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 Romosozumab (Osteoporosis, Postmenopausal Women)

of 3 September 2020

At its session on 3 September 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 romosozumab as follows:

Romosozumab

Resolution of: 3 September 2020
Entry into force on: 3 September 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 9 December 2019):

EVENITY is indicated in treatment of severe osteoporosis in postmenopausal women at high risk of fracture (see section 5.1).

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

Postmenopausal women with severe osteoporosis and high risk of fracture

Appropriate comparator therapy:

Alendronic acid or risedronic acid or zoledronic acid or denosumab or teriparatide

Extent and probability of the additional benefit of romosozumab followed by alendronic acid compared with alendronic acid alone:

Indication of a minor additional benefit

Study results according to endpoints:[1]

Postmenopausal women with severe osteoporosis and high risk of fracture

ARCH study: Romosozumab (12 months) followed by alendronic acid (at least 12 months) vs alendronic acid (at least 24 months), data cut-offs for Month 12 (romosozumab vs alendronic acid, data cut-off presented additionally), and for Month 24 or total study period (romosozumab followed by alendronic acid vs alendronic acid alone)

[1] Data from the dossier assessment of the IQWiG (A20-24) and the addendum (A20-67) unless otherwise indicated.

Mortality

Endpoint	Romosozumab (Month 12) or romosozumab followed by alendronic acid		Alendronic acid		Romosozumab or romosozumab followed by alendronic acid vs alendronic acid alone
	N	**Median time to event [95% CI]** Patients with event n (%)	**N**	**Median time to event [95% CI]** Patients with event n (%)	**HR [95% CI];** p value
Mortality					
Overall mortality[a]					
Month 12 (presented additionally)	2040	no data available 30 (1.5)	2014	no data available 22 (1.1)	1.37 [0.79; 2.37]; 0.26
Total study period[s]	2040	no data available 101 (5.0)	2014	no data available 103 (5.1)	0.98 [0.74; 1.29]; 0.87

Morbidity

Clinical vertebral fractures					
Month 12 (presented additionally)	2046	– 10 (0.5)	2047	– 18 (0.9)	RR: 0.56 [0.26; 1.20]; 0.135[c]
Month 24 [b]	2046	– 18 (0.9)	2047	– 44 (2.1)	RR: 0.41 [0.24; 0.71]; < 0.001[c]
Major non-vertebral fractures					
Month 12 (presented additionally)	2046	n.a. 59 (2.9)	2047	n.a. 88 (4.3)	0.67 [0.48; 0.94]; 0.019
Month 24	2046	no data available 146 (7.1)	2047	no data available 196 (9.6)	0.73 [0.59; 0.90]; 0.004

- **Hip fractures**					
Month 12 (presented additionally)	2046	n.a. 14 (0.7)	2047	n.a. 22 (1.1)	0.64 [0.33; 1.26]; 0.19
Month 24	2046	no data available 41 (2.0)	2047	no data available 66 (3.2)	0.62 [0.42; 0.92]; 0.015
- **Pelvic fractures**					
Month 12 (presented additionally)	2046	n.a. 1 (< 0.1)	2047	n.a. 8 (0.4)	0.13 [0.02; 1.03]; 0.022
Month 24	2046	no data available 5 (0.2)	2047	no data available 17 (0.8)	0.29 [0.11; 0.78]; 0.009
- **Distal femoral fractures**					
Month 12 (presented additionally)	2046	n.a. 1 (< 0.1)	2047	n.a. 1 (< 0.1)	1.01 [0.06; 16.10]; > 0.999
Month 24	2046	no data available 11 (0.5)	2047	no data available 7 (0.3)	1.56 [0.60; 4.01]; 0.36
- **Proximal tibial fractures**					
Month 12 (presented additionally)	2046	n.a. 2 (< 0.1)	2047	n.a. 4 (0.2)	0.48 [0.09; 2.63]; 0.39
Month 24	2046	no data available 4 (0.2)	2047	no data available 6 (0.3)	0.65 [0.18; 2.29]; 0.49
- **Rib fractures**					
Month 12 (presented additionally)	2046	n.a. 5 (0.2)	2047	n.a. 10 (0.5)	0.49 [0.17; 1.44]; 0.19
Month 24	2046	no data available 13 (0.6)	2047	no data available 23 (1.1)	0.56 [0.29; 1.11]; 0.094
- **Proximal humeral fractures**					

Month 12 (presented additionally)	2046	n.a. 5 (0.2)	2047	n.a. 10 (0.5)	0.51 [0.17; 1.50]; 0.21
Month 24	2046	no data available 17 (0.8)	2047	no data available 28 (1.4)	0.60 [0.33; 1.09]; 0.091
- **Forearm fractures**					
Month 12 (presented additionally)	2046	n.a. 33 (1.6)	2047	n.a. 42 (2.1)	0.80 [0.50; 1.25]; 0.32
Month 24	2046	no data available 65 (3.2)	2047	no data available 73 (3.6)	0.89 [0.63; 1.24]; 0.47
Non-major non-vertebral fractures					
Month 12 (presented additionally)	Endpoint not evaluated separately				
Month 24	Endpoint not evaluated separately				

Endpoint	**Romosozumab (Month 12) or romosozumab followed by alendronic acid**		**Alendronic acid**		**Romosozumab or romosozumab followed by alendronic acid vs alendronic acid alone**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p value[g]**
Health status (EQ-5D VAS) ≥ 10 points[p]					
Month 12 (presented additionally)	1658	590 (35.6)	1676	571 (34.1)	1.05 [0.95; 1.15]; 0.421
Month 24	1665	795 (47.7)	1684	791 (47.0)	1.02 [0.95; 1.09]; 0.742

Endpoint	**Romosozumab (Month 12) or romosozumab followed by alendronic acid**	**Alendronic acid**	**Romosozumab or romosozumab followed by alendronic acid**

							vs alendronic acid alone
	N	Values at start of study MV (SD)	Change at Month 12 or Month 24 MV (SE)	N	Values at start of study MV (SD)	Change at Month 12 or Month 24 MV (SE)	MD [95% CI]; p value
Strongest pain (mBPI-SF)[d]							
Month 12 (presented additionally)	1547	3.9 (2.8)	−0.7 (0.1)	1532	4.0 (2.9)	−0.5 (0.1)	−0.1 [−0.29; 0.05]; 0.18
Month 24	No usable data[e]						
Health status (EQ-5D VAS)							
Month 12 (presented additionally)	1557	67.7 (20.5)	3.6 (0.4)	1540	67.8 (20.6)	3.0 (0.4)	0.5 [−0.63; 1.67]; 0.37
Month 24	No usable data[e]						

Health-related quality of life

Endpoint	Romosozumab (Month 12) or romosozumab followed by alendronic acid			Alendronic acid			Romosozumab or romosozumab followed by alendronic acid vs alendronic acid alone
	N	Values at start of study MV (SD)	Change at Month 12 or Month 24 MV (SE)	N	Values at start of study MV (SD)	Change at Month 12 or Month 24 MV (SE)	MD [95% CI]; p value
OPAQ-SV[q]							
Month 12 (presented additionally)							
Physical functionality	1562	67.6 (23.4)	2.7 (0.4)	1550	67.1 (23.0)	1.6 (0.4)	1.1 [0.06; 2.15]; 0.038 Hedges' g[r]: 0.07 [0.004; 0.14]
Emotional status	1560	53.7 (22.9)	1.7 (0.4)	1544	52.8 (22.8)	1.7 (0.4)	0.0 [−1.05; 1.13]; 0.94
Back pain	1561	51.3 (26.9)	7.1 (0.5)	1546	51.6 (26.9)	6.1 (0.5)	1.0 [−0.44; 2.44]; 0.17
Month 24	No usable data[f]						

