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Roxadustat (renal anaemia) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Roxadustat (renale Anämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 December 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Uwe Korst.

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment as well as their treatment goals. The respondents were not involved in the actual preparation of the dossier assessment.

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CKD	chronic kidney disease
EPAR	European Public Assessment Report
ESA	erythropoiesis-stimulating agent
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug roxadustat. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 6 September 2021.

Research question

The aim of this report is to assess the added benefit of roxadustat in comparison with an erythropoiesis-stimulating agent (ESA) as the appropriate comparator therapy (ACT) in adults with symptomatic anaemia associated with chronic kidney disease (CKD).

For the approved therapeutic indication, the Summary of Product Characteristics (SPC) of roxadustat describes 2 treatment situations: (1) initiation of anaemia therapy in patients not previously treated with an ESA and (2) conversion of anaemia therapy from an ESA to roxadustat.

According to the SPC, the conversion of patients who are stable on ESA treatment must be indicated for conversion. For nondialysis patients, this should be based on a benefit-risk consideration for the individual patients. Given that dialysis patients have a higher cardiovascular and mortality risk, conversion should be considered only in the presence of a valid clinical reason. Conversion to roxadustat in patients stable on ESA treatment without conversion indication is not covered by approval and is therefore disregarded in the present benefit assessment.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of roxadustat

Therapeutic indication	**ACT[a]**
Adults with symptomatic anaemia associated with CKD[b] ▪ who were not previously treated with an ESA ▪ who are converting from an ESA ▫ namely adults stable on prior ESA treatment only in the presence of an indication for conversion[c]	An ESA[b,d,e]
a. Presented is the respective ACT specified by the G-BA. b. For both study arms, the treatment of nutrient deficiencies which could trigger related specific anaemia (e.g. iron, water-soluble vitamins) is assumed to have been ensured in accordance with approval. c. Adult nondialysis patients: benefit-risk consideration for the individual patient; dialysis patients: conversion to be considered only when there is a valid clinical reason. d. Other causes of anaemia (particularly iron deficiency) excluded. e. Treatment of symptomatic anaemia. ACT: appropriate comparator therapy; CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; G-BA: Federal Joint Committee	

The company followed the G-BA's specification by identifying an ESA as the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

Beyond the studies presented in the company's dossier, the check of completeness of the study pool did not find any relevant RCTs for assessing the added benefit of roxadustat versus ACT. Initially, the company had identified 10 RCTs, but it did not use them for deriving any added benefit of roxadustat. Each of these studies compares roxadustat with the ACT, an ESA. However, the studies are unsuitable for deriving any added benefit of roxadustat: In 2 RCTs with adult CKD patients who were not previously treated with ESA, roxadustat treatment was administered largely in deviation from the SPC. The remaining 8 RCTs are irrelevant for the present research questions mostly because they each included adult CKD patients stable on prior ESA treatment who did not have an indication for conversion.

All in all, no suitable data are therefore available for assessing the added benefit of roxadustat in comparison with an ESA as the ACT in adult patients with symptomatic anaemia associated with CKD. Consequently, there is no hint of added benefit of roxadustat in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of added benefit of roxadustat.

Table 3: Roxadustat – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with symptomatic anaemia associated with CKD[b] ▪ who were not previously treated with an ESA ▪ who are converting from an ESA ▫ namely adults stable on prior ESA treatment, only in the presence of an indication for conversion[c]	An ESA[b,d,e]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. For both study arms, the treatment of nutrient deficiencies which could trigger related specific anaemia (e.g. iron, water-soluble vitamins) is assumed to have been ensured in accordance with approval.
c. Adult nondialysis patients: benefit-risk consideration for the individual patient; dialysis patients: conversion to be considered only when there is a valid clinical reason.
d. Other causes of anaemia (particularly iron deficiency) excluded.
e. Treatment of symptomatic anaemia.

ACT: appropriate comparator therapy; CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of this report is to assess the added benefit of roxadustat in comparison with an ESA as the ACT in adults with symptomatic anaemia associated with CKD.

For the approved therapeutic indication, the SPC of roxadustat [3] describes 2 treatment situations: (1) initiation of anaemia therapy in patients not previously treated with an ESA and (2) conversion of anaemia therapy from an ESA to roxadustat.

