Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Neratinib (Breast Cancer, HR-Positive, HER2-Positive, Adjuvant Treatment)

of 14 May 2020

At its session on 14 May 2020, 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 Month 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 neratinib as follows:

Neratinib

Resolution of: 14 May 2020
Entry into force on: 14 May 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 31 August 2018):

Nerlynx is indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

For the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago

Appropriate comparator therapy:

Monitoring wait-and-see approach

Extent and probability of the additional benefit of neratinib compared with the monitoring wait-and-see approach:

Hint for a minor additional benefit

Study results according to endpoints[1]:

ExteNET study: Neratinib vs placebo

Study design: randomised, double-blind, two-armed, Phase III

Relevant sub-population: Patients hormone receptor-positive breast cancer who completed adjuvant trastuzumab-based therapy less than one year ago (approx. 47% of the study population)

Data cut-off: 7 July 2014

Mortality

Endpoint	**Neratinib**		**Placebo[a]**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[b]
Overall survival					
no evaluations planned at the relevant data cut-off[c]					

Morbidity

Endpoint	**Neratinib**		**Placebo[a]**		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value Absolute difference (AD)[b]
Relapse rate (event rate)					
Relapses (total)[d, e]	670	26 (3.9)	664	60 (9.0)	0.43 [0.27; 0.67] < 0.001 AD: 5.1%
Events included in the combined endpoint[f]					
Remote metastases	670	20 (3.0)	664	38 (5.7)	–
Invasive contralateral breast cancer	670	1 (0.1)	664	2 (0.3)	–
Invasive ipsilateral breast cancer	670	1 (0.1)	664	2 (0.3)	–

(Continuation)

[1] Data from the dossier assessment of the IQWiG (A19-98) and the addendum (A20-40) unless otherwise indicated.

local/regional invasive relapse	670	3 (0.4)	664	12 (1.8)	–
Ductal carcinoma in situ	670	0 (0)	664	5 (0.8)[d]	–
Death by any cause	670	1 (0.1)	664	1 (0.2)	–
Sensitivity analyses:					
Replacement in accordance with risk of the control group[g]	670	– (5.9)	664	– (10.4)	0.57 [0.37; 0.86]; 0.007 AD: 4.5%
Replacement in the intervention arm in accordance with the risk of the control group[h]	670	– (5.9)	664	– (9.0)	0.65 [0.42; 0.99]; 0.046 AD: 3.1%
Replacement in accordance with twice the risk of the control group[i]	670	– (7.8)	664	– (11.7)	0.67 [0.47; 0.97]; 0.032 AD: 3.9%

Endpoint	**Neratinib**		**Placebo[a]**		Intervention vs control
	N	Median time to event in months [95% CI]	N	Median time to event in months [95% CI]	Hazard ratio [95% CI] p value Absolute difference (AD)[b]
Relapse-free survival[d]					
	670	n.a.	664	n.a.	0.45 [0.28; 0.71] < 0.001 AD: n.c.

Endpoint	**Neratinib**			**Placebo[a]**			Intervention vs control
	N	Values at start of study MV (SD)	Change[j] MV [95% CI]	N	Values at start of study MV (SD)	Change[j] MV [95% CI]	MD [95% CI] p value
Health status							
EQ-5D-VAS[k]	549	no data available	−2.96 [−3.85; −2.07]	568	no data available	−2.50 [−3.32; −1.68]	−0.46 [−1.67; 0.75] 0.459

(Continuation)

Health-related quality of life

Endpoint	Neratinib			Placebo[a]			Intervention vs control
	N	Values at start of study MV (SD)	Change[j] MV [95% CI]	N	Values at start of study MV (SD)	Change[j] MV [95% CI]	MD [95% CI] p value
FACT-B total score[k]							
	541	no data available	−3.74 [−4.69; −2.79]	566	no data available	−3.09 [−3.97; −2.22]	−0.64 [−1.94; 0.65] 0.329
FACT b sub-scales (presented additionally)							
BCS	541	no data available	0.45 [0.15; 0.76]	566	no data available	−0.17 [−0.45; 0.11]	0.62 [0.20; 1.04] 0.004
PWB	no data available						
SWB	no data available						
EWB	no data available						
FWB	no data available						

Side effects

Endpoint	Neratinib		Placebo[a]		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[b]
Total adverse events (presented additionally)					
	662	0.1 [no data available] *649 (98.0)*	657	0.8 [0.6; 0.9] *567 (86.3)*	−
Serious adverse events (SAE)					
	662	n.a. *45 (6.8)*	657	n.a. *36 (5.5)*	1.56 [1.00; 2.43] 0.047 AD: n.c.