Side effects

Endpoint	Romosozumab (Month 12) or romosozumab followed by alendronic acid		Alendronic acid		Romosozumab or romosozumab followed by alendronic acid vs alendronic acid alone
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[g]
Adverse events (presented additionally)[h]					
Month 12 (presented additionally)	2040	1528 (74.9)	2014	1560 (77.5)	-
Total study period[s]	2040	1761 (86.3)	2014	1776 (88.2)	-
Serious adverse events (SAE) [h]					
Month 12 (presented additionally)	2040	238 (11.7)	2014	239 (11.9)	0.98 [0.83; 1.16]; 0.846
Total study period[s]	2040	568 (27.8)	2014	553 (27.5)	1.01 [0.92; 1.12]; 0.806
Discontinuation because of AE[h,i]					
Month 12 (presented additionally)	2040	68 (3.3)	2014	64 (3.2)	1.05 [0.75; 1.47]; 0.791
Total study period[s]	2040	142 (7.0)	2014	152 (7.5)	0.92 [0.74; 1.15]; 0.505
Osteonecrosis of the jaw [j]					
Month 12 (presented additionally)	2040	0 (0)	2014	0 (0)	-
Total study period[s]	2040	2 (< 0.1)	2014	1 (< 0.1)	1.97 [0.18; 21.76]; > 0.999
Symptomatic atypical femur fracture					
No usable data[k]					
Atypical femur fracture[o]					
Month 12 (presented additionally)	2040	0 (0.0)	2014	0 (0.0)	n.c.

Total study period[s]	2040	3 (0.1)	2014	4 (0.2)	0.74 [0.17; 3.30]; 0.725
Gastrointestinal disorders (SOC, AE)					
Month 12 (presented additionally)	2040	494 (24.2)	2014	541 (26.9)	0.90 [0.81; 1.00]; 0.056
Total study period[s]	2040	777 (38.1)	2014	796 (39.5)	0.96 [0.89; 1.04]; 0.350
Any adjudicated cardiovascular SAE[l]					
Month 12 (presented additionally)					
Total study population	2040	50 (2.5)	2014	38 (1.9)	1.30 [0.86; 1.97]; 0.237
Sensitivity analysis[m]	1916	44 (2.3)	1890	30 (1.6)	1.45 [0.91; 2.29]; 0.127
Total study period[s]					
Total study population	2040	144 (7.1)	2014	137 (6.8)	1.04 [0.83; 1.30]; 0.758
Sensitivity analysis[m]	1916	128 (6.7)	1890	119 (6.3)	1.06 [0.83; 1.35]; 0.646
- **Cardiac ischaemic event**					
Month 12 (presented additionally)					
Total study population	2040	16 (0.8)	2014	6 (0.3)	2.63 [1.03; 6.71]; 0.052
Sensitivity analysis[m]	1916	15 (0.8)	1890	5 (0.3)	2.96 [1.08; 8.13]; 0.041
Total study period[s]					
Total study population	2040	32 (1.6)	2014	25 (1.2)	1.26 [0.75; 2.12]; 0.424
Sensitivity analysis[m]	1916	28 (1.5)	1890	23 (1.2)	1.20 [0.69; 2.08]; 0.574
- **Cerebrovascular event**					
Month 12 (presented additionally)					
Total study population	2040	16 (0.8)	2014	7 (0.3)	2.26 [0.93; 5.47]; 0.092

