# Resolution

Gemeinsamer Bundesausschuss

## 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

At its session on 6 July 2017, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD MM YYYY (Federal Gazette, BAnz AT DD MM YYYY BX) as follows:

**I. Annex XII shall be amended in alphabetical order to include the active ingredient ixazomib as follows:**

**Ixazomib**

Resolution of: 6 July 2017
Entry into force on: 6 July 2017
Federal Gazette, BAnz AT DD MM YYYY Bx

**Approved therapeutic indication (according to the marketing authorisation of 21 November 2016):**

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. Extent of the additional benefit of the medicinal product

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 on orphan drugs. According to Section 35a, paragraph 1, sentence 10, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO). This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).



**Extent of the additional benefit:**

Non-quantifiable

**Study results according to endpoints: Study C16010**

| | Ixazomib + lenalidomide + dexamethasone | | lenalidomide + dexamethasone | | Ixazomib + lenalidomide + dexamethasone vs lenalidomide + dexamethasone |
|---|---|---|---|---|---|
| **Endpoint category**<br>**Endpoint** | **N** [a] | **Median time to event (months)**<br>**[95% CI]**<br>***Patients with event***<br>***n (%)*** | **N** [a] | **Median time to event (months)**<br>**[95% CI]**<br>***Patients with event***<br>***n (%)*** | **Hazard ratio** [b]<br>**[95% CI]**<br>**p value** [c]<br>**Absolute difference (AD)** |
| **Mortality** | | | | | |
| Overall survival | | | | | |
| 1. Interim analysis<br>(Data cut-off of 30 October 2014) [d] | 360 | n.a.<br>*51 (14)* | 362 | n.a.<br>*56 (15)* | 0.90<br>[0.62; 1.32]<br>p = 0.59 |
| 2. Interim analysis<br>(Data cut-off of 12 July 2015) [e] | 360 | n.a.<br>*81 (23)* | 362 | n.a.<br>[30.9; n.a.]<br>*90 (25)* | 0.87<br>[0.64; 1.18]<br>p = 0.36 |
| **Morbidity** | | | | | |
| Progression-free survival | | | | | |
| 1. Interim analysis<br>(Data cut-off of 30 October 2014) [d, f] | 360 | 20.6<br>[17.2; n.a.]<br>*129 (36)* | 362 | 14.7<br>[12.9; 17.6]<br>*157 (43)* | 0.74<br>[0.59; 0.94]<br>p = 0.012<br>AD: +5.9 months |
| 2. Interim analysis<br>(Data cut-off of 12 July 2015) [e, f] | 360 | 20.0<br>[18.0; 23.4]<br>*177 (49)* | 362 | 15.9<br>[13.2; 18.8]<br>*195 (54)* | 0.82<br>[0.67; 1.0] [g]<br>p = 0.054 |

| | Ixazomib + lenalidomide + dexamethasone | | | lenalidomide + dexamethasone | | | Ixazomib + lenalidomide + dexamethasone vs lenalidomide + dexamethasone |
|---|---|---|---|---|---|---|---|
| **Endpoint category**<br>**Endpoint** | **N [a]** | **n** | **LS Mean (SE)** | **N [a]** | **n** | **LS Mean (SE)** | **LS MD [95% CI]**<br>**p value [h]** |
| **Morbidity** | | | | | | | |
| BPI-SF (data cut-off of 12 July 2015) | | | | | | | |
| Strongest pain within last 24 hours (BPI-SF question 3) | | | | | | | |
| Start of study | 360 | 350 | 4.4 (0.62) | 362 | 353 | 4.3 (0.62) | 0.0 [−0.4; 0.4]<br>p = 0.849 |
| Cycle 8 | 360 | 252 | −0.4 (0.41) | 362 | 255 | −0.3 (0.41) | −0.1 [−0.5; 0.3]<br>p = 0.554 |
| End of treatment | 360 | 150 | 0.4 (0.42) | 362 | 158 | 0.3 (0.42) | 0.1 [−0.4; 0.5]<br>p = 0.744 |
| Lowest pain within last 24 hours (BPI-SF question 4) | | | | | | | |
| Start of study | 360 | 349 | 2.7 (0.46) | 362 | 352 | 2.7 (0.45) | 0.0 [−0.3; 0.3]<br>p = 0.901 |
| Cycle 8 | 360 | 251 | −0.1 (0.31) | 362 | 253 | 0.1 (0.31) | −0.1 [−0.4; 0.2]<br>p = 0.382 |
| End of treatment | 360 | 149 | 0.4 (0.32) | 362 | 158 | 0.5 (0.31) | −0.1 [−0.4; 0.2]<br>p = 0.593 |
| Pain in this moment (BPI-SF question 6) | | | | | | | |
| Start of study | 360 | 348 | 3.4 (0.56) | 362 | 352 | 3.3 (0.56) | 0.0 [−0.3; 0.4]<br>p = 0.843 |
| Cycle 8 | 360 | 251 | −0.3 (0.36) | 362 | 254 | 0.0 (0.36) | −0.2 [−0.6; 0.1]<br>p = 0.132 |
| End of treatment | 360 | 149 | 0.2 (0.37) | 362 | 157 | 0.3 (0.37) | 0.0 [−0.4; 0.4]<br>p = 0.868 |
| Impairment due to pain within last 24 hours (Pain Interference Score, BPI-SF question 9) | | | | | | | |
| Start of study | 360 | 345 | 3.5 (0.56) | 362 | 351 | 3.5 (0.56) | 0.0 [−0.4; 0.4]<br>p = 0.950 |
| Cycle 8 | 360 | 247 | 0.4 (0.35) | 362 | 253 | 0.5 (0.35) | −0.1 [−0.4; 0.2]<br>p = 0.439 |
| End of treatment | 360 | 145 | 1.1 (0.36) | 362 | 153 | 1.1 (0.36) | 0.0 [−0.4; 0.3]<br>p = 0.877 |

| | Ixazomib + lenalidomide + dexamethasone | | | lenalidomide + dexamethasone | | | Ixazomib + lenalidomide + dexamethasone vs lenalidomide + dexamethasone |
|---|---|---|---|---|---|---|---|
| **Endpoint category**<br>**Endpoint** | **N [a]** | **n** | **Mean (SD)** | **N [a]** | **n** | **Mean (SD)** | **SMD [95% CI]**<br>**p value [k]** |
| EQ-5D VAS (data cut-off of 12 July 2015) | | | | | | | |
| Start of study [i] | 360 | 352 | 62.1 (21.3) | 362 | 354 | 60.5 (20.8) | 0.08 [−0.07; 0.22]<br>p = 0.31 |
| Cycle 8 | 360 | 259 | 68.9 (17.8) | 362 | 260 | 67.0 (18.5) | 0.10 [−0.07; 0.28]<br>p = 0.23 |
| End of treatment | 360 | 156 | 61.5 (19.6) | 362 | 163 | 59.1 (22.6) | 0.11 [−0.11; 0.33]<br>p = 0.31 |

| | Ixazomib + Lenalidomide + dexamethasone | | | Lenalidomide + dexamethasone | | | Ixazomib + lenalidomide + dexamethasone vs Lenalidomide + dexamethasone |
|---|---|---|---|---|---|---|---|
| **Endpoint category**<br>**Endpoint** | **N [a]** | **n** | **LS Mean (SE)** | **N [a]** | **n** | **LS Mean (SE)** | **LS MD [95% CI]**<br>**p value [l]** |
| **Health-related quality of life** | | | | | | | |
| EORTC-QLQ-C30 (data cut-off of 12 July 2015) | | | | | | | |
| Start of study [i] | 360 | 355 | 54.4 (1.54) | 362 | 359 | 53.3 (1.55) | 2.1 [−1.1; 5.4]<br>p = 0.195 |
| Cycle 8 | 360 | 252 | 0.4 (1.26) | 362 | 257 | 0.6 (1.27) | −0.2 [−3.2; 2.8]<br>p = 0.891 |
| End of treatment | 360 | 155 | −6.4 (1.46) | 362 | 158 | −8.0 (1.45) | 1.6 [−2.0; 5.2]<br>p = 0.393 |
| EORTC-QLQ-MY20 (data cut-off of 12 July 2015)<br>Date | | | | | | | |
| Start of study [i] | 360 | 354 | 32.6 (1.52) | 362 | 359 | 33.4 (1.53) | −0.8 [−4.0; 2.4]<br>p = 0.626 |
| Cycle 8 | 360 | 256 | −7.2 (1.10) | 362 | 256 | −7.4 (1.11) | 0.2 [−2.3; 2.8]<br>p = 0.869 |
| End of treatment | 360 | 155 | −1.5 (1.26) | 362 | 156 | −2.0 (1.26) | 0.5 [−2.6; 3.5]<br>p = 0.755 |

| | Ixazomib + Lenalidomide + dexamethasone | | Lenalidomide + dexamethasone | | Ixazomib + lenalidomide + dexamethasone vs Lenalidomide + dexamethasone |
|---|---|---|---|---|---|
| **Endpoint category**<br>**Endpoint** | **N [a,m]** | **Patients with event**<br>**n (%)** | **N [a, n]** | **Patients with event**<br>**n (%)** | **RR**<br>**[95% CI]**<br>**p value [k]** |
| **Side effects**<br>(Data cut-off of 12 July 2015) | | | | | |
| AE | 361 | 355 (98) | 359 | 357 (97) | – |
| AE<br>(CTCAE grade ≥ 3) | 361 | 267 (74) | 359 | 247 (97) | 1.07<br>[0.98; 1.18]<br>p = 0.13 |
| SAE | 361 | 168 (47) | 359 | 177 (49) | 0.94<br>[0.81; 1.10]<br>p = 0.46 |
| Therapy discontinuations because of AE | 361 | 60 (17) | 359 | 50 (14) | 1.19<br>[0.84; 1.69]<br>p = 0.32 |
| **Most frequent AE by SOC and PT (Cut-off at > 10%)** | | | | | |
| **Nervous system disorders** | **361** | **22 (61)** | **359** | **207 (58)** | **1.07**<br>**[0.95; 1.20]**<br>**p = 0.29** |
| Headache | 361 | 44 (12) | 359 | 42 (12) | |
| Peripheral sensory neuropathy | 361 | 69 (19) | 359 | 53 (15) | |
| Vertigo | 361 | 49 (14) | 359 | 35 (10) | |
| Tremor | 361 | 21 (6) | 359 | 37 (10) | |
| **Blood and lymphatic system disorders** | **361** | **184 (51)** | **359** | **172 (48)** | **1.06**<br>**[0.92; 1.23]**<br>**p = 0.41** |
| Anaemia | 361 | 103 (29) | 359 | 98 (27) | |
| Neutropoenia | 361 | 103 (29) | 359 | 92 (26) | |
| Thrombocytopoenia | 361 | 86 (24) | 359 | 41 (11) | |

(Continuation)

| | Ixazomib + Lenalidomide + dexamethasone | | Lenalidomide + dexamethasone | | Ixazomib + lenalidomide + dexamethasone vs Lenalidomide + dexamethasone |
|---|---|---|---|---|---|
| **Endpoint category**<br>**Endpoint** | **N** | **Patients with event**<br>**n (%)** | **N** | **Patients with event**<br>**n (%)** | **RR**<br>**[95% CI]**<br>**p value** [k] |
| **Gastrointestinal disorders** | **361** | **268 (74)** | **359** | **245 (68)** | **1.09**<br>**[0.99; 1.19]**<br>**p = 0.08** |
| Diarrhoea | 361 | 164 (45) | 359 | 139 (39) | |
| Vomiting | 361 | 84 (23) | 359 | 42 (12) | |
| Constipation | 361 | 126 (35) | 359 | 94 (26) | |
| Nausea | 361 | 104 (29) | 359 | 79 (22) | |
| **Respiratory, thoracic and mediastinal disorders** | **361** | **163 (45)** | **359** | **155 (43)** | **1.05**<br>**[0.89; 1.23]**<br>**p = 0.59** |
| Dyspnoea | 361 | 40 (11) | 359 | 40 (11) | |
| Coughing | 361 | 58 (16) | 359 | 57 (16) | |
| **Skin and subcutaneous tissue disorders** | **361** | **185 (51)** | **359** | **140 (39)** | **1.31**<br>**[1.12; 1.55]**<br>**p = 0.001** |
| Itching | 361 | 38 (11) | 359 | 25 (7) | |
| **General disorders and administration site conditions** | **361** | **237 (66)** | **359** | **232 (65)** | **1.02**<br>**[0.91; 1.13]**<br>**p = 0.77** |
| Fatigue | 361 | 106 (29) | 359 | 102 (28) | |
| Asthenia | 361 | 58 (16) | 359 | 57 (16) | |
| Peripheral oedema | 361 | 101 (28) | 359 | 73 (20) | |
| Fever | 361 | 56 (16) | 359 | 75 (21) | |
| **Infections and infestations** | **361** | **276 (76)** | **359** | **266 (74)** | **1.03**<br>**[0.95; 1.12]**<br>**p = 0.46** |
| Upper respiratory tract infections | 361 | 83 (23) | 359 | 70 (19) | |
| Nasopharyngitis | 361 | 81 (22) | 359 | 73 (20) | |
| Bronchitis | 361 | 60 (17) | 359 | 51 (14) | |

(Continuation)

| | Ixazomib + lenalidomide + dexamethasone | | Lenalidomide + dexamethasone | | Ixazomib + lenalidomide + dexamethasone vs Lenalidomide + dexamethasone |
|---|---|---|---|---|---|
| **Endpoint category**<br>**Endpoint** | **N** | **Patients with event**<br>**n (%)** | **N** | **Patients with event**<br>**n (%)** | **RR**<br>**[95% CI]**<br>**p value [k]** |
| Pneumonia | 361 | 41 (11) | 359 | 44 (12) | |
| **Eye disorders** | **361** | **116 (32)** | **359** | **83 (23)** | **1.39**<br>**[1.09; 1.77]**<br>**p = 0.007** |
| Cataracts | 361 | 28 (8) | 359 | 37 (10) | |
| **Metabolism and nutrition disorders** | **361** | **131 (36)** | **359** | **123 (34)** | **1.06**<br>**[0.87; 1.29]**<br>**p = 0.57** |
| Loss of appetite | 361 | 46 (13) | 359 | 38 (11) | |
| Hypoglycaemia | 361 | 47 (13) | 359 | 37 (10) | |
| **Musculoskeletal and connective tissue disorders** | **361** | **233 (65)** | **359** | **226 (63)** | **1.03**<br>**[0.92; 1.14]**<br>**p = 0.66** |
| Arthralgia | 361 | 45 (12) | 359 | 39 (11) | |
| Muscle spasms | 361 | 66 (18) | 359 | 95 (28) | |
| Back pain | 361 | 87 (24) | 359 | 62 (17) | |
| Pain in the extremities | 361 | 43 (12) | 359 | 31 (9) | |
| **Psychiatric disorders** | **361** | **124 (34)** | **359** | **144 (40)** | **0.86**<br>**[0.71; 1.04]**<br>**p = 0.11** |
| Insomnia | 361 | 73 (20) | 359 | 98 (27) | |

a: Number of patients in the assessment

b: Calculation of the hazard ratio based on a Cox proportional hazard regression model stratified according to the following factors: Prior therapies (1, 2 or 3), proteasome inhibitor (exposed vs naïve), ISS Stage in screening (I or II, III).

c: Calculation of the p values based on a log-rank test stratified according to the factors: Prior therapies (1, 2 or 3), proteasome inhibitor (exposed vs naïve), ISS Stage in screening (I or II, III).

d: Median observation time ixazomib+LenDex 14.8 months (min; max: [13.63; 15.41]) and placebo+LenDex 14.6 months (min; max: [13.57; 15.44]).

e: Median observation time 23.3 months (min; max: [21.91; 23.79]), placebo+LenDex 22.9 months (min; max: [21.78; 23.56]).

f: 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.

g: Source: European public assessment report (EPAR) of ixazomib (Ninlaro®) of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) of 15 September 2016

h: Calculation of change from baseline of subscale values based on an MMRM, including covariate treatment group, round, baseline, ISS stage at screening, prior therapies, proteasome inhibitor, age, sex, and ancestry. The average pain is not included in the analysis because of a lack of convergence in MMRM.

i: Start of study defined as the last time before the administration of the first dose of the study medication

k: Own calculation

l: Based on an MMRM, including covariate treatment group, round, baseline, ISS stage at screening, prior therapies, proteasome inhibitor, age, sex, and ancestry

m: n = 2 patients were excluded because they did not receive study medication. In addition, n = 3 patients were enrolled because of erroneous administration of ixazomib.

n: n = 3 patients were excluded because of inadvertent administration of Ixazomib.

Abbreviations:

BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-VAS: European Quality of Life 5-Dimensional-Visual Analogue Scale; ITT: Intention to treat; Ixa: ixazomib; CI: confidence interval; LenDex: lenalidomide + dexamethasone; LS MD: least squares mean difference; LS mean: Least squares mean Value; MedDRA: Medical dictionary for regulatory activities; MMRM: mixed model repeated measures); n: number of patients with event; n.a. not achieved; RR: relative risk; SD: standard deviation; SMD: standardised mean difference; SE: standard error; SAE: serious adverse events; AE: adverse events

## 2. Number of patients or demarcation of patient groups eligible for treatment

approx. 4,700–7,000 patients

## 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.

## 4. Treatment costs

**Annual treatment costs:**

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Ixazomib | € 122,417.36 |
| Lenalidomide | € 96,968.95 |
| dexamethasone | € 292.32 |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 June 2017)

Costs for additionally required SHI services: not applicable



## II. Entry into force

1. **The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 6 July 2017.**
2. **The period of validity of the resolution is limited to 1 July 2020.**

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de .

Berlin, 6 July 2017

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

Prof Hecken