IQWiG Reports – Commission No. A19-76

Andexanet alfa (acute severe bleeding) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Andexanet alfa (akute schwere Blutungen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 November 2019). 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) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

30 August 2019

Internal Commission No.:

A19-78

Address of publisher:

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Keywords: andexanet alfa, hemorrhage, benefit 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
AE	adverse event
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)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

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 andexanet alfa. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 30 August 2019.

Research question

The aim of the present report was to assess the added benefit of andexanet alfa compared with the appropriate comparator therapy (ACT) in adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban), when anticoagulation treatment has to be discontinued due to life-threatening or uncontrollable bleeding.

For the benefit assessment, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of andexanet alfa

Research question	Subindication	ACT[a]
1	Adults treated with a direct FXa inhibitor (apixaban or rivaroxaban) in whom anticoagulation had to be terminated due to life-threatening or uncontrollable bleeding events	Optimized standard therapy[b] of the life-threatening or uncontrollable bleeding events

a: Presentation of the ACT specified by the G-BA.
b: The standard therapy can, for instance, comprise blood products, fluid substitution, plasma expanders or prothrombin concentrates.
FXa: Factor Xa; G-BA: Federal Joint Committee

The company followed the G-BA's specification on the ACT.

The assessment was made by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Study pool of the company

The company identified no randomized controlled trials (RCTs) on the direct comparison or on the adjusted indirect comparison of andexanet alfa versus the ACT. Due to the lack of directly comparative data, the company presented results of individual arms from different studies in the Section "Further investigations".

The company presented the single-arm, multicentre approval study ANNEXA-4 on andexanet alfa. The study included 352 adult patients who were being treated with an FXa inhibitor (apixaban, rivaroxaban, edoxaban, enoxaparin). Patients had to have acute severe bleeding and termination of anticoagulation had to be required. In compliance with the approval, treatment with andexanet alfa for haemostasis was performed with an initial intravenous bolus and subsequent continuous IV infusion with 2 different dosage schemes each depending on the last dose and the time point of the last administration of an FXa inhibitor.

The study pool on the ACT included by the company comprised 18 prospective and retrospective observational studies. In all studies, patients who had bleeding events under anticoagulants were investigated. The smallest study included 13 patients; the larger (registry) study comprised 1776 patients who underwent follow-up observation for few days to several months. In all studies, prothrombin concentrates could be administered for haemostasis; further measures included the administration of transfusions of various blood products (thrombocytes, erythrocytes, plasma), coagulation factor VII preparations, tranexamic acid, fibrinogen concentrates or vitamin K.

Approach of the company

The company conducted a descriptive comparison of the results of the ANNEXA-4 study with those of the studies on the ACT. The company presented no effect estimations for the comparison of the intervention with the comparator therapy and did not use the identified studies on the ACT for the derivation of an added benefit due to methodological differences. For instance, it justified this approach specifically with methodological differences in the recording for the outcomes “achievement of effective haemostasis” and “recurrence of bleeding”, or with heterogeneous results - potentially caused by the different patient populations with regard to site and severity of bleeding or previous diseases - for the outcome “30-day mortality”.

A comparison with the ACT is impossible

The approach of the company not to use the studies of the comparator therapy for the derivation of the added benefit is adequate. An important reason speaking against a comparison of the results of the individual studies is that the operationalization of the outcomes differs considerably between the studies. An illustrative example of this is the outcome “recurrence of bleeding”. In the ANNEXA-4 interventional study, only patients who initially showed good or very good haemostasis and who experienced recurrence of bleeding at the same anatomical site within 24 hours were considered for this outcome. The studies on the comparator therapy, in contrast, reported the total population of patients with recurrence of bleeding, regardless of the initial haemostasis or restriction to the same anatomical site; hereby, the recording period was at least 48 hours. This renders a comparison of the occurred events meaningless in terms of content.

