Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Calcifediol (secondary hyperparathyroidism in chronic kidney disease)

of 21 July 2022

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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 the 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The medicinal product Rayaldee, containing the active ingredient calcifediol, was first placed on the market on 1 February 2022. Relevant date according to Chapter 5, Section 8, paragraph 1, number 7 of the Rules of Procedure of the G-BA (VerfO) for the start of the assessment procedure for the active ingredient calcifediol is within three months of the request by the G-BA. If the medicinal product has not yet been placed on the market at that time, the procedure shall start on the date on which it is first placed on the market.

At its session on 29 January 2019, the Federal Joint Committee (G-BA) decided to initiate a benefit assessment for the active ingredient calcifediol in the indication secondary hyperparathyroidism in chronic kidney disease according to Section 35a, paragraph 6 SGB V in conjunction with Chapter 5, Section 16, paragraph 1 VerfO.

The final dossier was submitted to the G-BA in due time on 28 January 2022. On 1 February 2022, the assessment procedure started.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 2 May 2022, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a decision on whether an additional benefit of calcifediol compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated 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 calcifediol.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to 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 calcifediol (Rayaldee) in accordance with the product information

Rayaldee is indicated for the treatment of secondary hyperparathyroidism (sHPT) in adults with stage 3 or 4 chronic kidney disease (CKD) and vitamin D deficiency.

Therapeutic indication of the resolution (resolution of 21.07.2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult secondary hyperparathyroidism (sHPT) patients with stage 3 or 4 chronic kidney disease and vitamin D deficiency

Appropriate comparator therapy for calcifediol:

- Paricalcitol

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 in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA 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. In addition to calcifediol, paricalcitol is approved in the present therapeutic indication.

on 2. In principle, parathyroidectomy can be considered as non-medicinal treatment in the therapeutic indication.

on 3. In the mentioned therapeutic indication, there are no resolutions approved by the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V or of non-medicinal treatments.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the indication secondary hyperparathyroidism and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

In this regard, it should be noted that the robust evidence on treatment options in the present therapeutic indication is limited overall.

The KDIGO (Kidney Disease-Improving Global Outcomes) 2017 guideline recommends the use of the vitamin D analogues paricalcitol, alphacalcidol and calcitriol, particularly in adults with severe and progressive secondary hyperparathyroidism (sHPT) and stage 4 to 5 chronic kidney disease.

Even if no general therapy recommendation can be derived for adults with secondary hyperparathyroidism and stage 3 chronic kidney disease, it can be assumed that these patients will also receive some form of medicinal replacement in clinical practice, especially against the background that the patients in the planned therapeutic indication also have low serum vitamin D levels and that non-medicinal treatment can have a negative effect on bone metabolism (e.g. bone softening).

Parathyroidectomy is only recommended when medicinal therapy has failed. Therefore, parathyroidectomy cannot be considered as an appropriate comparator therapy in the present treatment setting.

Based on the available evidence and taking into account the authorisation status of vitamin D analogues, paricalcitol is determined as an appropriate comparator therapy in the present therapeutic indication for the treatment of secondary

hyperparathyroidism (sHPT) in adults with stage 3 or 4 chronic kidney disease and vitamin D deficiency.

It is assumed that patients will receive additional phosphate binders if needed.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of calcifediol is assessed as follows:

For adults with secondary hyperparathyroidism (sHPT) with stage 3 or 4 chronic kidney disease and vitamin D deficiency, an additional benefit of calcifediol compared to the appropriate comparator therapy is not proven.

Justification:

For the assessment of the additional benefit of calcifediol for the treatment of adults with secondary hyperparathyroidism (sHPT) with stage 3 or 4 chronic kidney disease and vitamin D deficiency, no suitable data were submitted by the pharmaceutical company compared to the appropriate comparator therapy determined by the G-BA.

The pharmaceutical company states that no suitable studies are available for the assessment of the additional benefit of calcifediol compared to the appropriate comparator therapy determined by the G-BA, but presents the results of the two placebo-controlled, randomised CTAP-CL-3001 and CTAP-CL-3002 studies.

The CTAP-CL-3001 and CTAP-CL-3002 studies enrolled adult patients with secondary hyperparathyroidism who had stage 3 or 4 chronic kidney disease and vitamin D deficiency. Vitamin D deficiency was defined as serum 25-hydroxyvitamin D levels of ≥ 10 to < 30 ng/ml. The treatment with calcifediol took place over 26 weeks. Primary endpoints were the percentage of patients with a reduction in intact parathyroid hormone levels of ≥ 30% compared to the start of the study and adverse events.

In accordance with the assessment of the pharmaceutical company, the CTAP-CL-3001 and CTAP-CL-3002 studies are unsuitable for assessing the additional benefit of calcifediol compared to the appropriate comparator therapy, since the appropriate comparator therapy was not implemented.

Conclusion:

In the overall assessment, no conclusions can be made on the additional benefit of calcifediol compared to the appropriate comparator therapy on the basis of the studies presented. An additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Rayaldee with the active ingredient calcifediol.

Calcifediol is approved for the treatment of adult patients with secondary hyperparathyroidism (sHPT) with stage 3 or 4 chronic kidney disease and vitamin D deficiency.

The G-BA determined paricalcitol as appropriate comparator therapy.

For the assessment of the additional benefit of calcifediol for the treatment of adults with secondary hyperparathyroidism (sHPT) with stage 3 or 4 chronic kidney disease and vitamin D deficiency, no suitable data were submitted by the pharmaceutical company compared to the appropriate comparator therapy determined by the G-BA.

In the overall assessment, an additional benefit of calcifediol for this patient population compared to the appropriate comparator therapy is not proven.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, subject to uncertainties. Assuming that even a lower threshold value of the PTH level triggers a sHPT requiring treatment, the number of patients in the SHI target population may be higher.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account.

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: 1 July 2022).

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 intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

According to the indications of the consented appropriate comparator therapy, it is assumed that patients receive any additional phosphate binders required. Phosphate binders are not used to treat secondary hyperparathyroidism. They are used in the control of hyperphosphataemia potentially occurring in patients with chronic kidney disease. For this reason, the corresponding costs are not presented.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Calcifediol	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Paricalcitol	continuously, 1 x daily	365	1	365
	or			
	continuously, 3 x every 7 days	156.4	1	156.4

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					
Calcifediol	30 µg - 60 µg	30 µg 60 µg	1 x 30 µg 2 x 30 µg	365 365	365 x 30 µg - 730 x 30 µg
Appropriate comparator therapy					
Paricalcitol	1 µg - 3 µg	1 µg - 3 µg	1 x 1 µg - 1 x 2 µg + 1 x 1 µg	365 365	365 x 1 µg - 365 x 2 µg + 365 x 1 µg
	or				
	2 µg - 6 µg	2 µg - 6 µg	1 x 2 µg - 3 x 2 µg	156.4 156.4	156.4 x 2 µg - 469.2 x 2 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 Section 130 and Section 130a 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 products:

Designation of the therapy	Packaging 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					
Calcifediol 30 µg	90 REC	€ 649.63	€ 1.77	€ 35.34	€ 612.52
Appropriate comparator therapy					
Paricalcitol 1 µg[2]	28 SC	€ 119.25	€ 1.77	€ 5.12	€ 112.36
Paricalcitol 2 µg[2]	28 SC	€ 230.76	€ 1.77	€ 10.42	€ 218.57
Paricalcitol 2 µg[3]	30 SC	€ 247.03	€ 1.77	€ 11.19	€ 234.07
Abbreviations: REC = retard capsules, SC = soft capsules					

LAUER-TAXE® last revised: 1 July 2022

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 evaluated 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 the standard expenditure in the course of the treatment are not shown.

Because there are no 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 evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs calculation

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 29 October 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

[2] Most favourable proprietary medicinal products for dosage 1 x daily, 1 - 3 µg.
[3] Most favourable proprietary medicinal product for dosage 3 x every 7 days, 2 - 6 µg.

The appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 25 February 2020.

On 28 January 2022, the pharmaceutical company submitted a dossier for the benefit assessment of calcifediol to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 7 VerfO.

By letter dated 31 January 2022 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 calcifediol.

The dossier assessment by the IQWiG was submitted to the G-BA on 25 April 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 2 May 2022. The deadline for submitting written statements was 23 May 2022.

The oral hearing was held on 7 June 2022.

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 was discussed at the session of the subcommittee on 12 July 2022, and the proposed resolution was approved.

At its session on 21 July 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	29 October 2019	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	25 February 2020	New determination of the appropriate comparator therapy
Working group Section 35a	31 May 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 June 2022	Conduct of the oral hearing
Working group Section 35a	14 June 2022 6 July 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	12 July 2022	Concluding discussion of the draft resolution
Plenum	21 July 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 21 July 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken