IQWiG Reports – Commission No. A20-02

Andexanet alfa (acute severe bleeding) –

Addendum to Commission A19-76[1]

Addendum

Commission: A20-02
Version: 1.0
Status: 31 January 2020

[1] Translation of addendum A20-02 *Andexanet alfa (akute schwere Blutungen) – Addendum zum Auftrag A19-76* (Version 1.0; Status: 31 January 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Andexanet alfa (acute severe bleeding) – Addendum to Commission A19-76

Commissioning agency

Federal Joint Committee

Commission awarded on

6 January 2020

Internal Commission No.

A20-02

Address of publisher

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Keywords: Andexanet alfa, Haemorrhage, Benefit Assessment

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
FXa	Factor Xa
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NIHSS	National Institute of Health Stroke Scale
NOAK	non-vitamin-K-antagonist
PS	propensity score
VKA	vitamin K antagonist

1 Background

On 6 January 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-76 (Andexanet alfa – Benefit assessment according to §35a Social Code Book V) [1].

For the benefit assessment of andexanet alfa in adult patients treated with a direct Factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when anticoagulation has to be discontinued due to life-threatening or uncontrollable bleeding events, the pharmaceutical company (hereinafter referred to as "the company") presented a comparison of individual arms from different studies in its dossier [2], including the single-arm study ANNEXA-4 [3] on the side of andexanet alfa and a total of 18 single-arm studies on the side of the appropriate comparator therapy (ACT). Due to methodological differences between the studies, the data presented by the company could not be used for the benefit assessment. Detailed reasons can be found in dossier assessment A19-76 [1].

With its written comments, the company presented a propensity score (PS)-adjusted comparison of individual arms from different studies for the comparison of andexanet alfa with the ACT in patients with intracerebral bleeding [4]. For the intervention, it included the single-arm study ANNEXA-4, for the ACT the single-arm study RETRACE-II [5], because individual data were available for both studies.

The G-BA commissioned IQWiG to assess this comparison.

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

The company had already presented the ANNEXA-4 study in its dossier. The RETRACE-II study had already been part of the study pool for the ACT in the company's dossier. The company explained that the data of the RETRACE-II study were only available in published, aggregated form when the dossier was submitted [5]. Through the provision of the complete data set by the owners of the study and the individual data thus available, the company was able to make a PS-adjusted comparison of individual arms from different studies. Moreover, it only considered part of the approved therapeutic indication in this comparison, namely patients with intracerebral bleeding.

The comparison presented by the company was unsuitable to derive an added benefit of andexanet alfa in comparison with the ACT. This is justified below.

Comparison of individual arms from different studies

Studies included by the company

Dossier assessment A19-76 includes a description of the ANNEXA-4 on andexanet alfa [1].

The RETRACE-II study [5] was a retrospective German observational (registry) study including 1338 patients from 19 university centres who had vitamin K antagonist (VKA)-associated or non-vitamin-K-antagonist (NOAK)-associated intracerebral bleeding between 1 January 2011 and 31 December 2015. Patients with intracerebral bleeding in connection with trauma, tumour, arteriovenous malformation, aneurysmatic subarachnoid haemorrhage, acute thrombolysis or other coagulopathies were excluded. Outcomes of the study were haematoma enlargement, occurrence of intracranial and extracranial complications (ischemic and haemorrhagic adverse events) during hospitalization, mortality before leaving hospital or after 3 months, and neurological functionality after 3 months [6].

Table 2 and Table 3 in Appendix A describe the studies ANNEXA-4 and RETRACE-II presented by the company for the comparison.