Added benefit currently not proven

As described above, the currently available data are unsuitable to prove an added benefit of andexanet alfa versus the ACT - an optimized standard therapy. An international RCT of the company (18-513) launched this year compares treatment with andexanet alfa with the current standard of care in patients treated with a direct FXa inhibitor who experience intracranial bleeding. This study was a requirement of the European regulatory authority for the conditional approval of andexanet alfa and will presumably be completed in 2023.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug andexanet alfa in comparison with the ACT is assessed as follows:

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

Table 3: Andexanet alfa – probability and extent of added benefit

Subindication	**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 events	Optimized standard therapy[b] of the life-threatening or uncontrollable bleeding events	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: The standard therapy can, for instance, 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] 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 the present report was to assess the added benefit of andexanet alfa compared with the ACT in adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban), when anticoagulation treatment has to be discontinued due to life-threatening or uncontrollable bleeding events.

For the benefit assessment, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of andexanet alfa

Research question	Subindication	ACT[a]
1	Adults treated with a direct FXa inhibitor (apixaban or rivaroxaban) in whom anticoagulation had to be terminated due to life-threatening or uncontrollable bleeding events	Optimized standard therapy[b] of the life-threatening or uncontrollable bleeding events

a: Presentation of the ACT specified by the G-BA.
b: The standard therapy can, for instance, comprise blood products, fluid substitution, plasma expanders or prothrombin concentrates.
FXa: Factor Xa; G-BA: Federal Joint Committee

The company followed the G-BA's specification on the ACT.

The assessment was made by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on andexanet alfa (status: 18 July 2019)
- bibliographical literature search on andexanet alfa (last search on 12 July 2019)
- search in trial registries for studies on andexanet alfa (last search on 10 July 2019)
- bibliographical literature search on the ACT (last search on 12 July 2019)
- search in trial registries for studies on the ACT (last search on 8 July 2019)

To check the completeness of the study pool:

- search in trial registries for studies on andexanet alfa (last search on 11 September 2019)

The company identified no RCTs on the direct comparison or on the adjusted indirect comparison of andexanet alfa versus the ACT.

Concurring with the company, no relevant RCTs with available results enabling a direct comparison or an adjusted indirect comparison with the ACT via a common comparator were identified from the check. Results for the company's ongoing RCT 18-513 in the therapeutic indication are presently not available [3,4].

Due to the lack of directly comparative data, the company presented results of individual arms from different studies in the Section "Further investigations". For andexanet alfa, this is the single-arm approval study ANNEXA-4 [5]. Moreover, the company identified 18 studies on the ACT [6-23]. The data presented by the company were unsuitable for the derivation of an added benefit of andexanet alfa. This is justified below. For this purpose, the data considered by the company and the company's approach are described at first. Then it is explained why the data presented permit no derivation of conclusions on the added benefit of andexanet alfa in comparison with the ACT.

Data presented by the company

In the following, the studies presented by the company are described only briefly and, for the comparator therapy, in summarized form. A detailed representation is found in Module 4 of the company.

Study on andexanet alfa

The company presented the single-arm, multicentre approval study ANNEXA-4 on andexanet alfa. The study included 352 adult patients who were being treated with an FXa inhibitor (apixaban, rivaroxaban, edoxaban, enoxaparin). Patients had to have acute severe bleeding and termination of anticoagulation had to be required. In compliance with the approval, treatment with andexanet alfa for haemostasis was performed with an initial intravenous bolus and subsequent continuous IV infusion with 2 different dosage schemes, each depending on the last dose and the time point of the last administration of an FXa inhibitor. Patients underwent 30-day follow-up observation. Primary outcomes of the study were the percentage change of the anti-FXa activity and the achievement of effective haemostasis 12 hours following treatment with andexanet alfa. Secondary outcomes of the study were effects of intracranial bleeding on the neurological status of patients, the need for blood transfusions, the recurrence of bleeding and outcomes related to mortality and adverse events (AEs).

The underlying diseases in the majority of the patients of the ANNEXA-4 study were atrial fibrillation and hypertension (81.3% or 78.7%). Andexanet alfa is only approved for patients who experienced life-threatening or uncontrollable bleeding events under treatment with apixaban or rivaroxaban. The proportion of study participants who received edoxaban or enoxaparin was less than 10%; the company thus presented results on the basis of the total study population. The bleeding events requiring termination of the anticoagulation therapy were (severe) intracranial and gastrointestinal bleeding in 64.5% and 25.6% of the patients included in the study, respectively. The patients included in the ANNEXA-4 study corresponded to the therapeutic indication of andexanet alfa.

