Justification

Gemeinsamer Bundesausschuss

to the Resolution 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

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient romosozumab in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 March 2020. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 11 March 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 June 2020 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of romosozumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5,

Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of romosozumab.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at the following assessment:

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

2.1.1 Approved therapeutic indication of romosozumab (Evenity®) in accordance with the product information

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. Medicinal products with the following active ingredients are approved for the present therapeutic indication:
- Bisphosphonates (possibly in combination with colecalciferol):
  Zoledronic acid, risedronic acid, ibandronic acid, etidronic acid, and alendronic acid
- Denosumab

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

- Strontium ranelate
- Selective oestrogen receptor modulator (SERM): Raloxifene and bazedoxifene
- Osteoanabolic therapeutics: Teriparatide
- Vitamin D_3 and analogues
- Calcium preparations

On 2. A non-medicinal treatment is not indicated in this therapeutic indication.

On 3. The following resolutions and guidelines of the G-BA have been issued in the present therapeutic indication: Annex I of the Pharmaceuticals Directive (AM-RL) regulates the prescribability of calcium compounds (mono-preparations or in combination with vitamin D) or vitamin D (points 11 and 12).

On 4. The general state of medical knowledge on which the decision of the G-BA is based was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

The present therapeutic indication is the treatment of severe osteoporosis in postmenopausal women at high risk of fracture. Accordingly, all patients in the present approved therapeutic indication have osteoporosis requiring medication; all patients are eligible for osteoporosis-specific medication.

The systematic reviews and guidelines provide a comprehensive body of evidence for bisphosphonates, SERM (raloxifene and bazedoxifene), denosumab, and teriparatide. Other therapeutic options (including strontium ranelate) are mentioned only subordinately and are therefore not considered as an appropriate comparator therapy. In detail:

In accordance with the guideline, the three bisphosphonates (alendronic acid, risedronic acid, and zoledronic acid) as well as denosumab show a very good therapeutic efficiency for the reduction of fractures with high degrees of recommendation. For the bisphosphonates, extensive data are available for alendronic acid, risedronic acid, and zoledronic acid. Thus, they represent the primary selection of bisphosphonates according to the evidence available as well as the efficacy and side effects profile.
For denosumab, there is further good evidence from aggregated endpoint studies. In systematic reviews, denosumab showed similar results to the bisphosphonates.
In Germany there is no marketing authorisation for the treatment of osteoporosis with hormone replacement therapy. It is approved only for the prevention of osteoporosis in postmenopausal women at high risk of fractures who have an intolerance or contraindication to other medicinal products approved for osteoporosis prevention. Hormone replacement therapies are therefore not equally appropriate here.
Taking into account the evidence available, the lack of head-to-head comparisons, and the side effects profile, strontium ranelate does not currently represent an equally appropriate comparator therapy for patients in the present therapeutic indication. Moreover, there is currently no medicinal product containing strontium ranelate available on the German market.
Raloxifene and bazedoxifene do not have an equally high level of recommendation for all fracture types. However, according to the guideline, a preparation with a high level of recommendation should be used for the specific therapy. SERMs are therefore not considered equally appropriate treatment options.

Extensive endpoint studies have shown benefits of teriparatide in terms of fracture reduction, particularly in the patient population in the therapeutic indication.

In summary, international guidelines recommend alendronic acid, risedronic acid, zoledronic acid, and denosumab as initial therapy in most patients with osteoporosis with a high risk of fracture. Teriparatide, denosumab, or zoledronic acid are particularly recommended and used if the risk of fracture is particularly high.
It should be noted that all patients with osteoporosis must ensure that they are getting enough calcium and vitamin D.
In Germany there is no marketing authorisation for the treatment of osteoporosis with hormone replacement therapy. It is approved only for the prevention of osteoporosis in postmenopausal women at high risk of fractures who have an intolerance or contraindication to other medicinal products approved for osteoporosis prevention.

In the overall consideration of the evidence, bisphosphonates (alendronic acid, risedronic acid, or zoledronic acid), denosumab, or teriparatide are thus determined as an appropriate comparator therapy for the present approved therapeutic indication of romosozumab.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of romosozumab followed by alendronic acid compared with alendronic acid alone is evaluated as follows:

For the treatment of severe osteoporosis in postmenopausal women at high risk of fracture, there is an indication of a minor additional benefit.

Justification:

The pharmaceutical company presented the results of the ARCH study to prove the additional benefit of romosozumab.

The ARCH study is a randomised, double-blind, multi-centre, dual-arm, parallel group study in which romosozumab followed by alendronic acid is compared with alendronic acid alone in postmenopausal women with severe osteoporosis and a significant risk of fracture.
The study included patients who, prior to the start of study, had fractures based on bone mineral density (BMD).[2]

In the ARCH study, 4093 patients were randomised at a ratio of 1:1 to the study arms romosozumab (N = 2046) or alendronic acid (N = 2047). In the study, patients were stratified by age at screening (<75/ ≥75 years). In both study arms, alendronic acid treatment was administered from month 13 after screening. For all patients, the duration of treatment was at least 24 months from the time of randomisation.

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- *BMD T-Score[2] ≤ −2.5 at the hip or femoral neck and either at least 1 moderate or severe vertebral fracture or at least 2 mild vertebral fractures*
- *BMD T-Score ≤ −2.0 at the hip or femoral neck and either at least 2 moderate or severe vertebral fractures or 1 fracture of the proximal femur occurring within 3 to 24 months prior to randomisation*

The ARCH study thus examines the therapeutic concept of a 12-month treatment with romosozumab followed by anti-resorptive therapy with alendronic acid versus continuous anti-resorptive therapy with the bisphosphonate alendronic acid.

The results for Month 12, which show the exclusive comparison of romosozumab versus alendronic acid, are presented additionally. In accordance with the product information, a switch to an anti-resorptive therapy should take place after the therapy with romosozumab is completed. In principle, a study duration of 24 months is considered adequate to assess the effect on possible reduction of fractures. As a result, for the present assessment of the additional benefit of romosozumab, the data cut-off for Month 24 or the total study period from the ARCH study is considered, and the results for Month 12 are presented additionally.

The occurrence of new clinical and vertebral fractures was the primary endpoint of the ARCH study. Patient-relevant secondary endpoints were overall mortality, morbidity endpoints (major non-vertebral fractures, major non-vertebral fractures, atypical femoral fractures, severe pain, health status), health-related quality of life, and side effects.

All patients received a daily patient-individual concomitant treatment with calcium and vitamin D supplements. The documentation of concomitant medication shows that supportive measures are below the daily dosages recommended in national and international guidelines. In accordance with the product information, romosozumab is contraindicated in patients with a history of myocardial infarction or stroke. In the ARCH study, 6.1% of patients suffered a myocardial infarction or stroke. For a comprehensive assessment of the effects of romosozumab on vascular events, sensitivity analyses, excluding patients with previous myocardial infarction or stroke, were presented.

Extent and probability of the additional benefit

Mortality

For the endpoint overall mortality, there was no statistically significant difference in overall study duration between treatment groups of the ARCH study.

Morbidity

Clinical vertebral fractures

For the endpoint clinical vertebral fractures, fractures independent of trauma intensity or cause were used. In the ARCH study, the endpoint was defined a priori as new or worsened vertebral fracture associated with back pain.

It is noted that after Month 12 for the endpoint clinical vertebral fractures, there is still no statistically significant benefit for the treatment of romosozumab compared with alendronic acid. For the endpoint clinical vertebral fractures, there was a statistically significant difference between treatment groups at Month 24 in favour of romosozumab followed by alendronic acid. Thus, for the endpoint clinical vertebral fractures there is an advantage of romosozumab followed by alendronic acid vs alendronic acid alone.

Major non-vertebral fractures

For the endpoint major non-vertebral fractures, high trauma intensity fractures and pathological fractures resulting from disease other than osteoporosis were not considered.

For the endpoint, there was a statistically significant difference between treatment groups at Month 24 in favour of romosozumab followed by alendronic acid. The statistically significant advantage of romosozumab followed by alendronic acid is shown for hip and pelvic fractures.

After treatment of Romosozumab versus alendronic acid for 12 months, a statistically significant benefit of romosozumab on major non-vertebral fractures as well as for the single component pelvic fractures of the combined endpoint is already evident.

Non-major non-vertebral fractures

The endpoint non-major non-vertebral fractures was not evaluated separately.

Strongest pain (mBPI-SF)

In the ARCH study, the endpoint pain was assessed using item 3 (strongest pain in the last 24 hours) of the mBPI-SF. However, none of the data submitted can be used. The endpoint can therefore not be included in the assessment of the additional benefit of romosozumab.

Health status (EQ-5D VAS)

No usable data are available for the health status endpoint as measured by the VAS of EQ-5D. This endpoint can also not be included in the assessment of the additional benefit of romosozumab.

Quality of life

Data based on the Osteoporosis Assessment Questionnaire Short Version (OPAQ-SV) as well as Limited Activity Days (LAD) were submitted by the pharmaceutical company to assess the health-related quality of life.

In the analysis of the results of the OPAQ-SV, more than 30% of patients were not included in the analysis for the relevant data cut-off at Month 24. Therefore, regardless of the question of the validity of the instrument for the endpoint health-related quality of life, no usable data are available.

The LAD consists of 3 individual questions and can therefore not be regarded as an instrument for the survey of quality of life. In particular, physical components are queried. The LAD is therefore not a suitable construct for assessing health-related quality of life and at best deals with aspects of morbidity. However, because it remains unclear by which evaluation method the collected data were analysed, the data presented are not considered for quality of life or morbidity.

Side effects

SAE and discontinuation because of AE

For the assessment of the endpoints SAE and discontinuation because of AE, the pharmaceutical company presents evaluations in which osteoporotic events defined were not considered. These evaluations are used for the present benefit assessment. For the endpoints SAE and discontinuation because of AE, there was no statistically significant difference between treatment groups.

Specific AE

Atypical femur fracture

For the endpoint atypical femur fractures, there was no statistically significant difference in overall study duration between treatment groups of the ARCH study.

Osteonecrosis of the jaw

For the endpoint osteonecrosis of the jaw, there was no statistically significant difference between the treatment groups.

Symptomatic atypical femur fractures

For the endpoint “symptomatic atypical femur fractures”, there is no usable data.

Gastrointestinal disorders (SOC, AE)

For the endpoint gastrointestinal disorders, there was no statistically significant difference between the treatment groups.

Any adjudicated cardiovascular SAE

In accordance with the European Medicines Agency (EMA), treatment with romosozumab is contraindicated in patients with prior vascular disease. Thus, the evaluation of specific adverse vascular events is relevant for the present procedure.
In the ARCH study, the deaths that occurred as well as all potentially cardiovascular-related SAE that matched a PT on a list of PT predefined by the pharmaceutical company were evaluated by an adjudication committee with regard to cardiovascular classification. In addition, all SAE marked for adjudication by the investigator were also evaluated by the described Adjustment Committee. For the assessment of the additional benefit, 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).
For the endpoint any adjusted cardiovascular events as well as for the individual components cardiac ischaemic event, death, cardiac insufficiency, non-coronary revascularisation, and peripheral vascular ischaemic event, there is no statistically significant difference between treatment groups in the overall study population at Month 24. The sensitivity analyses presented, which exclude patients with previous vascular diseases, also show no statistically significant difference between the treatment groups.

For the individual components “cerebrovascular event” and “cardiac ischaemic event”, there was no statistically significant difference between romosozumab and alendronic acid at Month 12 in the total study population. In contrast, the sensitivity analyses, which exclude patients with previous vascular diseases, show a statistically significant difference as early as Month 12 to the disadvantage of romosozumab compared with alendronic acid.

For the individual component “cerebrovascular event”, a significant effect to the detriment of romosozumab was shown at month 24 – both for the total study population and for patients without previous vascular disease.

<u>Overall assessment/conclusion</u>

For the assessment of the additional benefit of romosozumab followed by alendronic acid, results on mortality (overall mortality), morbidity, quality of life, and side effects compared with the appropriate comparator therapy (alendronic acid) were presented from the blinded, controlled, randomised parallel group study ARCH.

It should be noted that data on romosozumab were submitted in accordance with the ARCH study submitted for the therapeutic concept romosozumab followed by alendronic acid.

In terms of mortality, the data presented for the endpoint overall mortality show no statistically significant difference in overall survival between the study arms. An additional benefit for romosozumab is not proven for overall mortality.

For clinically vertebral fractures and major non-vertebral fractures (hip fractures and pelvic fractures), statistically fewer fractures occurred under treatment with romosozumab followed by alendronic acid than for alendronic acid alone. The extent of this effect is assessed as a significant improvement in therapy-relevant benefit. The prevention of fractures is an essential therapeutic goal in this indication.

For the assessment of the influence of romosozumab followed by alendronic acid on quality of life, there are no usable data for the treatment period of 24 months.

In terms of side effects, there is a disadvantage for romosozumab in terms of cerebrovascular events. At the end of the 24-month treatment phase, both the total study population and the sub-population without previous vascular disease were at a disadvantage when treated with romosozumab followed by alendronic acid compared with alendronic acid alone for the adverse cerebrovascular event.

In the overall assessment of the results for the patient-relevant endpoints, a clear advantage, the prevention of fractures, which is particularly relevant in the present indication, is offset by the negative effect on cerebrovascular side effects. Taking into account the present disease, severe osteoporosis at a high risk of fracture, the disadvantage in terms of cerebrovascular side effects is weighed against the advantage in avoiding fractures.
In a balancing decision, the G-BA concluded that romosozumab followed by alendronic acid has a minor additional benefit compared with alendronic acid alone in the treatment of severe osteoporosis in postmenopausal women at a high risk of fracture.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the blinded, controlled, randomised parallel group study ARCH, in which romosozumab followed by alendronic acid is compared with the appropriate comparator therapy alendronic acid alone.
The benefit assessment is based on the results of only one study, hence, at best, only an indication of an additional benefit can be derived with regard to the reliability of data.
At study level, the risk of bias is considered to be low.

At the endpoint level, the risk of bias for the endpoints overall mortality, clinical vertebral fractures, major non-vertebral fractures, SAE, discontinuation because of AE, osteonecrosis of the jaw, gastrointestinal disorders, and any cardiovascular SAE (adjusted) is considered low.

In view of the overall low risk of bias at the study and endpoint levels, the reliability of data for the identified additional benefit is classified in the “indication” category.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of the new medicinal product Evenity® with the active ingredient romosozumab.

Romosozumab is approved for the treatment of severe osteoporosis in postmenopausal women at a high risk of fracture.

The appropriate comparator therapy was determined by the G-BA as follows:
Alendronic acid or risedronic acid or zoledronic acid or denosumab or teriparatide.

For the assessment, the pharmaceutical company presents results from the blinded, controlled, randomised parallel group study ARCH in which romosozumab (12 months) followed by alendronic acid (at least 12 months) is compared with alendronic acid alone (at least 24 months).
With regard to mortality, the results for the endpoint overall mortality show no statistically significant effect.
Romosozumab followed by alendronic acid shows a clear advantage over alendronic acid alone in preventing fractures (clinical vertebral fractures, and major non-vertebral fractures (hip fractures and pelvic fractures)) The prevention of fractures is an essential therapeutic goal in the present therapy situation of severe osteoporosis at a high risk of fracture.
Regarding the health-related quality of life, there are no usable data for the ARCH study at Month 24.
For the side effects, cerebrovascular events were observed under romosozumab. This observation is shown in the total population as well as in the study sub-population without previous vascular diseases.

When looking at the overall results, a clear advantage in the prevention of fractures (clinical vertebral fractures, major non-vertebral fractures (hip fractures and pelvic fractures)) is offset by negative effects in terms of cerebrovascular side effects.

In the overall view, there is an indication of a minor additional benefit of romosozumab followed by alendronic acid compared with alendronic acid alone.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on patient numbers is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the information from the dossier of the pharmaceutical company.

It is pointed out that in deriving the patient numbers, the pharmaceutical company assumes that the results of the routine data analysis by the Institut für Pharmakoökonomie und Arzneimittellogistik e. V. (IPAM; Institute for Pharmacoeconomics and Drug Logistics) is representative for the entire medical treatment situation in Germany. Therefore, only an adjustment according to age and sex is made for extrapolation to the German population as a whole. From a methodological point of view, however, the data refer to individual regional health insurance funds. There are thus uncertainties with regard to representativeness (including morbidity structure). In addition, there is no extrapolation to the current year (2020) in which a higher prevalence can be assumed. Uncertainties also exist with regard to the classification of postmenopausal patients as well as the criteria used to identify patients with a high risk of fracture.

The derivation of the patient numbers is basically comprehensible. However, because of the uncertainties described above, the number of patients may have been underestimated.

2.3 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 a 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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2020).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, time between individual treatments, and for maximum treatment duration if specified in the product information.

Treatment with romosozumab (EVENITY) is limited to 12 months.

The recommended dose is 210 mg romosozumab once a month (as two subcutaneous injections of 105 mg each) for 12 months.

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

Treatment with teriparatide (Movymia) is limited to 24 months.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Romosozumab	1 × monthly for 12 months	12	1	12
Appropriate comparator therapy				
Postmenopausal women with severe osteoporosis and a high risk of fracture				
Alendronic acid	continuously; 1 × every 7 days	52.1	1	52.1
Risedronic acid	continuously; 1 × every 7 days	52.1	1	52.1
Zoledronic acid	1 × annually	1	1	1
Denosumab	1 × every 6 months	2	1	2
Teriparatide	1 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Romosozumab	210 mg	210 mg	2 × 105 mg	12	24 × 105 mg
Appropriate comparator therapy					
Postmenopausal women with severe osteoporosis and a high risk of fracture					
Alendronic acid	70 mg	70 mg	1 × 70 mg	52.1	52.1 × 70 mg
Risedronic acid	35 mg	35 mg	1 × 35 mg	52.1	52.1 × 35 mg
Zoledronic acid	5 mg	5 mg	1 × 5 mg	1	1 × 5 mg
Denosumab	60 mg	60 mg	1 × 60 mg	2	2 × 60 mg
Teriparatide	20 µg	20 µg	1 × 20 µg	365	365 × 20 µg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Romosozumab	2 SFI	€ 929.62	€ 1.77	€ 52.19	€ 875.66
Appropriate comparator therapy					
Alendronic acid[3]	12 TAB	€ 49.37	€ 1.77	€ 3.13	€ 44.47
Risedronic acid[3]	12 FCT	€ 58.16	€ 1.77	€ 3.85	€ 52.54
Zoledronic acid[3]	1 IS	€ 499.67	€ 1.77	€ 39.67	€ 458.23
Denosumab	1 PS	€ 318.07	€ 1.77	€ 17.45	€ 298.85
Teriparatide	3 SFI of 600 µg each	€ 1,232.05	€ 1.77	€ 59.46	€ 1,170.82
Teriparatide	1 SFI of 600 µg with PEN	€ 490.18	€ 1.77	€ 62.24	€ 426.17
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; SFI = solution for injection; IS = solution for infusion; TAB = tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 August 2020

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

[3] Fixed reimbursement rate

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 12 September 2017, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy established by the G-BA was reviewed. At its session on 11 February 2020, the Subcommittee on Medicinal Products redefined the appropriate comparator therapy.

On 11 March 2020, the pharmaceutical company submitted a dossier for the benefit assessment of romosozumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 11 March 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient romosozumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 June 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 June 2020. The deadline for submitting written statements was 6 July 2020.

The oral hearing was held on 27 July 2020.

By letter dated 28 July 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 14 August 2020.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 25 August 2020, and the proposed resolution was approved.

At its session on 3 September 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on	12 September 2017	Determination of the appropriate comparator therapy

Medicinal Products		
Subcommittee on Medicinal Products	11 February 2020	Redefinition of the appropriate comparator therapy
Working group Section 35a	14 July 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	27 July 2020	Conduct of the oral hearing Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	4 August 2020 18 August 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	25 August 2020	Concluding discussion of the draft resolution
Plenum	3 September 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 3 September 2020

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

Prof. Hecken