Unsuitable approach of the company

As described above, the comparison of the company did not cover the entire range of adult patients who were treated with a direct FXa inhibitor (apixaban or rivaroxaban) when anticoagulation had to be discontinued due to life-threatening or uncontrollable bleeding. It limited the population for the comparison to patients with intracerebral bleeding. Accordingly, the company only used a subpopulation of the two studies ANNEXA-4 and RETRACE-II. The population defined by the company is limited to patients who had received treatment with apixaban or rivaroxaban within the last 18 hours and had intracerebral, non-trauma-associated or non-tumour-associated bleeding. To further align patient collectives, the company excluded patients with abnormal liver function or alcohol abuse from the RETRACE II study because, although not specifically prohibited, no patients with abnormal liver function or alcohol abuse had been included in the ANNEXA 4 study. The subpopulations selected for the comparison

included 85 patients from ANNEXA-4 and 97 from RETRACE-II. Table 4 in Appendix A shows the patient characteristics of the patient populations included by the company.

The patient characteristics presented by the company show that 5.2% of the patients in the comparator arm received vitamin K and 15.5% received no specific treatment. It is thus unclear whether these patients received treatment in the sense of the ACT specified by the G-BA. Further data on the interventions performed, e.g. on concomitant medication, local and intensive care measures are missing, so that no information is available on how these patients were treated.

To adjust for differences in the patient populations, the company performed a PS-adjusted comparison of the individual arms from the different studies. Therefore, the PS is modelled on the basis of patient characteristics. The inverse of the estimated PS is then used for the weighting of patients.

The company considered the following outcomes for its comparison:

- 30-day mortality before discharge from hospital
- volume changes (baseline to follow-up) of the intracerebral bleeding lesion
- neurological condition measured using the Modified Ranking scale after treatment

The company presented no analyses on the outcomes on health-related quality of life and on side effects. It justifies this by the fact that the data available from the RETRACE II study for these outcomes are insufficient.

The results from a comparison of individual arms from different studies are subject to an inherent uncertainty due to the lack of randomization, even if an adjustment was made in the analysis with regard to potentially relevant effect modifiers or prognostic factors. Potentially unknown confounders can cause systematic bias of the results, so that an added benefit can only be derived if the effects are sufficiently large.

Moreover, in the comparison presented by the company patient characteristics could not be considered in the modelling of PS due to missing values. For instance, for the National Institute of Health Stroke Scale (NIHSS), recordings were only available for 45% of the patients in the ANNEXA-4 population, so that an adequate adjustment for this characteristic was not possible. Here, higher mean values were found in patients who received the comparator therapy (8 in ANNEXA-4 vs. 10 in RETRACE-II), which indicates a higher severity of intracerebral bleeding in these patients.

A statistically significant difference in favour of andexanet alfa was shown for the outcome “volume changes of the intracerebral bleeding lesion” (difference of the mean volume change between the groups [ml]: −7.21; 95% CI [−11.41; −2.83]; p = 0.001). The observed effect was not large enough not to be explicable by systematic bias alone. It is also unclear how this

outcome relates as a surrogate to directly patient-relevant outcomes, such as neurological function or mortality. These two outcomes were recorded, however, there were no statistically significant differences between the two groups.

Moreover, balancing of benefit and harm of the intervention versus the ACT is not possible without a comparative analysis on the side effect-related outcomes.

Overall, the data presented by the company are unsuitable for deriving an added benefit of andexanet alfa in comparison with the ACT.

Added benefit currently not proven

As described above, the subsequently submitted data are also unsuitable for deriving an added benefit of andexanet alfa versus an optimized standard therapy. This resulted in no hint of an added benefit of andexanet alfa versus the ACT; an added benefit is therefore not proven. As already described in dossier assessment A19-76, a randomized controlled study on andexanet alfa in comparison with the common standard treatment in patients treated with an FXa inhibitor and having intracranial bleeding is presently ongoing. This study is expected to be completed in 2023 [7,8].

2.1 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of andexanet alfa from dossier assessment A19-76.

The following Table 1 shows the result of the benefit assessment of andexanet alfa under consideration of dossier assessment A19-76 and the present addendum.

Table 1: Andexanet alfa – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults treated with a direct FXa inhibitor (apixaban or rivaroxaban) in whom anticoagulation had to be terminated due to life-threatening or uncontrollable bleeding	Optimized standard treatment[b] of the life-threatening or uncontrollable bleeding events	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Standard treatment can comprise blood products, fluid substitution, plasma expanders or prothrombin concentrates.

FXa: Factor Xa; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

3 References

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

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Appendix A – Supplementary information

Table 2: Characteristics of the studies included by the company – non-RCT, comparison of individual arms from different studies: andexanet alfa vs. optimized standard therapy (multipage table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ANNEXA-4	Single-arm, prospective	Adult patients treated with an FXa inhibitor[b] and for whom anticoagulation had to be discontinued[d] due to acute severe bleeding[c]	Andexanet alfa (N = 352) subpopulation analysed by the company[e]: Andexanet alfa (n = 85)	Screening: < 1 day treatment: < 1 day[f] observation: ≤ 3 days follow-up[g]: 30 + 7 days	63 centres in Europe and North America 06/2015–ongoing[h] data cut-off: 28 November 2018	Primary: achievement of effective haemostasis 12 hours after treatment with andexanet alfa and percentage change of the anti-FXa activity at baseline in comparison with nadir during treatment with andexanet alfa secondary: mortality, morbidity[i], AEs
RETRACE–II	Single-arm, retrospective	Patients who received treatment with VKA or NOAK and had intracerebral bleeding[j]	Optimized standard therapy (N = 1338) subpopulation analysed by the company[k]: optimized standard therapy (n = 97)	Screening[l]: not applicable treatment: < 1 day observation[m]: ~ 14 days follow-up: 3 months	19 centres in Germany 01/2011–12/2015	Primary: haematoma enlargement secondary: mortality, morbidity[n]

Table 2: Characteristics of the studies included by the company – non-RCT, comparison of individual arms from different studies: andexanet alfa vs. optimized standard therapy (multipage table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant outcomes for this benefit assessment.
b. Apixaban, rivaroxaban, edoxaban or enoxaparin (≥ 1 mg/kg/day).
c. Acute, potentially life-threatening bleeding or acute bleeding with a decrease in the Hb value ≥ 2 g/dl or an Hb ≤ 8 g/dl (if no baseline Hb is detectable or if, at the investigator's discretion, the Hb would fall to ≤ 8 g/dl after resuscitation) or acute bleeding in a critical anatomical region, such as pericardial, intracranial or intraspinal bleeding.
d. Last administration of the FXa inhibitor had to be ≤ 18 hours ago. Patients with a Glasgow Coma Score (GCS) < 7 or an initial intracerebral bleeding volume > 60 ml estimated by CT or MRI were not included in the study.
e. Patients who had received treatment with apixaban or rivaroxaban and had intracerebral, non-trauma-associated and non-tumour-associated bleeding.
f. Re-administration of andexanet alfa was possible within 24 hours after administration of the initial dose.
g. Mortality and treatment-associated adverse events.
h. Study presently ongoing for further recruitment of patients under treatment with edoxaban. Recruitment of patients under treatment with apixaban and rivaroxaban has been completed.
i. Effects of intracranial bleeding on the neurological condition, occurrence of rebleeding, need for blood products and use of other haemostatic products.
j. Patients with intracerebral bleeding due to trauma, tumour, arteriovenous malformation, subarachnoid aneurysm-related bleeding, acute thrombolysis or other coagulation disorders were not included in the study.
k. Patients with GCS ≥ 7 and an initial intracerebral bleeding volume ≤ 60 ml at baseline who had received treatment with apixaban or rivaroxaban within the last 18 hours. Patients with abnormal liver function or alcohol abuse were excluded (n = 11).
l. Retrospective analyses of the patient records.
m. Duration of hospitalization.
n. Onset of intracranial and extracranial complications (ischaemic and haemorrhagic adverse events) during hospitalization, mortality before leaving hospital, mortality after 3 months, neurological functionality after 3 months.

AE: adverse event; CT: computed tomography; FXa: Factor Xa; GCS: Glasgow Coma Score; MRI: magnetic resonance imaging; n: relevant subpopulation; N: number of patients included; NOAK: non-vitamin-K-antagonist-associated; RCT: randomized controlled trial; VKA: vitamin K antagonist; vs.: versus

Table 3: Characteristics of the intervention – non-RCT, comparison of individual arms from different studies: andexanet alfa vs. optimized standard therapy (multipage table)

Study	Intervention
ANNEXA–4	Intravenous administration of andexanet alfa[a] Low dosage ▪ intravenous initial bolus 15 min, 400 mg, ≤ 30 mg/min ▪ continuous intravenous injection 120 min, 480 mg, 4 mg/min High dosage ▪ intravenous initial bolus 30 min, 800 mg, ≤ 30 mg/min ▪ continuous intravenous injection 120 min, 960 mg, 8 mg/min
	Required pretreatment: The patient received or presumably received one of the following FXa inhibitors within 18 hours prior to administration of andexanet alfa: apixaban, rivaroxaban, edoxaban or enoxaparin (enoxaparin dose ≥ 1 mg/kg/day). **Non-permitted pretreatment[b]:** ▪ VKA (e.g. warfarin) ▪ Dabigatran ▪ PPSB (e.g. Kcentra) or rfVIIa (e.g. NovoSeven) ▪ whole blood, plasma fractions **Concomitant treatment:** ▪ avoidance of anticoagulants and antiplatelet drugs until the evaluation of haemostasis (12 hours after treatment with andexanet alpha) ▪ application of blood derivatives: ▫ erythrocyte transfusion, recommended if haemoglobin value ≤ 8.0 g/dl (±1 g/dl) ▫ avoidance of procoagulatory infusions (e.g. PPSB, rfVIIA, plasma) and whole blood until haemostasis is evaluated (12 hours after treatment with andexanet alfa) ▫ platelet transfusion depending on local requirements and guidelines. ▪ Haemostatic agents: ▫ administration of antifibrinolytics (e.g. aminocaproic acid and tranexamic acid) and other systemic haemostatic agents according to local requirements and guidelines ▫ local haemostatics agents (e.g. microfibrillary collagen and products containing chitosan) and topical vasoconstrictors (e.g. adrenaline), if clinically necessary
RETRACE II	Standard therapy[c]: no restrictions
	required pretreatment: treatment with VKA or NOAK **non-permitted pretreatment:** no restrictions **concomitant treatment:** no restrictions

a. Depending on dose and time of the last administration of FXa inhibitors, low or high doses of andexanet alfa were given. Further follow-up treatment (rebolus and continuous infusion) with andexanet alfa was recommended if bleeding persisted or reoccurred after initial administration and the treating physician had clinical suspicion that the patient still had FXa inhibitor levels contributing to bleeding, and readministration took place within 24 hours after completion of the 1st andexanet alfa treatment.
b. ≤ 7 days before screening.
c. With the beginning of a hospitalisation due to intracerebral bleeding.

FXa: Factor Xa; NOAK: non-vitamin-K-antagonist-associated; PPSB: Prothrombin Complex Concentrate; RCT: randomized controlled trial; rfVIIa: recombinant factor VIIa; VKA: vitamin K antagonist; vs.: versus

Table 4: Characteristics of the study population –non-RCT, comparison of individual arms from different studies: andexanet alfa vs. optimized standard therapy (multipage table)

