).

In the overall assessment of the results on side effects, there are no relevant difference for the benefit assessment between the treatment arms.

As a result, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

This assessment is based on the results of the randomised, controlled, double-blind, multicentre phase III C16010 study. The available results from the C16010 study do not allow a quantification of the extent of the additional benefit in the overall assessment. The significance of the results for the additional benefit identified is classified in the "hint" category.

2.1.3 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient ixazomib in combination with lenalidomide and dexamethasone due to the expiry of the limitation of the resolution of 6 July 2017.

Ixazomib in combination with lenalidomide and dexamethasone was approved as an orphan drug under special conditions.

This assessment relates to the use of ixazomib in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in the following patient population:

adult patients with multiple myeloma who have received at least one prior therapy

For the benefit assessment, the pharmaceutical company submits the final results of the randomised, controlled, double-blind, multicentre phase III C16010 study, in which ixazomib in combination with lenalidomide and dexamethasone (ixazomib / LenDex) was compared to lenalidomide and dexamethasone (LenDex) in the treatment of adults with multiple myeloma who have received at least one prior therapy.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment groups.

In the category of morbidity (pain, symptomatology and general health status) and in the category of health-related quality of life, there are no relevant differences in the overall analysis.

In the overall view of the results on side effects, there are also no differences between the treatment arms that are relevant for the benefit assessment.

As a result, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

A hint can be derived regarding the reliability of data.

Overall, a hint for a non-quantifiable additional benefit is thus derived for ixazomib in combination with lenalidomide and dexamethasone.

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

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

The resolution is based on the number of patients from the last resolution on multiple myeloma after at least one therapy (isatuximab (4 November 2021)).

The figures were already used as a basis for other resolutions on multiple myeloma after at least one therapy (resolutions on carfilzomib dated 15 July 2021, 15 February 2018; initial resolution on ixazomib dated 6 July 2017 and resolution on elotuzumab dated 1 December 2016).

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 Ninlaro (active ingredient: ixazomib) at the following publicly accessible link (last access: 1 February 2022):

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

Treatment with ixazomib should only be initiated and monitored by specialists in internal medicine, haematology and, oncology experienced in the treatment of patients with multiple myeloma.

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

A careful risk-benefit assessment by the treating physician should be made for patients who were refractory to bortezomib and carfilzomib, as these were not studied in the marketing authorisation study for ixazomib (C16010). This information is neither associated with a restriction of the prescribability of ixazomib according to Section 92 paragraph 1 SGB V, nor with a therapy recommendation to generally not prescribe the active ingredient for this patient group.

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: 1 April 2022).

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 is patient-individual 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. Treatment should be continued until disease progression or occurrence of unacceptable toxicity. Treatment with ixazomib in combination with lenalidomide and dexamethasone for more than 24 cycles should be based on an individual risk-benefit assessment, as data on tolerability and toxicity beyond 24 cycles are limited.

The annual treatment costs shown refer to the first year of treatment.

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				
Ixazomib in combination with lenalidomide and dexamethasone				
Ixazomib	Day 1, 8 and 15 of a 28-day cycle	13.0	3	39
Lenalidomide	Day 1 – 21 of a 28-day cycle	13.0	21	273
Dexamethasone	Day 1, 8, 15 and 22 of a 28-day cycle	13.0	4	52

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					
Ixazomib in combination with lenalidomide and dexamethasone					
Ixazomib	4 mg	4 mg	1 x 4 mg	39	39 x 4 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52	52 x 40 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.

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					
Ixazomib 4 mg	3 HC	€ 6,431.26	€ 1.77	€ 364.00	€ 6,065.49
Lenalidomide 25 mg	21 HC	€ 2,420.96	€ 1.77	€ 115.69	€ 2,303.50
Dexamethasone 40 mg**Fehler! T extmarke nicht definiert.**	50 TAB	€ 188.00	€ 1.77	€ 0.00	€ 186.23
Abbreviations: HC = hard capsules, TAB = tablets					

LAUER-TAXE® last revised: 1 April 2022

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.

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 29 October 2021, the pharmaceutical company submitted a dossier for the benefit assessment of ixazomib to the G-BA in due time in accordance with Chapter 5, Section 8, number 5 VerfO.

The benefit assessment of the G-BA was published on 1 February 2022 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 written statements was 22 February 2022.

The oral hearing was held on 9 March 2022.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 7 April 2022.

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 12 April 2022, and the proposed resolution was approved.

At its session on 21 April 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	25 January 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	2 March 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	9 March 2022	Conduct of the oral hearing
Working group Section 35a	16 March 2022 6 April 2022	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 product	12 April 2022	Concluding discussion of the draft resolution
Plenum	21 April 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 21 April 2022

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

Prof. Hecken