According to the SPC, the conversion of patients who are stable on ESA treatment requires an indication for conversion. For nondialysis patients, this should be based on a benefit-risk consideration for the individual patients. Given that dialysis patients have a higher cardiovascular and mortality risk, conversion should be considered only in the presence of a valid clinical reason. Conversion to roxadustat in patients stable on ESA treatment without conversion indication is not covered by approval and is therefore disregarded in the present benefit assessment.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of roxadustat

Therapeutic indication	**ACT**[a]
Adults with symptomatic anaemia associated with CKD[b] ▪ who were not previously treated with an ESA ▪ who are converting from an ESA ▫ namely adults stable on prior ESA treatment only in the presence of an indication for conversion[c]	An ESA[b,d,e]
a. Presented is the respective ACT specified by the G-BA. b. For both study arms, the treatment of nutrient deficiencies which could trigger related specific anaemia (e.g. iron, water-soluble vitamins) is assumed to have been ensured in accordance with approval. c. Adult nondialysis patients: benefit-risk consideration for the individual patient; dialysis patients: conversion to be considered only when there is a valid clinical reason. d. Other causes of anaemia (particularly iron deficiency) excluded. e. Treatment of symptomatic anaemia. ACT: appropriate comparator therapy; CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; G-BA: Federal Joint Committee	

The company followed the G-BA's specification by identifying an ESA as the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study list on roxadustat (status: 2 July 2021)
- Bibliographical literature search on roxadustat (last search on 2 July 2021)
- Search in trial registries / trial results databases on roxadustat (last search on 2 July 2021)
- Search on the G-BA website on roxadustat (last search on 2 July 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on roxadustat (most recent search on 28 September 2021); see Appendix A of the full dossier assessment for search strategies.

Beyond the studies presented in the company's dossier, the check of completeness did not reveal any relevant RCTs for assessing the added benefit of roxadustat in comparison with the ACT. The company found 10 RCTs, each of which comparing roxadustat with the ACT, an ESA. However, these studies are unsuitable for assessing the added benefit of roxadustat. In 2 RCTs with adult CKD patients who were not previously treated with ESA, roxadustat treatment was administered largely in deviation from the SPC. The remaining 8 RCTs are irrelevant for the present research question, mainly because they each included adult CKD patients who had been stable on prior ESA treatment without the available data suggesting an indication for conversion. The sections below first describe the company's approach and then provide a detailed justification of why the studies presented by the company are irrelevant for the benefit assessment.

Inappropriate approach chosen by the company

For assessing the added benefit of roxadustat in comparison with an ESA as the ACT, the company had initially identified 9 studies carried out by the company or a cooperation partner (with the company's financial support) as well as 1 investigator-initiated trial (IIT): DOLOMITES [4], HIMALAYAS [5], 1517-CL-0310 [6], ROCKIES [7], SIERRAS [8], PYRENEES [9], FGCL-4592-806 [10], 1517-CL-0307 [11], 1517-CL-0304 [12], ChiCTR2000035054 [13]. These 10 RCTs feature a sufficient study duration and compare roxadustat with the ACT in adults with anaemia associated with CKD (renal anaemia).

The company checked whether these studies involved on-label treatment, both regarding the dosing of roxadustat and the ESA as per the respective German SPCs [3,14,15] and regarding the presence of adequate iron stores at baseline. In reference to the IQWiG Methods paper [1], treatment with the study medication as approved in ≥ 80% of the study population has been designated by the company as the higher-level inclusion criterion.

The company ended up rating all 10 studies it investigated as irrelevant for the benefit assessment because in each of them, far fewer than 80% of the study population met the requirement of on-label treatment with roxadustat or an ESA as per the respective SPCs. The company has documented this separately for the individual arms of each study without forming adequate subpopulations. Overall, the company does not claim any added benefit for roxadustat.

Nevertheless, the company's dossier presents the 10 studies including their results on the basis of the total populations.

The company's justification based on the 80% criterion is inappropriate. Generally, a benefit assessment can be carried out on the basis of analyses of a relevant subpopulation even if fewer than 80% of the total population of a study fully met inclusion criteria [1]. Contrary to the company's assertion, this also applies to the inclusion criteria regarding the intervention or comparator therapy so long as they can be adequately operationalized while preserving randomization.

Roxadustat is used in adults with symptomatic renal anaemia and confirmed adequate iron stores, depending on the therapy situation [3]. In patients not previously treated with ESA, the starting dose of roxadustat depends on body weight (< 100 kg: 70 mg roxadustat 3 times per week, ≥ 100 kg: 100 mg roxadustat 3 times per week). In patients converting from an ESA, the equivalence dose of roxadustat is based on the average prescribed ESA dose in the 4 weeks before conversion.

The suitability of the studies presented in the company's dossier was therefore assessed particularly with regard to the starting dose of roxadustat or the equivalence dose in case of treatment conversion as well as the presence of symptomatic anaemia and adequate iron stores at baseline. Module 4 A of the company's dossier states that symptoms of anaemia were not systematically surveyed or documented in any of the company's studies. However, the SPC specifies symptomatic anaemia as the prerequisite for treatment with the study medication.

Patients not previously treated with ESA

Table 5 shows an overview of the studies presented by the company with patients not previously treated with an ESA.

Table 5: Overview of the RCTs presented in the company's dossier with patients not previously treated with an ESA

Study	Dialysis patients	Specifications of the roxadustat SPC[a]				
		Starting dose of roxadustat		Symptomatic anaemia	Patients with adequate iron stores[b] at baseline n (%)	
		As per SPC	Departure from SPC		Roxadustat arm	ESA arm
Studies with patients not previously treated with an ESA						
DOLOMITES[c] (NCT02021318)	No	(●)	Different body weight cutoff (70 kg)	●	182 (56.3)	152 (51.9)
HIMALAYAS (NCT02052310)	Yes	(●)	Different body weight cutoff (70 kg)	○[d]	406 (77.8)	406 (77.9)

● Criterion met / (●) Criterion partially met
○ Criterion not met
a. Other specifications of the SPC, including dose adjustment and recommended maximum dose, were not checked.
b. Operationalized as serum ferritin ≥ 100 µg/L and transferrin saturation (TSAT) ≥ 20%.
c. Company was the sponsor of the study.
d. Anaemia symptoms were not an inclusion criterion and were not systematically surveyed in the study.

ESA: erythropoiesis-stimulating agent; n: number of patients in the category; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; TSAT: transferrin saturation

The two studies DOLOMITES and HIMALAYAS are nonblinded, randomized, actively controlled studies comparing roxadustat in patients not previously treated with an ESA versus the ESA darbepoetin alpha (DOLOMITES) or epoetin alpha (HIMALAYAS). The DOLOMITES inclusion criteria specify that patients had to be suitable for treatment with an ESA, as defined, in part, by medically verified anaemia symptoms. None of the patients in the study were on dialysis. The patients in the HIMALAYA study, in contrast, were on dialysis.

In both studies, the starting dose of roxadustat was determined by body weight but using a cutoff different from that in the roxadustat SPC [3]. As a result, patients with a body weight between 70 and 100 kg received too high a dose of roxadustat, at least for the first 4 weeks of the study. ESA was dosed in compliance with approval in each case [14,15].

In addition, only about half of the patients in both DOLOMITE study arms had adequate iron stores at baseline. However, the roxadustat SPC defines these iron stores as a prerequisite for the start of roxadustat therapy. Hence, the total population of the study is irrelevant for the benefit assessment.

The fact that patients were included regardless of the presence of symptoms in itself already makes HIMALAYAS unsuitable for the assessment of roxadustat in the present therapeutic indication of symptomatic renal anaemia.

Patients converting from an ESA

With the exception of the double-blind RCT 1517-CL-0307, the company's studies investigating conversion of anaemia therapy in patients pretreated with an ESA are nonblinded, randomized, actively controlled studies. The studies investigate a comparison of roxadustat with darbepoetin alpha (1517-CL-0310, 1517-CL-0307, 1517-CL-0304) or epoetin alpha (FGCL-4592-806, ROCKIES, SIERRAS, ChiCTR2000035054). The PYRENEES study compares roxadustat with both darbepoetin alpha and with epoetin alpha. The 1517-CL-0310 study included only nondialysis patients. All other studies included dialysis patients. Supplementary information on the studies presented by the company with patients converting from an ESA are found in Table 10 in Appendix B of the full dossier assessment.

