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 Roxadustat (symptomatic anaemia in chronic kidney disease)

of 3 March 2022

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 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 relevant date for the first placing on the (German) market of the active ingredient roxadustat 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 September 2021. 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 3 September 2021.

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 15 December 2021, 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 roxadustat 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 roxadustat.

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 Roxadustat (Evrenzo) according to product information

Evrenzo is indicated for treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD).

Therapeutic indication of the resolution (resolution of 3 March 2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Treatment of adult patients with anaemia associated with chronic renal failure

- An erythropoiesis-stimulating agent (ESA) (darbepoetin alfa or epoetin (alfa, zeta) or epoetin beta or epoetin theta or methoxy-PEG-epoetin beta)

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 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.

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

3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit 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 roxadustat, the following erythropoiesis-stimulating agents are approved in the present therapeutic indication: Darbepoetin alfa, epoetin alfa, epoetin beta, epoetin theta, epoetin zeta, methoxy-PEG-epoetin beta.

Medicinal products with the active ingredient variant epoetin zeta are designated as essentially identical bioengineered biological medicinal products to the original/reference medicinal product with the active ingredient variant epoetin alfa.

on 2. Red blood cell transfusion is considered a non-medicinal treatment option that can be covered by the statutory health insurance in Germany.

on 3. There are several resolutions of the G-BA on the therapeutic indication and the active ingredients used for it. Annex I to the Medicinal Products Guideline (AM-RL) regulates the prescribability of iron (II) compounds as well as water-soluble vitamins in parts of the therapeutic indication under points 17., 43. and 44. In Annex III to the AM-RL, point 8 excludes the prescription of antianaemic combinations. Annex IV contains relevant therapeutic information on erythropoiesis-stimulating agents for the treatment of symptomatic renal anaemia.

By resolution of the G-BA on Annex VIIa (biologics and biosimilars) - first version of 19 November 2021, medicinal products with the active ingredient variant epoetin zeta are designated as essentially identical bioengineered biological medicinal products to the original/reference medicinal product with the active ingredient variant epoetin alfa.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication.

Guidelines unanimously recommend treatment with an erythropoiesis-stimulating agent in the present treatment setting. Within the product class, all approved options (darbepoetin alfa, epoetin alfa, epoetin beta, epoetin theta, epoetin zeta, methoxy-PEG-epoetin beta) are equally appropriate. In particular, treatment with red blood cell transfusions is only recommended as a secondary option due to the possible alloimmunisation and resulting potential complications in subsequent kidney transplantation.

In the overall assessment, the G-BA comes to the conclusion that an erythropoiesis-stimulating agent (darbepoetin alfa or epoetin (alfa, zeta) or epoetin beta or epoetin theta or methoxy-PEG-epoetin beta) is considered an appropriate comparator therapy in the present therapeutic indication.

It is assumed that other causes of anaemia (especially iron deficiency) have been excluded and that the treatment of deficiencies that could trigger specific anaemia (e.g. iron, water-soluble vitamins) has been ensured in accordance with the guidelines and the marketing authorisation.

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 roxadustat is assessed as follows:

For adults with symptomatic anaemia associated with chronic kidney disease (CKD), an additional benefit of roxadustat compared to the appropriate comparator therapy has not been proven.

Justification:

For the assessment of the additional benefit of roxadustat for the treatment of adults with symptomatic anaemia associated with chronic kidney disease, no suitable data were submitted by the pharmaceutical company compared to the appropriate comparator therapy. Thus, the additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Evrenzo with the active ingredient roxadustat.

Roxadustat is approved for the treatment of adults with symptomatic anaemia associated with chronic kidney disease (CKD).

The G-BA determined an erythropoiesis-stimulating agent (ESA) (darbepoetin alfa or epoetin (alfa, zeta) or epoetin beta or epoetin theta or methoxy-PEG-epoetin beta) as an appropriate comparator therapy.

For the patient population of adults with symptomatic anaemia associated with chronic kidney disease, no data were submitted by the pharmaceutical company that would have been suitable for the assessment of the additional benefit of roxadustat compared to the appropriate comparator therapy.

In the overall assessment, an additional benefit of roxadustat 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 uncertainty due to various methodological aspects. The pharmaceutical company's assumptions on prevalence and incidence are associated with limitations, which is why an underestimation/overestimation of the patient numbers must be assumed.

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 Evrenzo (active ingredient: roxadustat) at the following publicly accessible link (last access: 3 January 2022):

https://www.ema.europa.eu/en/documents/product-information/evrenzo-epar-product-information_en.pdf

Treatment with roxadustat should only be initiated and monitored by doctors experienced in treating adults with symptomatic anaemia associated with chronic kidney disease.

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 February 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 dosages depending on body weight (BW) or body surface area (BSA), the average body measurements were applied (average body height: 1.72 m; average body weight: 77 kg).[2]

The dosage is given individually to achieve a haemoglobin level of 10 to 12 g/dl. The calculation of the annual treatment costs is based on the dosage data of the initial and maximum dosages in the product information. For the active ingredients methoxy-PEG-epoetin beta and darbepoetin alfa, no maximum dosage can be taken from the product information as a basis for calculation.

From the substance class of erythropoiesis-stimulating agents (ESA), the following active ingredients are available for the treatment of symptomatic anaemia associated with chronic kidney disease: Darbepoetin alfa, epoetin alfa, epoetin beta, epoetin theta, epoetin zeta, methoxy-PEG-epoetin beta. The erythropoiesis-stimulating agents are grouped together in

[2] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

the reference price group "Anti-anaemic preparations, other, group 1" in level 2. By resolution of the G-BA on Annex VIIa (biologics and biosimilars) - first version of 19 November 2021, medicinal products with the active ingredient variant epoetin zeta are designated as essentially identical bioengineered biological medicinal products to the original/reference medicinal product with the active ingredient variant epoetin alfa.

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				
Roxadustat	continuously, 3 x within 7 days	52.1	3	156.3
Appropriate comparator therapy				
Erythropoiesis-stimulating agent				
Epoetin alfa, epoetin zeta	continuously, 2 x within 7 days	52.1	2	104.2
	continuously, 3 x within 7 days	52.1	3	156.3
Epoetin beta	continuously, 3 x within 7 days	52.1	3	156.3 -
	continuously, 1 x every 7 days	52.1	1	52.1
Epoetin theta	continuously, 3 x within 7 days	52.1	3	156.3
	continuously, 2 x within 7 days	52.1	2	104.2

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					
Roxadustat	20 mg - 3 mg/kg = 231 mg	20 mg - 240 mg	1 x 20 mg - 1 x 100 mg + 2 x 70 mg	156.3	156.3 x 20 mg - 156.3 x 100 mg + 312.6 x 70 mg
Appropriate comparator therapy					
Erythropoiesis-stimulating agent					
Epoetin alfa, epoetin zeta	25 I.U. kg/BW = 1,925 I.U. -	1,925 I.U.	1 x 2,000 I.U. -	104.2	104.2 x 2,000 I.U. -
	150 I.U. kg/BW = 11,550 I.U.	11,550 I.U.	1 x 10,000 I.U. + 1 x 2,000 I.U.	156.3	156.3 x 10,000 I.U. + 156.3 x 2,000 I.U.
Epoetin beta	20 I.U./kg BW = 1,540 I.U. -	1,540 I.U.	1 x 2,000 I.U.	156.3	156.3 x 2,000 I.U. -
	720 I.U./kg BW = 54,440 I.U.	54,440 I.U.	2 x 30,000 I.U.	52.1	104.2 x 30,000 I.U.
Epoetin theta	20 I.U./kg BW = 1,540 I.U.	1,540 I.U.	1 x 2,000 I.U.	156.3	156.3 x 2,000 I.U.
	350 I.U./kg BW = 26,950 I.U.	26,950 I.U.	1 x 30,000 I.U.	104.2	104.2 x 30,000 I.U.

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					
Roxadustat 20 mg	12 FCT	€ 132.65	€ 1.77	€ 6.72	€ 124.16
Roxadustat 100 mg	12 FCT	€ 618.15	€ 1.77	€ 33.60	€ 582.78
Roxadustat 70 mg	12 FCT	€ 436.09	€ 1.77	€ 23.52	€ 410.80
Appropriate comparator therapy					
Epoetin alfa, epoetin zeta 2,000 I.U.[3]	6 PS	€ 100.31	€ 1.77	€ 7.06	€ 91.48
Epoetin alfa, epoetin zeta 10,000 I.U.[3]	6 PS	€ 488.28	€ 1.77	€ 37.75	€ 448.76
Epoetin beta 2,000 I.U.[3]	6 SFI	€ 100.31	€ 1.77	€ 7.06	€ 91.48
Epoetin beta 30,000 I.U.[3]	4 SFI	€ 980.62	€ 1.77	€ 76.69	€ 902.16
Epoetin theta 2,000 I.U.[3]	6 PS	€ 100.31	€ 1.77	€ 7.06	€ 91.48
Epoetin theta 30,000 I.U.[3]	4 PS	€ 980.62	€ 1.77	€ 76.69	€ 902.16
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; SFI = solution for injection					

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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.

[3] Fixed reimbursement rate

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 20 June 2017, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 3 September 2021, the pharmaceutical company submitted a dossier for the benefit assessment of roxadustat to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 6 September 2021 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 roxadustat.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 December 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 December 2021. The deadline for submitting written statements was 5 January 2022.

The oral hearing was held on 24 January 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 22 February 2022, and the proposed resolution was approved.

At its session on 3 March 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	20 June 2017	Determination of the appropriate comparator therapy
Working group Section 35a	18 January 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	24 January 2022	Conduct of the oral hearing
Working group Section 35a	1 February 2022 15 February 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	22 February 2022	Concluding discussion of the draft resolution
Plenum	3 March 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 March 2022

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

Prof. Hecken