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

Resolution of: 21 April 2022 Valid until: unlimited
Entry into force on: 21 April 2022
Federal Gazette, BAnz AT 01 06 2022 B4

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.

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

see therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Ixazomib is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 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) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. 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).

Adults with multiple myeloma who have received at least one prior therapy

Extent of additional benefit and significance of the evidence of ixazomib in combination with lenalidomide and dexamethasone:

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

Study results according to endpoints:[1]

Adults with multiple myeloma who have received at least one prior therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment
Morbidity	↔	No relevant differences for the benefit assessment
Health-related quality of life	↔	No relevant differences for the benefit assessment
Side effects	↔	No relevant differences for the benefit assessment
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

[1] Data from the dossier assessment of the G-BA (published on 1. Februar 2022), unless otherwise indicated.

16010 study: Ixazomib + lenalidomide + dexamethasone **versus** lenalidomide + dexamethasone

Data cut-off: 28.09.2020 (final data cut-off on overall survival)

Mortality

Endpoint	**Ixazomib + Lenalidomide + dexamethasone (Ixazomib / LenDex)**		**Lenalidomide + dexamethasone (LenDex)**		Ixazomib / LenDex vs LenDex
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI][b] p value[c] Absolute difference (AD)[a]
Overall survival					
	360	53.6 [49.3; 63.0] 240 (67)	362	51.6 [44.8; 59.1] 244 (67)	0.94 [0.78; 1.13] 0.495

Morbidity

Endpoint	**Ixazomib + Lenalidomide + dexamethasone (Ixazomib / LenDex)**		**Lenalidomide + Dexamethasone (LenDex)**		Ixazomib / LenDex vs LenDex
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS)[d] (2nd interim analysis: data cut-off of 12.07.2015)					
	360	20.0 - 177 (49.2)	362	15.9 - 195 (53.9)	0.82 [0.67; 1.00] 0.0543

	Ixazomib + Lenalidomide + dexamethasone (Ixazomib / LenDex)		Lenalidomide + Dexamethasone (LenDex)		Ixazomib / LenDex vs LenDex
	N	MV (SD)[g]	N	MV (SD)[g]	MD [95% CI] p value[h]
BPI-SF (mean change until cycle 8)					
Strongest pain (Item 3)[d]	252	-0.95 (2.75)	255	-0.76 (2.65)	-0.10 [-0.48; 0.28] 0.662
Least pain (Item 4)	251	-0.43 (1.83)	253	-0.22 (2.02)	-0.09 [-0.38; 0.19] 0.595
Moderate pain (Item 5)	251	-0.73 (2.20)	251	-0.57 (2.32)	-0.05 [-0.37; 0.27] 0.807
Momentary pain (Item 6)	251	-0.73 (2.37)	254	-0.40 (2.60)	-0.23 [-0.56; 0.10] 0.251
Pain interference (Items 9A - 9G)	247	-0.37 (2.11)	253	-0.40 (2.10)	-0.11 [-0.43; 0.20] 0.559
Endpoint	**Ixazomib + Lenalidomide + dexamethasone (Ixazomib / LenDex)**		**Lenalidomide + Dexamethasone (LenDex)**		Ixazomib / LenDex vs LenDex
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI][b] p value[c, e] Absolute difference (AD)[a]
Disease symptomatology					
Symptom scales of the EORTC QLQ-C30 - time to first deterioration by ≥ 10 points[i]					
Fatigue	360	3.06 [2.79; 5.03] 258 (72)	362	2.79 [1.87; 3.09] 270 (75)	0.88 [0.74; 1.05] 0.123

Endpoint	**Ixazomib + Lenalidomide + dexamethasone (Ixazomib / LenDex)**		**Lenalidomide + Dexamethasone (LenDex)**		Ixazomib / LenDex vs LenDex
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI][b] p value[c, e] Absolute difference (AD)[a]
Nausea / vomiting	360	13.86 [12.12; 16.89] 197 (55)	362	17.97 [14.42; 26.74] 177 (49)	1.17 [0.95; 1.43] 0.138
Pain	360	7.62 [4.90; 10.15] 236 (66)	362	6.54 [4.63; 8.48] 244 (67)	0.92 [0.76; 1.10] 0.344
Dyspnoea	360	13.83 [10.15; 18.23] 195 (54)	362	9.00 [6.54; 12.45] 212 (59)	0.85 [0.70; 1.04] 0.100
Insomnia	360	6.47 [4.67; 10.28] 218 (61)	362	10.12 [6.44; 13.80] 200 (55)	1.12 [0.92; 1.36] 0.238
Appetite loss	360	14.52 [10.22; 19.32] 197 (55)	362	8.75 [6.77; 11.99] 228 (63)	0.76 [0.63; 0.92] 0.004
Constipation	360	4.63 [3.02; 6.57] 219 (61)	362	6.28 [3.71; 10.15] 217 (60)	1.03 [0.85; 1.25] 0.744
Diarrhoea	360	8.28 [6.51; 9.89] 248 (69)	362	9.17 [6.74; 12.12] 229 (63)	1.13 [0.95; 1.36] 0.169
Symptom scales of the EORTC QLQ-MY20 – time to first deterioration by ≥ 10 points[i]					
Symptoms of disease	360	14.78 [10.84; 20.57] 194 (54)	362	13.83 [10.38; 18.20] 202 (56)	0.96 [0.79; 1.18] 0.708
Side effects of the treatment	360	6.70 [4.86; 9.46] 221 (61)	362	7.62 [5.32; 11.07] 230 (64)	0.97 [0.80; 1.17] 0.724

