Justification

Gemeinsamer Bundesausschuss

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

of 6 July 2017

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 10, 1st half of the sentence SGB V, the additional medical benefit is deemed 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 10, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 10 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, 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 11 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, 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 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 11 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 ixazomib in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 January 2017. 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 13 January 2017.

Ixazomib is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

According to Section 35a, paragraph 1, sentence 10, 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 18 April 2017 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 G17-02) 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 ixazomib.

In the light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of ixazomib (Ninlaro®) in accordance with the 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.

[1] General Methods, Version 4.2 dated 22 April 2015. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

2.1.2 Extent of the additional benefit

In summary, the additional benefit of ixazomib in combination with lenalidomide and dexamethasone is assessed as follows:

For adult patients with multiple myeloma who have received at least one prior therapy, there is a non-quantifiable additional benefit.

Justification:

In order to answer the question on the extent of the additional benefit of ixazomib, the results of the C16010 study, which is relevant for conditional marketing authorisation, are available.

The C16010 study is a randomised, double-blind, multi-centre Phase III study comparing ixazomib in combination with lenalidomide and dexamethasone versus placebo in combination with lenalidomide and dexamethasone. The study started at the end of August 2012, will be conducted at 147 centres in 26 countries in Europe, North America, and the Asia-Pacific region, and will continue blinded until 2020. The data cut-offs took place on 30 October 2014 and 12 July 2015. A total of 722 patients (360 and 362 patients in the intervention and control arm, respectively) relapsed and/or refractory multiple myeloma who had received at least one previous therapy were included. The patients included were stratified randomly according to previous therapies (1 vs 2 or 3), previous proteasome inhibitor exposure (yes/no), and International Staging System (ISS) stage at screening (I or II vs III). Treatment was continued until disease progression or unacceptable toxicity occurred.

The randomised population of 722 patients is the ITT population of the original study protocol on which the marketing authorisation of ixazomib and the publication of study results [2] are based. These were recruited from the end of August 2010 until the end of May 2014. Following the second amendment to the study protocol, an additional 115 exclusively Chinese patients in 11 Chinese centres (China Continuation Study, CCS) were included and randomised in the period from mid-April 2014 to early May 2015 in order to characterise pharmacokinetics, efficacy, and safety in Chinese patients.

The present benefit assessment is based on the ITT population of the original study protocol with 722 patients, which is the basis for marketing authorisation. This globally recruited ITT population can be assumed to be transferable to the German healthcare context. The population from the Chinese extension study (China Continuation Study, CCS) is not included in the present benefit assessment mainly because of medical aspects but also because of methodological aspects.

The medical aspects are reflected in the different baseline characteristics of the Chinese population. In contrast to the globally recruited ITT population of the original study protocol, the Chinese CCS population was younger (73% vs 42% were under 65 years of age), more severely ill (ISS Stage I: 20% vs 32%; ISS Stage III: 36% vs 22%), more frequently refractory (55% vs 11%), less affected by relapses (23% vs 77%), and included more men (68% vs 57%), and the average time from initial diagnosis to first study dose was significantly shorter (37.4 vs 57.1 months). In the interaction tests for overall survival within the Cox regression model for the pooled study populations (ITT population plus CCS population) submitted by the pharma-

[2] Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, Sandhu I, Ganly P, Baker BW, Jackson SR, Stoppa AM, Simpson DR, Gimsing P, Palumbo A, Garderet L, Cavo M, Kumar S, Touzeau C, Buadi FK, Laubach JP, Berg DT, Lin J, Di Bacco A, Hui AM, van de Velde H, Richardson PG; TOURMALINE-MM1 Study Group.. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Apr 28; 374 (17):1621–34

