Ixazomib

Resolution of: 6 July 2017 / 5 September 2019   Valid until: 01 08 2021
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Federal Gazette, BAnz AT 27 07 2017 B2 / BAnz AT 17 10 2019 B1

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.

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1.   Extent of the additional benefit of the medicinal product

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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

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

Endpoint category Endpoint	Ixazomib + lenalidomide + dexamethasone			lenalidomide + dexamethasone			Ixazomib + lenalidomide + dexamethasone vs lenalidomide + dexamethasone
	N [a]	n	LS Mean (SE)	N [a]	n	LS Mean (SE)	LS MD [95% CI] 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] p = 0.849
Cycle 8	360	252	−0.4 (0.41)	362	255	−0.3 (0.41)	−0.1 [−0.5; 0.3] p = 0.554
End of treatment	360	150	0.4 (0.42)	362	158	0.3 (0.42)	0.1 [−0.4; 0.5] 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] p = 0.901
Cycle 8	360	251	−0.1 (0.31)	362	253	0.1 (0.31)	−0.1 [−0.4; 0.2] p = 0.382
End of treatment	360	149	0.4 (0.32)	362	158	0.5 (0.31)	−0.1 [−0.4; 0.2] 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] p = 0.843
Cycle 8	360	251	−0.3 (0.36)	362	254	0.0 (0.36)	−0.2 [−0.6; 0.1] p = 0.132
End of treatment	360	149	0.2 (0.37)	362	157	0.3 (0.37)	0.0 [−0.4; 0.4] 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] p = 0.950
Cycle 8	360	247	0.4 (0.35)	362	253	0.5 (0.35)	−0.1 [−0.4; 0.2] p = 0.439
End of treatment	360	145	1.1 (0.36)	362	153	1.1 (0.36)	0.0 [−0.4; 0.3] p = 0.877

	Ixazomib + lenalidomide + dexamethasone			lenalidomide + dexamethasone			Ixazomib + lenalidomide + dexamethasone vs lenalidomide + dexamethasone
Endpoint category Endpoint	N [a]	n	Mean (SD)	N [a]	n	Mean (SD)	SMD [95% CI] 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] p = 0.31
Cycle 8	360	259	68.9 (17.8)	362	260	67.0 (18.5)	0.10 [−0.07; 0.28] p = 0.23
End of treatment	360	156	61.5 (19.6)	362	163	59.1 (22.6)	0.11 [−0.11; 0.33] p = 0.31

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

Endpoint category Endpoint	N [a,m]	Ixazomib + Lenalidomide + dexamethasone Patients with event n (%)	N [a,n]	Lenalidomide + dexamethasone Patients with event n (%)	Ixazomib + lenalidomide + dexamethasone vs Lenalidomide + dexamethasone RR [95% CI] p value [k]
Side effects (Data cut-off of 12 July 2015)					
AE	361	355 (98)	359	357 (97)	–
AE (CTCAE grade ≥ 3)	361	267 (74)	359	247 (97)	1.07 [0.98; 1.18] p = 0.13
SAE	361	168 (47)	359	177 (49)	0.94 [0.81; 1.10] p = 0.46
Therapy discontinuations because of AE	361	60 (17)	359	50 (14)	1.19 [0.84; 1.69] 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 [0.95; 1.20] 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 [0.92; 1.23] 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 Endpoint	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value [k]
Gastrointestinal disorders	**361**	**268 (74)**	**359**	**245 (68)**	**1.09 [0.99; 1.19] 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 [0.89; 1.23] 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 [1.12; 1.55] p = 0.001**
Itching	361	38 (11)	359	25 (7)	
General disorders and administration site conditions	**361**	**237 (66)**	**359**	**232 (65)**	**1.02 [0.91; 1.13] 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 [0.95; 1.12] 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)

Endpoint category Endpoint	N	Ixazomib + lenalidomide + dexamethasone Patients with event n (%)	N	Lenalidomide + dexamethasone Patients with event n (%)	Ixazomib + lenalidomide + dexamethasone vs Lenalidomide + dexamethasone RR [95% CI] p value [k]
Pneumonia	361	41 (11)	359	44 (12)	
Eye disorders	**361**	**116 (32)**	**359**	**83 (23)**	**1.39 [1.09; 1.77] p = 0.007**
Cataracts	361	28 (8)	359	37 (10)	
Metabolism and nutrition disorders	**361**	**131 (36)**	**359**	**123 (34)**	**1.06 [0.87; 1.29] 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 [0.92; 1.14] 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 [0.71; 1.04] 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