Sensitivity analysis[m]	1916	15 (0.8)	1890	4 (0.2)	3.70 [1.23; 11.12]; 0.019
Total study period[s]					
Total study population	2040	47 (2.3)	2014	27 (1.3)	1.72 [1.07; 2.75]; 0.025
Sensitivity analysis[m]	1916	41 (2.1)	1890	23 (1.2)	1.76 [1.06; 2.92]; 0.032
- **Death[n]**					
Month 12 (presented additionally)					
Total study population	2040	17 (0.8)	2014	12 (0.6)	1.40 [0.67; 2.92]; 0.457
Sensitivity analysis[m]	1916	14 (0.7)	1890	11 (0.6)	1.26 [0.57; 2.76]; 0.689
Total study period[s]					
Total study population	2040	67 (3.3)	2014	68 (3.4)	0.97 [0.70; 1.36]; 0.930
Sensitivity analysis[m]	1916	63 (3.3)	1890	61 (3.2)	1.02 [0.72; 1.44]; 0.928
- **Cardiac insufficiency**					
Month 12 (presented additionally)					
Total study population	2040	4 (0.2)	2014	8 (0.4)	0.49 [0.15; 1.64]; 0.263
Sensitivity analysis[m]	1916	4 (0.2)	1890	6 (0.3)	0.66 [0.19; 2.33]; 0.546
Total study period[s]					
Total study population	2040	14 (0.7)	2014	25 (1.2)	0.55 [0.29; 1.06]; 0.078
Sensitivity analysis[m]	1916	12 (0.6)	1890	21 (1.1)	0.56 [0.28; 1.14]; 0.118
- **Non-coronary revascularisation**					
Month 12 (presented additionally)					
Total study population	2040	3 (0.1)	2014	5 (0.2)	0.59 [0.14; 2.48]; 0.505
Sensitivity analysis[m]	1916	1 (< 0.1)	1890	5 (0.3)	0.20 [0.02; 1.69]; 0.122

Total study period[s]					
Total study population	2040	7 (0.3)	2014	10 (0.5)	0.69 [0.26; 1.81]; 0.477
Sensitivity analysis[m]	1916	3 (0.2)	1890	8 (0.4)	0.37 [0.10; 1.39); 0.143
- **Peripheral vascular ischaemic event without revascularisation**					
Month 12 (presented additionally)					
Total study population	2040	0 (0)	2014	2 (< 0.1)	0.20 [0.01; 4.11]; 0.247
Sensitivity analysis[m]	1916	0 (0)	1890	1 (< 0.1)	0.33 [0.01; 8.07]; 0.497
Total study period[s]					
Total study population	2040	2 (< 0.1)	2014	5 (0.2)	0.39 [0.08; 2.03]; 0.286
Sensitivity analysis[m]	1916	2 (0.1)	1890	4 (0.2)	0.49 [0.09; 2.69]; 0.450

a. Data from the safety population; in Module 4 A, for the endpoint overall mortality, the pharmaceutical company presents AE that led to death. According to the sources available, 106 patients in the intervention arm and 113 patients in the comparator arm died in relation to the randomised patients; however, there is no HR for these data.
b. These are the data for the period for which the values for all women are received for the individual observation period from the start of study to Month 24; no data are available for the primary analysis period (median observation period 33 months).
c. IQWiG calculation of RR and CI (asymptotic) and p value (unconditional exact test, CSZ method).
d. Measured with the scale “strongest pain in the last 24 hours” (item 3); lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for romosozumab.
e. No usable data because > 30% of patients were not included in the analysis No statistically significant results are shown in the evaluations available.
f. At Month 24, > 30% of patients were not included in the analysis.
g. Mantel-Haenszel method without covariate adjustment, Fisher’s exact test
h. Based on evaluations presented by the pharmaceutical company without the recording of osteoporotic events. The pharmaceutical company does not take into account the PT bone pain, spinal pain, and fracture of the foot, although these events are also most likely related to the underlying disease. However, because these events occurred in less than 3% of patients, this has no consequence for the benefit assessment.
i. These refers to therapy discontinuation because of AE; 43 patients (2.1%) in the intervention arm and 44 patients (2.2%) in the comparator arm also discontinued the study because of AE.
j. Events of a MedDRA query predefined by the pharmaceutical company in accordance with the list of PT; the PT that occurred were assessed by an adjudication committee. The pharmaceutical company states in Module 4 A that events that were identified after review of the trial sheets and assigned by an adjudication committee were also recorded. There are discrepancies between register entry and module 4 A. The register entry shows that in the comparator arm, an event of the PT “osteonecrosis”, “osteonecrosis of the jaw”, “jaw pain”, and “osteomyelitis” occurred in one patient each. According to the register entry, no events occurred in the intervention arm. Because of the small number of events, this is not relevant for the benefit assessment.
k. The pharmaceutical company provides data on atypical femoral fractures but not separately on symptomatic atypical femoral fractures.
l. All deaths as well as all potentially cardiovascular-related SAE that were consistent with a PT (MedDRA terminology) of a PT list predefined by the pharmaceutical company and all SAE identified by the investigator for adjudication were evaluated by an adjudication committee with respect to cardiovascular classification. Any positively adjudicated cardiovascular SAE were presented as well as for the SAE of the individual components ischaemic event, cerebrovascular event, death, cardiac insufficiency, non-coronary revascularisation, and peripheral vascular ischaemic event (without revascularisation). With regard to the PTs considered, there are isolated inconsistencies between the data in Module 4 A and Module 5. However, the respective overall rates do not differ between Module 4 A and Module 5.
m. Sensitivity analysis: excluding patients with a history of myocardial infarction or stroke, total study period
n. In addition to “death involving the cardiovascular system”, “death by undetermined cause” was also included in this individual component.
o. Events of a MedDRA query predefined by the pharmaceutical company in accordance with the list of PT; the PT that occurred were assessed by an adjudication committee.
p. Patients with a clinically relevant deterioration; defined as a decrease of the score by ≥ 10 points compared with baseline
q. Higher (increasing) values indicate a better health status; positive effects (intervention minus control) indicate an advantage for the intervention.
r. Calculation of the IQWiG

s. The analysis of the endpoints is based on the total study period (last available analysis date for these endpoints is 29 June 2017).

Abbreviations used:
EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR = hazard ratio; ITT: Intention to treat; CI: confidence interval; LAD: Limited Activity Days; MD: mean difference; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; mBPI-SF: Modified Brief Pain Inventory Short Form; MW: mean value; n: Number of patients with (at least 1) event; N: number of patients evaluated; OPAQ-SV: Osteoporosis Assessment Questionnaire Short Version; PT: preferred term; RCT: randomised controlled study; RR: relative risk; SD: standard deviation; SE: standard error; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No difference relevant for the benefit assessment.
Morbidity	↑↑	Advantages in the prevention of clinical vertebral fractures, major non-vertebral fractures (hip and pelvic fractures)
Health-related quality of life	n.a.	not assessable
Side effects	↓↓	Disadvantages in the endpoint cerebrovascular event.

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

Postmenopausal women with severe osteoporosis and high risk of fracture

approx. 475,000 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 Evenity® (active ingredient: romosozumab) at the following publicly accessible link (last access: 19 August 2020):
https://www.ema.europa.eu/documents/product-information/evenity-epar-product-information_de.pdf

Treatment with romosozumab should only be initiated and monitored by specialists who are experienced in the treatment of patients with osteoporosis.

In accordance with the requirements of the European Medicines Agency (EMA) regarding additional risk minimisation measures, the pharmaceutical company must implement a training program for the approved indication for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture.
The training program is designed to further minimise the risks for the serious cardiovascular events myocardial infarction and stroke as well as hypocalcaemia and osteonecrosis of the jaw (ONJ) by emphasising the key safety information contained in product and package information.
The training program consists of training material for doctors and patient information card.

In accordance with the product information, romosozumab is contraindicated in patients with hypocalcaemia, previous myocardial infarction, or stroke. If a patient suffers a myocardial infarction or stroke during therapy, treatment with romosozumab must be discontinued.

Before starting therapy with romosozumab, hypocalcaemia should be treated, and patients should be monitored for signs and symptomatology of hypocalcaemia.

Patients suspected or developing ONJ during treatment with romosozumab should be treated by a dentist or oral surgeon with expertise in ONJ.

After completion of therapy with romosozumab, a switch to anti-resorptive therapy is appropriate to maintain the benefits achieved with romosozumab beyond 12 months.

4. Treatment costs

Annual treatment costs:

Postmenopausal women with severe osteoporosis and high risk of fracture

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	

Designation of the therapy	Annual treatment costs/patient
Romosozumab	€ 10,507.92
Appropriate comparator therapy:	
Alendronic acid	€ 193.07
Risedronic acid	€ 228.11
Zoledronic acid	€ 458.23
Denosumab	€ 597.70
Teriparatide	€ 5123.39

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 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 3 September 2020.

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

Berlin, 3 September 2020

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

Prof. Hecken