ceutical company in the written statement procedure, evidence was found for an effect modification both for the “Asia vs non-Asia” factor and for “ITT population (original protocol population) vs CCS population (amendment 2 population)” factor. The transferability of the results of the exclusively Chinese CCS population to the German healthcare context is subject to uncertainties because of the different baseline characteristics of the Chinese population and the effect modifications shown. In the European assessment report on ixazomib, the European Medicines Agency (EMA) also stated that the CCS study could only support the pivotal results of the globally recruited population that was the basis for marketing authorisation to a limited extent because of different baseline characteristics: “An extension study performed in China and submitted as supporting evidence of efficacy showed a prolongation of PFS, but in a population of patients that differed markedly in terms of the rate of disease progression, probably explained by different baseline characteristics and treatment options. Hence, this study brings limited support to the pivotal results and does not constitute a second pivotal study.” [3]. The study report also points out that, despite identical inclusion criteria, there are differences in disease progression and baseline characteristics between the Chinese CCS population and the global population [4]. In addition, the Chinese patients in the CCS study were treated with significantly fewer cycles (CCS study): median 5.0 or 7.0 cycles under ixazomib or control; ITT population: median 15 cycles) and observed more briefly in the follow-up process (CCS study: median follow-up for OS or PFS of 8.0 and 8.1 months under ixazomib or control; ITT population: median follow-up for OS and PFS of 23.3 or 22.9 months under ixazomib or control) [5].

In addition to these medical aspects, there are methodological problems: Thus, the recruitment periods between the global and Chinese study overlap by only one month. This led to the methodological problem that the 2nd data cut-off for the statistical evaluations of both populations in both studies, which was relevant for the benefit assessment, was not carried out at the same time but rather with a time delay of about one year in each case (12 July 2015 for ITT population and 19 July 2016 for the CCS population). In addition, the patient-relevant endpoint of health-related quality of life was not collected in the CCS study.

In summary, an additional effect distortion by the CCS population cannot be ignored because of mainly medical but also methodological aspects. This is why the present benefit assessment is based on the ITT population size of 722 patients, which is the basis for approval.

Mortality

Three interim analyses and one final analysis are planned for overall survival.

The results of the first two interim analyses on overall survival are available, and no statistically significant difference could be shown between the two treatment arms (data cut-off 30 October 2014: hazard ratio (HR) = 0.90; 95% confidence interval (CI) [0.62; 1.32]; p = 0.59; data cut-off of 15 July 2015: HR = 0.87; 95% CI) [0.64; 1.18]; p = 0.36). The median overall survival was not achieved at both interim analyses. With 22% and 35% death events, respectively (1st and 2nd interim analysis of overall survival), these data are not sufficiently meaningful to be able to validly assess effects on overall survival.

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3 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003844/WC500217623.pdf (p. 152)

4 CLINICAL STUDY REPORT China Continuation of Study C16010: A Phase 3, Randomised, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexame-thasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma (p. 190)

5 CLINICAL STUDY REPORT China Continuation of Study C16010: A Phase 3, Randomised, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexame-thasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma (p. 95 ff.)

More mature and thus more meaningful data will be available with the planned 3rd interim analysis (66% data maturity) or final overall survival analysis (expected in the 4th quarter of 2017 and 1st quarter of 2020).

Morbidity

Progression-free survival

An interim analysis (after 262 events) and a final analysis (after 365 events) were planned for the progression-free survival (PFS) endpoint.

At the time of the first interim analysis (data cut-off of 30 October 2014), a statistically significant advantage in favour of ixazomib compared with the comparator arm was shown (HR: 0.74; 95% CI [0.59; 0.94]; p = 0.012), whereby the median PFS under ixazomib was extended by 5.9 months compared with the control arm (median PFS 20.6 months vs 14.7 months in intervention vs control arm). In the second interim analysis (data cut-off of 12 July 2015), the effect of ixazomib on the PFS between both study arms was less pronounced in favour of ixazomib (4.1 months) and was no longer statistically significant (HR: 0.82; 95% CI [0.67; 1.00] p = 0.054; median PFS 20.0 months vs 15.9 months in intervention vs control arm) [6].

PFS was defined as the time from randomisation to the time of the first documented disease progression (as defined by the International Myeloma Working Group, IMWG) or death of the patient regardless of the cause of death, whichever occurred earlier. The PFS was then evaluated by an Independent Review Committee (IRC).

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" was already collected as an independent endpoint via the endpoint overall survival. The survey of the morbidity component "disease progression" was not symptom-related according to the operationalisation by the above response criteria but rather exclusively based on radiographic and laboratory parametric findings.

Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The overall statement on the extent of the additional benefit remains unaffected.

General health status (EQ-5D VAS)

The self-assessment of the general health status was performed by means of the visual analogue scale (VAS) of the EQ-5D questionnaire every four weeks beyond the disease progress until the end of study. With an average of 16 therapy cycles administered, the return rate in relation to the expected responses was already below 70% from half of the treatment cycles administered (from the 9th cycle onwards). A rate of 72% was finally achieved on the 8th cycle in both treatment arms. There was no statistically significant difference between the comparator arms.

Because of the low return rate in relation to the expected return rates, which cannot be explained by mortality rates or other comprehensible reasons, the results cannot be used.

Pain (BPI-SF)

[6] The p value for PFS reached the efficacy limit for statistical significance (p = 0.0163) and met the planned primary analysis. According to the requirements described in the study protocol and statistical analysis plan after reaching the planned level of significance, each subsequent PFS analysis was a non-inferential analysis and not intended by the pharmaceutical company for formal statistical testing purposes.

The self-assessment of pain was recorded using the Brief Pain Inventory-Short Form (BPI--SF) and was collected until the onset of a progress or death or termination of study. As with EQ-5D VAS, the return rate in relation to the total expected return was less than 70% for half of the average treatment cycles administered. Missing values should be compensated by statistical evaluation using a mixed model for repeated measurements (MMRM). For all questions of the BPI-SF presented (Questions 3, 4, 6, and 9), comparable values were obtained in both treatment arms over all observation times and only minimal changes in the mean values compared to the start of study. There was no statistically significant difference between the treatment arms.

Because of the low return rate in relation to the expected return rates, which cannot be explained by mortality rates or other comprehensible reasons, the results of this endpoint cannot be used.

Quality of life

Health-related quality of life was assessed every four weeks until disease progression using selected scales of EORTC QLQ-C30 and EORTC QLQ-MY20. A clinical relevance threshold (MID) of ≥ 10 points was used as a basis. The return rate in both arms after about half of the average treatment cycles administered (Cycle 8) was more than 70% in relation to the expected return rates. Missing values were compensated by statistical evaluation using a mixed model for repeated measurements (MMRM). A significant difference between the treatment arms was not achieved for either scale at any time.

Because of the low return rate in relation to the expected return rates, which cannot be explained by mortality rates or other comprehensible reasons, the results of this endpoint cannot be used.

In the written statement procedure, the pharmaceutical company submitted responder analyses for the pooled study population (ITT and CCS) for both questionnaires with a MID of ≥ 10 points. At the end of treatment, there was a significant improvement through ixazomib in the sub-scale “future perspective” of EORTC QLQ-MY20. However, because of the low return rate in relation to the expected returns at the end of treatment, these evaluations cannot be used.

Side effects

Safety analyses were performed for adverse events (AE) from the first dose of the study medication until 30 days after the last dose of the study medication based on the safety population (i.e. for patients who received at least one dose of the study medication). The 2nd data cut-off (12 July 2015) forms the basis of the benefit assessment for the AE. The number of patients with at least one event of the corresponding category is evaluated. Two patients received no study medication and were excluded from the analysis. Another three patients originally assigned to the control arm were inadvertantly given a dose of ixazomib. Thus, the safety population consists of 720 patients with 361 or 359 patients in the intervention or control arm.

The evaluations of all adverse events in the dossier and the documents submitted by the pharmaceutical company in the written statement procedure do not show to what extent events associated with a progression of the underlying disease are also included in the analysis.

In both arms, at least one adverse event occurred in almost every study participant. Event rates in serious AE, AE (CTCAE grade ≥ 3), and AE-related discontinuities were comparable in both study arms. A statistically significant difference between the two treatment arms was not observed.

Most frequent AE of special interest

The most frequent adverse events of particular interest (with a cut-off of > 10%) were nervous system disorders, blood and lymphatic system disorders, gastrointestinal disorders, skin and subcutaneous tissue disorders, respiratory, thoracic and mediastinal disorders, general disorders and administration site conditions, infections and infestations, metabolism and nutrition disorders, eye disorders, musculoskeletal and connective tissue disorders, and psychiatric disorders. The results are consistent with those of the first analysis (data cut-off 30 October 2014) except for cataract and tremor, which reached the 10% limit at the second data cut-off (12 July 2015) and only in the control arm.

Under ixazomib, significantly more patients showed skin and subcutaneous tissue disorders compared with the control arm (51% vs 39%; HR: 1.31; 95% CI [1.12; 1.55]; p = 0.001) and eye disorders (32% vs 23%; HR: 1.39; [95% CI 1.09; 1.77]; p = 0.007).

Overall assessment

For the assessment of the extent of additional benefit of ixazomib in combination with lenalidomide and dexamethasone for patients with multiple myeloma who have received at least one prior therapy, results on mortality (overall survival), morbidity, health-related quality of life, and side effects from the pivotal Phase III RCT C16010 compared with placebo in combination with lenalidomide and dexamethasone are available.

There were no statistically significant differences between the two treatment arms for the patient-relevant endpoints in the categories mortality (overall survival), morbidity (BPI-SF and EQ-5D) and health-related quality of life (EORTC-QLQ-C30 and EORTC-QLQ-MY20). The side effects were also comparable between both study arms and showed no statistically significant differences – with the exception of skin and subcutaneous tissue disorders and eye disorders, which showed a statistically significant effect to the detriment of ixazomib. The present benefit assessment is based on the two interim analyses of overall survival available to date with immature data (data maturity 22% and 35%). A final assessment of the overall survival endpoint is only possible at the time of the final analysis.

The G-BA classifies the extent of the additional benefit of ixazomib as non-quantifiable based on the criteria in Section 5, paragraph 7 of the AM-NutzenV, taking into account the severity of the disease and the therapeutic objective in the treatment of the disease. In accordance with Section 35a, paragraph 1, sentence 10, 1st half of the sentence SGB V, an additional benefit exists but is non-quantifiable because the scientific data basis does not permit this.

2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of ixazomib has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a, paragraph 1 SGB V.

The present assessment is based on an evaluation of the Phase III RCT C16010, which is the basis for marketing authorisation. Because there are no statistically significant advantages in the patient-relevant endpoints mortality (overall survival), morbidity, and health-related quality of life relevant for the benefit assessment, it is not possible to quantify the extent of the additional benefit of ixazomib based on the evidence submitted so far by the pharmaceutical company.

For the data on overall survival, which are currently too early and therefore not reliable for the benefit assessment, the final analysis is still pending. A limitation on the resolution in conjunction with the submission of more relevant data on overall survival and other patient-relevant

outcomes is therefore justified. The final analysis on overall survival, which must also be submitted to the European Medicines Agency (EMA) as part of a Post-Authorisation Efficacy Study (PAES), will take place in the first quarter of 2020 and the associated final report is expected in the third quarter of 2020 according to the current state of knowledge of the pharmaceutical company.

A limitation of the resolution until 1 July 2020 is therefore considered to be appropriate.

In accordance with Section 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of ixazomib shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline to prove the extent of the additional benefit of ixazomib (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 8, number 5 VerfO). The possibility that a benefit assessment of ixazomib can be carried out at an earlier point in time for other reasons (*cf* Chapter 5, Section 1, paragraph 2 VerfO) remains unaffected by this. The G-BA is able, in principle, to revise the limitation if it has been presented with clear justification that it is insufficient.

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 G-BA bases the resolution on the patient figures stated in the dossier of the pharmaceutical company, which also correspond to the patient figures from previous resolutions in the therapeutic indication in question. The range used here takes into account uncertainties in the data basis and reflects the minimum and maximum values obtained when deriving the patient numbers. Because of the uncertainty in the data basis, a more precise indication is not possible.

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: 23 May 2017):

www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/003844/WC500217620.pdf

Treatment with ixazomib should only be initiated and monitored by a specialist experienced in the field of oncology and treatment of patients with multiple myeloma (specialist in internal medicine and haematology and oncology).