	Study	
Characteristics **Category**	**ANNEXA–4**	**RETRACE–II**
	N[a] = 85	N[a] = 97
Age [years], mean (SD)	79 (9.0)	78 (7.6)
Sex [F/M], %	42/58[b]	53/47[b]
Countries, n (%)		
Germany	28 (32.9)	97 (100.0)
Other countries[c]	57 (67.1)[b]	0 (0.0)[b]
FXa inhibitor, n (%)		
Apixaban	49 (57.6)	19 (19.6)
Rivaroxaban	36 (42.4)	78 (80.4)
Anti-FXa activity [ng/ml], mean (SD)	158 (115.7)	174 (126.5)
Time since last administration of the FXa inhibitor [hours], mean (SD)	12 (4.3)	8 (4.3)
Underlying disease[d], n (%)		
Atrial fibrillation	75 (88.2)	82 (84.5)
Pulmonary embolism	4 (4.7)	6 (6.2)
Deep vein thrombosis	7 (8.2)	7 (7.2)
Other indications	4 (4.7)	2 (2.1)
Comorbidities, n (%)		
Hypertension	75 (88.2)	87 (90.6)
Diabetes mellitus	35 (41.2)	32 (33.3)
Dyslipidaemia	41 (48.2)	32 (33.3)
Abnormal renal function	13 (15.3)	18 (18.8)
Cardiac failure	11 (12.9)	19 (19.8)
Peripheral arterial occlusive disease	3 (3.5)	4 (4.2)
Previous myocardial infarction	9 (10.6)	12 (12.5)
Previous application of statins	47 (55.3)	27 (28.4)
Previous ischaemic stroke or transient ischaemic attack (TIA)	28 (32.9)	28 (29.5)
Previous haemorrhagic stroke or severe bleeding	6 (7.1)	8 (8.3)
Previous application of platelet aggregation inhibitors	26 (30.6)	12 (12.5)
Blood pressure [mmHg], mean (SD)		
Systolic	145 (24.5)	168 (33.9)
Diastolic	76 (20.7)	90 (20.2)
Haemoglobin [g/dL] – mean (SD)	13 (1.9)	13 (2.4)
Initial intracerebral haemorrhage volume, [cm³], mean (SD)	14 (14.0)	16 (17.0)
Intraventricular haemorrhage, n (%)	11 (12.9)	38 (40.0)
Infratentorial haemorrhage, n (%)	17 (20.0)	11 (11.3)
GCS, mean (SD)	13 (2.1)	13 (2.5)
NIHSS, mean (SD)	8 (6.5)[e]	10 (6.9)

Table 4: Characteristics of the study population –non-RCT, comparison of individual arms from different studies: andexanet alfa vs. optimized standard therapy (multipage table)

	Study	
Characteristics **Category**	**ANNEXA–4**	**RETRACE–II**
	N[a] = 85	N[a] = 97
Received intervention, n (%)		
Andexanet alfa[f]		
Low dosage	72 (84.7)	–[g]
High dosage	13 (15.3)	–[g]
PPSB	ND[h]	73 (75.3)[i]
Vitamin K	ND[h]	5 (5.2)
Fresh frozen plasma	ND[h]	1 (1.0)
Tranexamic acid	ND[h]	0 (0)
Antithrombin	ND[h]	0 (0)
Platelet concentrate	ND[h]	3 (3.1)
No specific therapy	0 (0)[b]	15 (15.5)
Treatment discontinuation, n (%)	ND[j]	ND
Study discontinuation, n (%)	ND	–[k]

a. Number of patients included in the analysis. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. Belgium, Canada, France, Netherlands, Spain, United Kingdom and USA.
d. Indication for treatment with the FXa inhibitor.
e. The determination of this score was only introduced in the course of the study. The score was only available for 38 (44.7%) of the 85 patients included in the analysis.
f. 3 patients of the total population (all three of them having intracerebral bleeding) received another treatment with andexanet alfa (re-dosing). There are no data available for the subpopulation considered here.
g. Andexanet alfa was not yet approved during the RETRACE II trial.
h. 16% or 31% of the patients of the total population pretreated with apixaban or rivaroxaban also received erythrocyte transfusions. Further data on additional therapies for the total population and the subpopulation considered here are not available.
i. The administered PPSB consisted of a 4-factor concentrate containing coagulation factors II, VII, IX and X, as well as protein C and S.
j. 90.3% of the patients in the total population received treatment as planned and without interruption. A total of 1.7% of the patients underwent modifications to the intervention, 7.1% had an interruption and 1.1% discontinued treatment. Data on the subpopulation considered here are lacking.
k. Retrospective analysis of the patient records.

F: female; GCS: Glasgow Coma Score; M: male; n: number of patients in the category; N: Number of patients included in the analysis; ND: no data; NIHSS: National Institute of Health Stroke Scale; PPSB: Prothrombin Complex Concentrate; RCT: randomized controlled trial; SD: standard deviation; USA: United States of America; vs.: versus