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Severe adverse events (CTCAE grade ≥ 3)					
	662	8.6 [5.8; n.c.] *327 (49.4)*	657	n.a. *76 (11.6)*	6.28 [4.92; 8.12] < 0.001 AD: n.c.
Therapy discontinuation because of adverse events					
	662	n.a. *178 (26.9)*	657	n.a. *30 (4.6)*	7.00 [4.83; 10.51] < 0.001 AD: n.c.
Specific adverse events					
Gastrointestinal disorders (SOC, CTCAE grade≥ 3)[l]	662	n.a. *280 (42.3)*	657	n.a. *14 (2.1)*	27.10 [16.47; 48.66] < 0.001 AD: n.c.
Including diarrhoea (PT, CTCAE grade ≥ 3)	662	n.a. *261 (39.4)*	657	n.a. *7 (1.1)*	49.55 [25.29; 116.28] < 0.001 AD: n.c.
Fatigue (PT, CTCAE grade ≥ 3)	662	n.a. *13 (2.0)*	657	n.a. *2 (0.3)*	7.51 [2.07; 48.08] 0.002 AD: n.c.
Metabolism and nutrition disorders (SOC, CTCAE grade ≥ 3)	662	n.a. *20 (3.0)*	657	n.a. *10 (1.5)*	2.36 [1.13; 5.26] 0.023 AD: n.c.
Muscle spasms (PT, AE)	662	n.a. *81 (12.2)*	657	n.a. *22 (3.3)*	4.71 [2.99; 7.73] < 0.001 AD: n.c.
Nervous system disorders (SOC, CTCAE grade ≥ 3)	662	n.a. *19 (2.9)*	657	n.a. *8 (1.2)*	2.73 [1.24; 6.64] 0.013 AD: n.c.
Skin and subcutaneous tissue disorders (SOC, AE)	662	n.a. *221 (33.4)*	657	n.a. *139 (21.2)*	2.05 [1.66; 2.54] < 0.001 AD: n.c.
Investigations (SOC, CTCAE grade ≥ 3)	662	n.a. *20 (3.0)*	657	n.a. *8 (1.2)*	3.10 [1.41; 7.49] 0.004 AD: n.c.

(Continuation)

[a] Adequate approximation to the appropriate comparator therapy monitoring wait-and-see approach
[b] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation.
[c] In the study, overall survival should not be evaluated until the 248th death. For the relevant sub-population, there are no data on deaths. For the first data cut-off, in the population of hormone receptor-positive patients, 9 deaths in the neratinib arm and 14 deaths in the placebo arm occurred regardless of the time from completion of trastuzumab therapy to randomisation.
[d] Combined endpoint consisting of the components: remote metastases, invasive contralateral breast cancer, invasive ipsilateral breast cancer, local/regional invasive relapse, ductal carcinoma in situ, or death by any cause, whichever occurred first; the components are shown as event rates in the lines below the relapse endpoint
[e] In both treatment groups, missing values of patients who discontinued the study and for whom no relapse had been documented up to the time of discontinuation are rated as “no event” (LOCF analysis).
[f] No calculation of effect estimates. The events shown do not fully represent the endpoint. Only the events that come into play during the formation of the combined endpoint are shown.
[g] In both treatment groups, missing values are replaced in accordance with the risk observed in the control group (10.4%).
[h] Missing values in the neratinib arm are replaced in accordance with the risk observed in the control group (10.4%). In the control group, missing values are rated as “no event”.
[i] In both treatment groups, missing values are replaced in accordance with twice the risk observed in the control group (20.7%).
[j] Averaged over Months 1–12
[k] A positive change from start of study to end of study means an improvement; a positive effect estimate means an advantage for the intervention.
[l] includes the PTs abdominal pain, diarrhoea, vomiting

Abbreviations used:
AD = absolute difference; BCS = breast cancer sub-scale; CTCAE = Common Terminology Criteria for Adverse Events; EWB = emotional well-being; EQ-5D = European Quality of Life-5 Dimensions; FACT-B = Functional Assessment of Cancer Therapy − Breast Cancer; FWB = functional well-being; CI = confidence interval; LOCF = Last Observation carried forward; MD = mean difference; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; PWB = physical well-being; SD = standard deviation; SOC = system organ class; SWB = social well-being; VAS = visual analogue scale; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	n.a.	not assessable
Morbidity	↑↑	Advantage in the endpoint relapse, operationalised as relapse rate and relapse-free survival
Health-related quality of life	↔	No differences relevant for the benefit assessment
Side effects	↓↓	Disadvantages in the endpoints serious AEs, severe AEs (CTCAE grade ≥ 3), and therapy discontinuation because of AEs; disadvantages in individual specific AEs

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

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

approx. 2,330–4,560 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 Nerlynx® (active ingredient: neratinib) at the following publicly accessible link (last access: 30 April 2020):

https://www.ema.europa.eu/documents/product-information/nerlynx-epar-product-information_de.pdf

Treatment with neratinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in gynaecology and obstetrics, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with breast cancer.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on neratinib:

- Training material for doctors
- Informational material for patients

The training and information material include, in particular, instructions on how to deal with the potential gastrointestinal toxicity (diarrhoea) associated with neratinib.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Neratinib	€ 79,229.54
Appropriate comparator therapy:	
Monitoring wait-and-see approach	not quantifiable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2020

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 14 May 2020.

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

Berlin, 14 May 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken