Vadadustat (symptomatic anaemia associated with dialysis-dependent chronic kidney disease)

Addendum to Project A24-67 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CKD	chronic kidney disease
CRF	case report form
EOS	End of Study
ESA	erythropoiesis-stimulating agent
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
Hb	haemoglobin
ICH	International Conference on Harmonisation
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IWRS	interactive web response system
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics

1 Background

On 8 October 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-67 (Vadadustat – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analyses of the outcomes of freedom from transfusion and serious adverse events (SAEs) presented by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [2], taking into account the information provided in the dossier [3].

In addition, this addendum describes the supplementary information provided by the company following the oral hearing [4] on the decommissioning of the web-based system for dosage adjustment (interactive web response system [IWRS]).

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

Benefit assessment A24-67 included the randomized controlled trials (RCTs) CI-0016 and CI-0017 to assess the added benefit of vadadustat in symptomatic anaemia associated with chronic kidney disease (CKD) in patients on chronic maintenance dialysis. In both studies, vadadustat was compared with the erythropoiesis-stimulating agent (ESA) darbepoetin alfa as appropriate comparator therapy (ACT). A detailed description of the studies can be found in dossier assessment A24-67 [1].

The analyses on the outcomes of freedom from transfusion and SAEs subsequently submitted by the company in the commenting procedure [2] are assessed below.

A supplementary description is provided of the information subsequently submitted by the company [4] on the decommissioning of the web-based system for dosage adjustment (IWRS) in the course of the studies presented.

2.1 Assessment of the subsequently submitted data on the outcome of transfusions

In the benefit assessment, the data on the outcome of freedom from transfusion presented by the company in Module 4 A were not used because recordings after patients' treatment discontinuation were not considered. Thus, patients who received a transfusion after discontinuing treatment were still counted as transfusion-free, but a connection between discontinuation and subsequent transfusion cannot be ruled out. In addition, information on the observation period per study arm was missing, or it was unclear to what extent there were different observation periods, and whether time-to-event analyses may therefore be necessary.

With its comments, the company presented analyses on the proportion of patients without red blood cell transfusion from the start of the study to the end of the study. In these analyses, the company also considered red blood cell transfusions that took place after premature treatment discontinuation. In addition, the company presented time-to-event analyses for the time to the first red blood cell transfusion.

The data subsequently submitted by the company on the proportion of patients without red blood cell transfusion cover the entire study period. These analyses therefore consider the same observation period for the vadadustat and for the darbepoetin alfa treatment arm. The presentation of the results as incidence rates over the entire course of the study is therefore appropriate. These analyses are therefore used for the present benefit assessment.

The risk of bias of the results of the outcome of freedom from transfusion is rated as low. However, as described in dossier assessment A24-67 [1], due to the limitations regarding the independence of the 2 studies (joint study design, parallel conduct and pooled analysis of both

studies, in particular with the linking of both studies by a cross-study criterion to define study end, while at the same time the study CI-0016 was small), the confirmation (replication) of results by a second study necessary for the derivation of proof is generally not given in this situation. The certainty of conclusions achievable by means of a meta-analysis (proof) is therefore reduced in the present situation. In the meta-analysis of both studies presented, at most an indication, e.g. of an added benefit, can therefore be determined for the outcome of freedom from transfusion.

Table 1 shows the result of the comparison of vadadustat with darbepoetin alfa for the outcome of freedom from transfusion, including all transfusion events until the end of the study.

Table 1: Results (morbidity, dichotomous) – RCT, direct comparison: vadadustat vs. darbepoetin alfa

Outcome category Outcome	Vadadustat		Darbepoetin alfa		Vadadustat vs. darbepoetin alfa
Study	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Morbidity					
Freedom from transfusion					
CI-0016	179	ND	186	ND	0.97 [0.90; 1.05][a]; ND
CI-0017	1768	ND	1769	ND	0.98 [0.96; 1.01][a]; ND
Total	1947	1621 (83.3)	1955	1659 (84.9)	0.98 [0.96; 1.01]; 0.190[b]

a. No information on methods in the comments; presumably as provided in M4: effect calculation via 2x2 table, CI via normal distribution assumption.
b. Meta-analysis with fixed effects (inverse variance), CI and p-value via normal distribution approximation.
CI: confidence interval; N: number of analysed patients; n: number of patients with event; ND: no data; RCT: randomized controlled trial; RR: relative risk

For the outcome of freedom from transfusion, the meta-analysis of the CI-0016 and CI-0017 studies does not show any statistically significant differences between treatment arms; an added benefit is therefore not proven.

2.2 Assessment of the subsequently submitted data on the outcome of SAEs

In the benefit assessment, the risk of bias for results of the outcome of SAEs was rated as high. On the one hand, this was due to the subjective definition of outcomes in the CI-0016 and CI-0017 studies presented; and on the other hand to uncertainties in the follow-up observation after treatment discontinuation, as visit schedule and assessments after premature end of treatment were left to the agreement between investigator and patient.

As described in the benefit assessment, the studies stipulated that any event that the investigator or sponsor judged to be serious was also considered serious. If there was any doubt as to whether the event constituted an adverse event (AE) or an SAE, it was to be treated as an SAE. This allows a subjective categorization of an AE as an SAE and goes beyond the standardized criteria of the International Conference on Harmonisation (ICH) [5] for SAE assessment.

With its comments, the company presented analyses of SAEs in which the "Other" category is excluded. This category of the case report form (CRF) contains the SAEs categorized as subjective in the benefit assessment. It should be noted that this category also excludes events whose categorization as SAE is not questionable. These are, for example, ICH-compliant medically relevant events that require an intervention to avoid an SAE. However, this has no consequence, as the number of patients with at least one SAE changed only slightly overall by excluding the "Other" category (< 3 percentage points in both arms in the meta-analytical summary).

The result of the comparison of both arms remains almost unchanged with the exclusion of the SAEs calculated by the company (see Table 2). It can therefore be assumed that the influence of the potentially subjective component in the operationalization of the SAEs in the present studies does not lead to any relevant bias of the results.

With regard to the individual visit schedules during the follow-up observation period possible in studies CI-0016 and CI-0017, the company stated that a lack of reporting of SAEs by the patients concerned was highly unlikely. It added that an End of Study (EOS) visit was still scheduled for all patients, regardless of the visit schedule, so that reporting of all occurred SAEs no later than at the time of each patient's EOS visit could be assumed.

Despite remaining uncertainties in the follow-up observation after treatment discontinuation, the risk of bias for the analyses presented for the outcome of SAEs is rated as low. The certainty of conclusions of the result on SAEs presented in the dossier assessment is thus changed from "hint" to "indication".

Table 2 shows the result of the comparison of vadadustat with darbepoetin alfa for the outcome of SAEs with and without events classified as "Other" in the CRF.

Table 2: Results (side effects, dichotomous) – RCT, direct comparison: vadadustat vs. darbepoetin alfa

Outcome category Outcome Study	Vadadustat		Darbepoetin alfa		Vadadustat vs. darbepoetin alfa
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Side effects					
SAEs					
CI-0016	179	89 (49.7)	186	105 (56.5)	0.87 [0.71; 1.05]; 0.151[a]
CI-0017	1768	973 (55.0)	1769	1032 (58.3)	0.94 [0.89; 0.99]; 0.029[a]
Total	1947	1062 (54.5)	1955	1137 (58.2)	0.93 [0.89; 0.99]; 0.013[b]
SAEs without CRF specification as "Other" (supplementary information)					
CI-0016	179	ND[c]	186	ND[c]	ND[c]
CI-0017	1768	ND[c]	1769	ND[c]	ND[c]
Total	1947	1013 (52.0)	1955	1092 (55.9)	0.93 [0.88; 0.98]; 0.008[b]

a. RR: stratified by geographic region (United States/Europe/rest of the world), NYHA heart failure class (0 or I / II or III), baseline Hb (< 9.5/≥ 9.5 g/dL in study CI-0016 and < 10.0/≥ 10.0 g/dL in study CI-0017), CI: normal distribution approximation, p-Wert: Cochran-Mantel-Haenszel test.
b. Meta-analysis with fixed effects (inverse variance), CI and p-value via normal distribution approximation.
c. At study level, the company only presented forest plot analyses with effect measures but without event numbers in its comments. These analyses are identical to the analyses in Module 4 A, which include the "Other" category. Furthermore, since the meta-analytical data presented in the forest plot contradict the tabular information in the company's comments, the data at study level are not used.

CI: confidence interval; Hb: haemoglobin; N: number of analysed patients; n: number of patients with (at least one) event; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

The meta-analysis of the studies showed a statistically significant difference in favour of vadadustat in comparison with darbepoetin alfa for the outcome of SAEs. There is an indication of lesser harm from vadadustat in comparison with the ACT.

2.3 Discontinuation of the programmed system for dose adjustment

In the hearing on the dossier assessment [6], the discontinued use of a web-based system for dosage adjustment in the course of the study (IWRS) due to malfunctions was addressed, discussing possible effects on the approval-compliant and guideline-compliant dosing in the comparator arm. The company submitted additional information on this in writing [4].

In the subsequently submitted information, the company explained that, according to the study protocols, possible dosage adjustments of vadadustat and darbepoetin alfa in studies CI-0016 and CI-0017 were controlled on the basis of haemoglobin (Hb) concentration and

defined algorithms for dose adjustment. In the adjustments, the investigator was to take into account Hb increase rate, Hb decrease rate, ESA response and variability as well as the patient's clinical condition. According to the company, the dosing regimens corresponded to the specifications in the respective valid regulatory documents (Prescribing Information for the United States and European Summary of Product Characteristics [SPC] for study centres outside the United States). It should be noted that these dosing regimens were only explicitly formulated in the protocol as of the protocol amendments in January 2018. Until then, these were implemented in the IWRS for the investigators but not presented in the study protocol.

After some investigators had reported, according to the company, that in some cases the web-based system had not recommended the correct dose adjustment, the use of the system in the study was discontinued in January 2018 (Protocol Amendment 2 for CI-0017, Amendment 3 for CI-0016, each 1/2018; observation period of the studies 6/2016 to 1/2020). The dose adjustment algorithm, which had previously been only programmed, was now formulated and included without changes in the appendix to the protocol.

One discrepancy between the protocol and the SPC for darbepoetin alfa described in the dossier assessment concerned the dose adjustment in the event of an Hb increase by more than 2 g/dL within 4 weeks. In this case, the SPC specifies a dose reduction, whereas the study protocol also allowed the dose to be maintained. It can be inferred from the information provided by the company that this dosing option deviating from the approval existed both during use and after discontinuation of the IWRS in both studies.

The company argued that this deviation has no consequences, as the procedure for dose adjustment of darbepoetin alfa has been established in everyday care for many years and the malfunctions leading to discontinuation of the system did not specifically concern this point.

It therefore still remains unclear which incorrect dosing recommendations were given to what extent, leading to the discontinuation of the system. The information subsequently submitted by the company thus does not dispel the uncertainties described in the benefit assessment.

2.4 Summary

The results for the outcome of freedom from transfusion subsequently submitted by the company are used for the benefit assessment. For the results of the outcome of SAEs, the certainty of conclusion changes from "hint" to "indication".

The resulting changes in the extent of the added benefit at outcome level are shown in Table 3.

Table 3: Extent of added benefit at outcome level: vadadustat vs. darbepoetin alfa (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Intervention vs. comparator** **Quantile of time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity		
Freedom from transfusion	83.3% vs. 84.9% RR: 0.98 [0.96; 1.01] p = 0.190	Lesser/added benefit not proven
Side effects		
SAEs	49.7%–55.0% vs. 56.5%–58.3% RR: 0.93 [0.89; 0.99] p = 0.013 Probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"
Discontinuation due to AEs	2.8%–5.2% vs. 1.1%–1.1% RR: 4.31 [2.72; 6.83] RR: 0.23 [0.15; 0.37][c] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: "considerable"
Cardiac disorders (SOC, AE)	12.8%–16.7% vs. 13.4%–20.0% RR: 0.85 [0.74; 0.97] p = 0.015 Probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"
Neoplasms benign, malignant and unspecified (SOC, SAE)	1.1%–2.1% vs. 2.2%–3.3% RR: 0.65 [0.44; 0.96] p = 0.030 Probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"
Urinary tract infection (PT, SAE)	0.8%–1.1% vs. 0.5%–1.8% RR: 0.51 [0.28; 0.93] p = 0.027 Probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"