Roxadustat is generally approved for the conversion of anaemia therapy of patients pretreated with ESA [3]. For patients already stable on ESA treatment, the roxadustat SPC defines the conditions for conversion. For nondialysis patients, a benefit-risk consideration for the individual patient is to be carried out before conversion. For dialysis patients, conversion should be considered only when there is a valid clinical reason. These restrictions for the conversion of patients who are stable on prior treatment are based on the results of the approval studies for roxadustat and are discussed at length in the European Public Assessment Report (EPAR [16]). In particular, an elevated cardiovascular risk and mortality risk was found especially in ESA conversion studies. The risk is suspected to be due to treatment conversion to roxadustat causing fluctuations in haemoglobin level in patients stable on ESA treatment. According to the EPAR,

in the absence of a valid clinical reason, this treatment conversion does not reflect common clinical practice.

The study documents of 1517-CL-0310, FGCL-4592-806, SIERRAS, PYRENEES, 1517-CL-0307, and 1517-CL-0304 show that only patients on stable prior ESA therapy were included. The ROCKIES study documents suggest that the majority of the study population was likewise stable on prior ESA treatment. If randomized into the roxadustat arm of the studies, all of these patients underwent conversion without necessarily having a clinical indication. For the ChiCTR2000035054 study, the Hou 2021 publication [13] includes no evidence suggesting that the included patients with prior treatment had an indication for conversion.

In Module 4 A of the dossier, the company itself acknowledges that none of the studies which included adult CKD patients on dialysis and with prior ESA treatment systematically had checked whether there were valid clinical reasons for conversion from an ESA to roxadustat therapy at study inclusion. Therefore, the company describes the treatment regimen of these studies as an artificial conversion scenario.

Overall, patients included in the 1517-CL-0310, FGCL-4592-806, ROCKIES, SIERRAS, PYRENEES, 1517-CL-0307, 1517-CL-0304, and ChiCTR2000035054 studies are assumed to have no indication for conversion from an ESA to roxadustat. This alone already renders the studies irrelevant for the present research question.

Additional aspects beyond the missing indication for conversion further support the view that the total populations of the 1517-CL-0310, FGCL-4592-806, 1517-CL-0307, 1517-CL-0304, and ChiCTR2000035054 studies are irrelevant for the benefit assessment of roxadustat. These aspects include substantial deviations from the approved dosage of roxadustat, inadequate iron stores at baseline as well as a treatment regimen departing from roxadustat approval (ESA washout before treatment start). For more information, see Table 10 in Appendix B of the full dossier assessment.

Summary

Overall, the studies' total populations as presented in the company's dossier are unsuitable for assessing the added benefit of roxadustat versus the ACT because of the described aspects regarding roxadustat dosing, symptoms, adequate iron stores at baseline, and the absence of an indication for conversion. For the DOLOMITES study, however, a relevant subpopulation might conceivably be formed while preserving randomization. The same might apply to other studies as well.

2.4 Results on added benefit

The dossier therefore provides no suitable data for assessing the added benefit of roxadustat in comparison with an ESA as the ACT in adults with symptomatic anaemia associated with CKD. Consequently, there is no hint of added benefit of roxadustat in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 6 presents a summary of the results of the benefit assessment of roxadustat in comparison with the ACT.

Table 6: Roxadustat – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with symptomatic anaemia associated with CKD[b] ▪ who were not previously treated with an ESA ▪ who are converting from an ESA ▫ namely adults stable on prior ESA treatment only in the presence of an indication for conversion[c]	An ESA[b,d,e]	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. For both study arms, the treatment of nutrient deficiencies which could trigger related specific anaemia (e.g. iron, water-soluble vitamins) is assumed to have been ensured in accordance with approval. c. Adult nondialysis patients: benefit-risk consideration for the individual patient; dialysis patients: conversion to be considered only when there is a valid clinical reason. d. Other causes of anaemia (particularly iron deficiency) excluded. e. Treatment of symptomatic anaemia. ACT: appropriate comparator therapy; CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; G-BA: Federal Joint Committee		

The above assessment concurs with that submitted by the company.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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