Endpoint	Ixazomib + Lenalidomide + dexamethasone (Ixazomib / LenDex)		Lenalidomide + Dexamethasone (LenDex)		Ixazomib / LenDex vs LenDex
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI][b] p value[c, e] Absolute difference (AD)[a]
Health status (EQ-5D VAS) – time to first deterioration by ≥ 15 points[k]					
	360	17.05 [13.57; 28.55] 211 (59)	362	16.59 [12.91; 26.68] 216 (60)	0.97 [0.80; 1.17] 0.731

Health-related quality of life

Endpoint	Ixazomib + Lenalidomide + dexamethasone (Ixazomib / LenDex)		Lenalidomide + Dexamethasone (LenDex)		Ixazomib / LenDex vs LenDex
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI][b] p value[c, e] Absolute difference (AD)[a]
Health-related quality of life – time to first deterioration [i]					
Global health status and functional scales of the EORTC QLQ-C30					
Global health status	360	4.63 [3.02; 6.51] 245 (68)	362	8.25 [6.21; 10.64] 221 (61)	1.21 [1.01; 1.45] 0.038
Physical functioning	360	13.14 [10.12; 17.51] 202 (56)	362	12.09 [9.46; 15.67] 212 (59)	0.90 [0.74; 1.10] 0.297
Role functioning	360	4.90 [4.11; 7.62] 238 (66)	362	4.86 [3.45; 8.25] 240 (66)	0.95 [0.79; 1.14] 0.571
Cognitive functioning	360	6.47 [4.80; 8.51] 238 (66)	362	5.19 [4.63; 6.70] 242 (67)	0.98 [0.82; 1.18] 0.833

Endpoint	**Ixazomib + Lenalidomide + dexamethasone (Ixazomib / LenDex)**		**Lenalidomide + Dexamethasone (LenDex)**		Ixazomib / LenDex vs LenDex
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI][b] p value[c, e] Absolute difference (AD)[a]
Emotional functioning	360	13.83 [10.94; 17.74] 197 (55)	362	10.15 [8.34; 14.92] 204 (56)	0.91 [0.75; 1.11] 0.355
Social functioning	360	5.13 [4.04; 8.48] 240 (67)	362	4.63 [3.02; 6.47] 248 (69)	0.90 [0.76; 1.08] 0.256
Health-related quality of life – time to first deterioration [i]					
Functional scales of the EORTC QLQ-MY20					
Physical perception	360	15.7 [10.4; 24.8] 190 (53)	362	12.32 [10.28; 18.43] 189 (52)	0.98 [0.80; 1.20] 0.815
Future prospects	360	17.51 [12.19; 31.77] 175 (49)	362	10.18 [6.47; 14.75] 206 (57)	0.75 [0.62; 0.92] 0.005

Side effects (related to the safety population)

Endpoint	**Ixazomib + Lenalidomide + dexamethasone (Ixazomib / LenDex)**		**Lenalidomide + Dexamethasone (LenDex)**		Ixazomib / LenDex vs LenDex
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] [b] p value [c, e] Absolute difference (AD)[a]
Total, excluding events related to the underlying disease					
AE	361	- 359 (99)	359	- 357 (99)	- -
SAE	361	19.78 [16.30; 25.23] 203 (56)	359	16.76 [13.44; 22.90] 200 (56)	0.93 [0.76; 1.13] 0.438
Severe AE (CTCAE grade ≥ 3)	361	4.37 [3.65; 6.47] 289 (80)	359	6.01 [4.40; 8.61] 265 (74)	1.17 [0.99; 1.39 0.061
Discontinuation due to AEs[f] (≥ 1 active ingredient component)	361	45.93 [33.81; 61.21] 138 (38)	359	44.71 [35.25; 60.06] 113 (31)	1.15 [0.89; 1.48] 0.280
Severe AEs with incidence ≥ 5% by system organ class in one of the two treatment groups					
Blood and lymphatic system disorders	361	51.87 [33.19; n.c.] 138 (38)	359	40.03 [28.03; n.c.] 130 (36)	1.03 [0.81; 1.31] 0.806
Infections and infestations	361	54.18 [45.45; n.c.] 110 (30)	359	50.84 [35.74; n.c.] 111 (31)	0.89 [0.68; 1.16] 0.384
Investigations	361	n.a. [n.c.; n.c.] 55 (15)	359	n.a. [n.c.; n.c.] 45 (13)	1.11 [0.75; 1.64] 0.603
Gastrointestinal disorders	361	n.a. [n.c.; n.c.] 55 (15)	359	n.a. [n.c.; n.c.] 21 (6)	2.63 [1.58; 4.35] < 0.001
Metabolic and nutrition disorders	361	n.a. [n.c.; n.c.] 48 (13)	359	n.a. [n.c.; n.c.] 41 (11)	1.07 [0.70; 1.63] 0.747
Nervous system disorders	361	n.a. [n.c.; n.c.] 46 (13)	359	n.a. [n.c.; n.c.] 34 (9)	1.28 [0.82; 1.99] 0.282

Endpoint	**Ixazomib + Lenalidomide + dexamethasone (Ixazomib / LenDex)**		**Lenalidomide + Dexamethasone (LenDex)**		Ixazomib / LenDex vs LenDex
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] [b] p value [c, e] Absolute difference (AD)[a]
General disorders and administration site conditions	361	n.a. [n.c.; n.c.] 41 (11)	359	n.a. [n.c.; n.c.] 36 (10)	1.12 [0.72; 1.76] 0.613
Musculoskeletal and connective tissue disorders	361	n.a. [n.c.; n.c.] 35 (10)	359	n.a. [n.c.; n.c.] 46 (13)	0.70 [0.45; 1.09] 0.115
Respiratory, thoracic and mediastinal disorders	361	n.a. [n.c.; n.c.] 31 (9)	359	n.a. [n.c.; n.c.] 28 (8)	1.12 [0.67; 1.89] 0.657
Cardiac disorders	361	n.a. [n.c.; n.c.] 30 (8)	359	n.a. [n.c.; n.c.] 23 (6)	1.15 [0.67; 1.97] 0.621
Vascular disorders	361	n.a. [n.c.; n.c.] 25 (7)	359	n.a. [n.c.; n.c.] 19 (5)	1.30 [0.72; 2.38] 0.385
Eye disorders	361	n.a. [n.c.; n.c.] 24 (7)	359	n.a. [n.c.; n.c.] 29 (8)	0.71 [0.41; 1.23] 0.221
Skin and subcutaneous tissue disorders	361	n.a. [n.c.; n.c.] 23 (6)	359	n.a. [n.c.; n.c.] 8 (2)	2.82 [1.26; 6.31] 0.008
Neoplasms benign, malignant and unspecified (including cysts and polyps)	361	n.a. [n.c.; n.c.] 20 (6)	359	n.a. [n.c.; n.c.] 18 (5)	0.97 [0.51; 1.84] 0.916
Psychiatric disorders	361	n.a. [n.c.; n.c.] 26 (7)	359	n.a. [n.c.; n.c.] 19 (5)	0.66 [0.36; 1.20] 0.171

Endpoint	**Ixazomib + Lenalidomide + dexamethasone (Ixazomib / LenDex)**		**Lenalidomide + Dexamethasone (LenDex)**		Ixazomib / LenDex vs LenDex
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] [b] p value [c, e] Absolute difference (AD)[a]
Injury, poisoning and procedural complications	361	n.a. [n.c.; n.c.] 17 (5)	359	n.a. [n.c.; n.c.] 20 (6)	0.80 [0.42; 1.53] 0.506
Renal and urinary disorders	361	n.a. [n.c.; n.c.] 12 (3)	359	n.a. [n.c.; n.c.] 28 (8)	0.40 [0.20; 0.79] 0.006
SAEs with incidence ≥ 5% by system organ class in one of the two treatment groups					
Infections and infestations	361	74.78 [47.07; n.c.] 102 (28)	359	57.09 [39.37; n.c.] 109 (30)	0.84 [0.64; 1.11] 0.220
Cardiac disorders	361	n.a. [n.c.; n.c.] 31 (9)	359	n.a. [n.c.; n.c.] 27 (8)	1.04 [0.62; 1.76] 0.876
Gastrointestinal disorders	361	n.a. [n.c.; n.c.] 28 (8)	359	n.a. [n.c.; n.c.] 11 (3)	2.46 [1.22; 4.96] 0.009
Respiratory, thoracic and mediastinal disorders	361	n.a. [n.c.; n.c.] 25 (7)	359	n.a. [n.c.; n.c.] 28 (8)	0.87 [0.50; 1.50] 0.607
General disorders and administration site conditions	361	n.a. [n.c.; n.c.] 24 (7)	359	n.a. [n.c.; n.c.] 28 (8)	0.81 [0.47; 1.40] 0.449
Neoplasms benign, malignant and unspecified (including cysts and polyps)	361	n.a. [n.c.; n.c.] 23 (6)	359	n.a. [n.c.; n.c.] 24 (7)	0.86 [0.48; 1.54] 0.614

Endpoint	Ixazomib + Lenalidomide + dexamethasone (Ixazomib / LenDex)		Lenalidomide + Dexamethasone (LenDex)		Ixazomib / LenDex vs LenDex
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] [b] p value [c, e] Absolute difference (AD)[a]
Injury, poisoning and procedural complications	361	n.a. [n.c.; n.c.] 19 (5)	359	n.a. [n.c.; n.c.] 20 (6)	0.88 [0.47; 1.66] 0.692
Nervous system disorders	361	n.a. [n.c.; n.c.] 19 (5)	359	n.a. [n.c.; n.c.] 16 (4)	1.03 [0.52; 2.03] 0.932
Blood and lymphatic system disorders	361	n.a. [n.c.; n.c.] 18 (5)	359	n.a. [n.c.; n.c.] 24 (7)	0.68 [0.37; 1.26] 0.213
Musculoskeletal and connective tissue disorders	361	n.a. [n.c.; n.c.] 16 (4)	359	n.a. [n.c.; n.c.] 24 (7)	0.58 [0.31; 1.09] 0.087
Renal and urinary disorders	361	n.a. [n.c.; n.c.] 10 (3)	359	n.a. [n.c.; n.c.] 19 (5)	0.49 [0.23; 1.04] 0.059
AE of special interest					
Malignant neoplasms	360		362		
Patients with at least 1 malignant neoplasm, n(%)	360	37 (10)	362	43 (12)	
Localisation, n (%) Haematological Non-haematological (solid tumours) Non-haematological (non-melanocytic skin cancer) Non-haematological (melanoma)	360	 2 (5) 17 (46) 19 (51) 1 (3)	362	 4 (9) 19 (44) 23 (53) 0 (0)	

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] Cox proportional hazards model stratified by number of prior therapies (1 versus 2 or 3), prior therapy with 1 proteasome inhibitor (yes versus no) and ISS stage at time of screening (I or II versus III)
[c] Log-rank test stratified by number of prior therapies (1 versus 2 or 3), prior therapy with 1 proteasome inhibitor (yes versus no) and ISS stage at the time of screening (I or II versus III)
[n] Information from the dossier of the pharmaceutical company
[e] HR, 95% CI and p value calculated post hoc

[f] Study participants received the study medication until disease progression, the occurrence of unacceptable toxicity, withdrawal of consent or death, whichever occurred earlier. Premature discontinuation of therapy for reasons other than AEs is a competing event for the endpoint of discontinuation due to AEs to be recorded. Therefore, the certainty of results and interpretability of the effect estimators is limited.
[g] mean change at cycle 8 compared to baseline per treatment group
[h] MMRM with treatment, visit, interaction term treatment × visit, baseline value and the 3 stratification factors number of prior therapies (1 versus 2 or 3), prior therapy with 1 proteasome inhibitor (yes versus no) and ISS stage at the time of screening (I or II versus III) as covariates, calculated post hoc, difference in mean change at cycle 8 compared to baseline between the treatment groups
[i] The time to first deterioration was defined as the time from randomisation to the first increase in score by ≥ 10 points compared to the baseline value.
[K] The time to first deterioration was defined as the time from randomisation to the first decrease in score by ≥ 15 points compared to the baseline value. Patients who did not have an event by the final data cut-off were censored at the time of the last available evaluable observation or at the time of death, and patients who did not complete the EQ-5D VAS at any time were censored at the time of randomisation.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; BPI-SF = Brief Pain Inventory - Short Form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30; EORTC QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Multiple Myeloma 20; HR = hazard ratio; ISS = International Staging System; ITT = intention to treat; CI = confidence interval; MD = mean difference; MMRM = mixed model with repeated measures; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; SD = standard deviation; SAE = serious adverse events; AE = adverse events; vs = versus

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

Adults with multiple myeloma who have received at least one prior therapy

approx. 4,700 to 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: 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". 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).

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Ixazomib in combination with lenalidomide and dexamethasone	
Ixazomib	€ 78,851.37
Lenalidomide	€ 29,945.50
Dexamethasone	€ 193.68
Total	€ 108,990.55

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 April 2022)

Costs for additionally required SHI services: not applicable