Table 3: Extent of added benefit at outcome level: vadadustat vs. darbepoetin alfa (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Intervention vs. comparator** **Quantile of time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mental status changed (PT, SAE) Baseline Hb[d]		
< 10.0 g/dL	0% vs. 1.8% RR: 0.10 [0.01; 0.84] p = 0.034 Probability: "indication"	Outcome category: serious/severe side effects $0.80 \leq CI_u < 0.90$ Lesser harm, extent: "considerable"
≥ 10.0 g/dL	0.9% vs. 0.9% RR: 1.00 [0.44; 2.29] p = 0.991	Lesser/added benefit not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. The subgroup characteristic of baseline Hb with the cut-off value of 10 g/dL was only analysed for the pooled data of the patients in both studies, but not separately for each study.

CI: confidence interval; CI_u: upper limit of the confidence interval; Hb: haemoglobin; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

Table 4 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 4: Positive and negative effects from the assessment of vadadustat in comparison with the ACT

Positive effects	**Negative effects**
Serious/severe side effects ▪ SAEs: indication of lesser harm – extent: “minor” ▫ Specific AEs (SAEs): - Cardiac disorders: indication of lesser harm – extent: “minor” - Neoplasms benign, malignant and unspecified (incl cysts and polyps): indication of lesser harm – extent “minor” - Urinary tract infection: indication of lesser harm – extent: “minor” - Mental status changed: Baseline Hb < 10.0 g/dL: indication of lesser harm – extent: “considerable”	–
–	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent: “considerable”
Only data on the outcome of freedom from transfusion are available for the morbidity category; no data were recorded for the health-related quality of life category.	
AE: adverse event; Hb: haemoglobin; SAE: serious adverse event	

Overall, the data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of vadadustat drawn in dossier assessment A24-67.

Overall, a positive effect of vadadustat in comparison with the ACT was shown for the outcome of SAEs. This already includes the effects shown in the subcategories of SAEs at the level of System Organ Classes (SOCs) and Preferred Terms (PTs). In contrast, there is a negative effect for the outcome of discontinuation due to AEs.

For the morbidity category, data are only available for the outcome of freedom from transfusion, which do not show a significant effect. In the present therapeutic indication, the outcome of freedom from transfusion covers only a small part of the patient-relevant morbidity. The main aims of anaemia treatment here are to alleviate symptoms and improve function. However, patient-reported outcomes in the morbidity category were not recorded, nor were outcomes in the health-related quality of life category. Thus, the possibility of evaluating an effect on the benefit side is severely limited in the present assessment.

Uncertainties remain in connection with the discontinuation of the IWRS and possible effects on dosing recommendations that deviate from the approval. These could not be dispelled in the hearing and the subsequent submission.

In summary, there is therefore no proof of an added benefit of vadadustat over the ACT for adult patients with symptomatic anaemia associated with CKD who are on chronic maintenance dialysis.

The following Table 5 shows the result of the benefit assessment of vadadustat taking into account both dossier assessment A24-67 and the present addendum.

Table 5: Vadadustat – probability and extent of added benefit

Therapeutic indication	**ACT[a, b]**	**Probability and extent of added benefit**
Adult patients with symptomatic anaemia associated with chronic kidney disease (CKD)[c] who are on chronic maintenance dialysis	▪ Darbepoetin alfa or ▪ epoetin alfa or ▪ epoetin beta or ▪ epoetin theta or ▪ epoetin zeta or ▪ methoxy polyethylene glycol-epoetin beta	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the use of erythropoiesis-stimulating agents (ESAs) requires that other causes of anaemia (in particular iron deficiency) have been ruled out. In addition, the specifications in the respective Summary of Product Characteristics and the specifics of the German health care context must be taken into account.
c. In the present therapeutic indication, it is assumed in accordance with the G-BA that guideline- and approval-compliant treatment is ensured in both study arms for any deficiency states that could cause corresponding specific types of anaemia (e.g. iron, water-soluble vitamins).

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.

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