This medicinal product was authorised by the EMA under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The EMA will evaluate new information on this medicinal product at least once per year and, if necessary, the summary of product characteristics will be updated.

Patients who were refractory to bortezomib and carfilzomib were not included in the pivotal study of Ixazomib (C16010). In these patients, a careful risk-benefit analysis should be carried out before starting therapy. The aim is to highlight relevant efficacy aspects based on the unclear evidence, which may be relevant in the treatment of patients refractory to bortezomib and carfilzomib who were included in the approved therapeutic indication of ixazomib. Therefore, the treating physician should give special consideration to the benefits and risks of ixazomib

when prescribing the active ingredient to this group of patients. The indication of a careful risk-benefit assessment does not imply a restriction of the prescribability of ixazomib according to Section 92, paragraph 1 SGB V nor does it imply a therapy recommendation not to prescribe the active ingredient in this patient group in general.

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 June 2017).

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates according to Section 130a SGB V and Section 130, paragraph 1 SGB V. To calculate the cost of medicines, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs by quantity, the pharmaceutical costs were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

The recommended initial dose of NINLARO is 4 mg orally once a week on Days 1, 8 and 15 of a 28-day treatment cycle. The recommended initial dose of lenalidomide is 25 mg once daily on Days 1 to 21 of a 28-day treatment cycle. The recommended initial dose of dexamethasone is 40 mg on Days 1, 8, 15, and 22 of a 28-day treatment cycle.

Treatment should be continued until disease progression or unacceptable toxicity occurs. Treatment with NINLARO in combination with lenalidomide and dexamethasone for more than 24 cycles should be based on an individual risk-benefit assessment because tolerability and toxicity data beyond 24 cycles are limited.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments per patient per year [7]	Treatment duration per treatment (days)	Treatment days per patient per year
Ixazomib	4 mg on Days 1, 8, and 15	39	3	39
Lenalidomide	25 mg on Days 1 through 21	273	21	273
Dexamethasone	40 mg on Days 1, 8, 15, and 22	52	4	52

Usage and consumption:

[7] Calculated and standardised for one year.

Designation of the therapy	Potency (mg)	Quantity per package (tablets)	Average annual consumption (tablets)
Ixazomib	4 mg	3	39
Lenalidomide	25 mg	21	273
Dexamethasone	8 mg	100	260

Costs:

Costs of the medicinal product:

Designation of the therapy	Cost (pharmacy selling price according to potency and package size)	Costs after deduction of statutory rebates
Ixazomib	€ 9985.49	€ 9416.72 [€ 1.77[8]; € 567.00[9]]
Lenalidomide	€ 7912.21	€ 7459.15 [€ 1.77 €; € 451.29[9]]
Dexamethasone	€ 123.07[10]	€ 112.43 [€ 1.77 €[8]; € 8.87[9]]

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 June 2017

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 standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed according to the product information, no costs for additionally required SHI services had to be taken into account.

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.

[8] Rebate according to Section 130 SGB V
[9] Rebate according to Section 130a SGB V
[10] Fixed amount of Stage 1

4. Process sequence

On 13 January 2017, 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 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 18 April 2017 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 9 May 2017.

The oral hearing was held on 22 May 2017.

A new version of the G-BA dossier evaluation was prepared on 8 June 2017. Version 1.1 of 8 June 2017 replaces version 1.0 of the dossier evaluation of 18 April 2017 and was brought to the attention of the Pharmaceuticals Subcommittee at its session on 20 June 2017. The evaluation result was not affected by the changes in version 1.1 compared with version 1.0.

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 were discussed at the session of the subcommittee on 20 June 2017, and the proposed resolution was approved.

At its session on 6 July 2017, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	11 April 2017	Knowledge of the benefit assessment of the G-BA
Working group Section 35a	16 May 2017	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	22 May 2017	Conduct of the oral hearing
Working group Section 35a	30 May 2017 13 June 2017	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 product	20 June 2017	Concluding discussion of the proposed resolution
Plenum	6 July 2017	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 July 2017

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

Prof Hecken