Information on the ACT

The study pool on the ACT included by the company comprised 18 prospective and retrospective observational studies. In all studies, patients who had bleeding events under anticoagulants were investigated. The smallest study included 13 patients, the larger (registry) study comprised 1776 patients who underwent follow-up observation for few days to several months. In all studies, prothrombin concentrates could be administered for haemostasis; further measures included e.g. the administration of transfusions of various blood products (thrombocytes, erythrocytes, plasma), coagulation factor VII preparations, tranexamic acid, fibrinogen concentrates or vitamin K. Results on the mortality are available for all studies. Moreover, some of the studies report results for the outcomes "achieving effective haemostasis", "need for blood transfusions" and "recurrence of bleeding" and "individual AEs".

In the studies that provide information on the therapeutic indication for anticoagulation therapy, the majority of the study participants (64% to 97%) had atrial fibrillation as underlying disease. The frequency distribution of the anticoagulants used (rivaroxaban, apixaban or other oral anticoagulants) and the type of bleeding that occurred (e.g. bleeding in general, severe or life-threatening bleeding or intracranial vs. gastrointestinal or extracranial bleeding in general) varies considerably between the investigated patient populations.

Approach of the company

The company conducted a descriptive comparison of the results of the ANNEXA-4 study with those of the studies on the ACT. The company presented no effect estimations for the comparison of the intervention with the comparator therapy and did not use the identified studies on the ACT for the derivation of an added benefit due to methodological differences. Specifically, it justified this, for example, with methodological differences in the recording for the outcomes "achievement of effective haemostasis" and "recurrence of bleeding", or with heterogeneous results for the outcome "30-day mortality" potentially caused by the different patient populations with regard to site and severity of bleeding or previous diseases. The company only provided a complete presentation of side effects for its study ANNEXA-4; in the comparative studies, it limits itself to the outcome "thrombotic events within 30 days". The company derived an indication of a non-quantifiable added benefit exclusively on the basis of the single-arm intervention study ANNEXA-4. It justified this with the results on mortality, the percentage change in the anti-FXa activity, the achievement of effective haemostasis, the effects of intracranial bleeding on the neurological status of patients, the need for blood transfusions, and the safety profile of andexanet alfa.

A comparison with the ACT is impossible

The approach of the company not to use the studies of the comparator therapy for the derivation of the added benefit is adequate. This is justified below:

An estimation of effects, as presented by the company, is not meaningful in the present situation. An important reason speaking against a comparison of the results of the individual

studies is that the operationalization of the outcomes differs considerably between the studies. An illustrative example of this is the outcome “recurrence of bleeding”. In the ANNEXA-4 interventional study, only patients who initially showed good or very good haemostasis and who experienced recurrence of bleeding at the same anatomical site within 24 hours were considered for this outcome. The studies on the comparator therapy, in contrast, reported the total population of patients with recurrence of bleeding, regardless of the initial haemostasis or restriction to the same anatomical site; hereby, the recording period was at least 48 hours. This renders a comparison of the occurred events meaningless in terms of content.

However, even for outcomes whose operationalization does not clearly differ - such as mortality - a calculation of effect estimates, as described by the company, would not be meaningful in terms of content due to the different methodology of the studies. In accordance with the company’s assessment, this is explained, among other things, by the fact that mortality, for example, is strongly dependent on the site and severity of the occurred bleedings as well as on the previous diseases of the patient populations included. Observed differences can thus be caused solely by different inclusion criteria or patient collectives.

Irrespective of this, a comparison of individual arms from different studies on the basis of the available data revealed no differences for any outcome that are large enough that they cannot be explained by systematic bias alone.

Moreover, it is not adequate that the company limits the presentation of the side effects in the studies on the ACT to the outcome “thrombotic events within 30 days”. A comparison of side effects between intervention and ACT for only one outcome is incomplete and a weighing of benefit and harm of the intervention versus the comparator therapy is thus impossible.

Added benefit currently not proven

The approach of the company to derive an indication of added benefit exclusively on the basis of the single-arm ANNEXA-4 study is not adequate, since usable data for a comparison with the ACT are lacking.

As described above, the currently available data are unsuitable to prove an added benefit of andexanet alfa versus the ACT - an optimized standard therapy. An international RCT of the company (18-513) launched this year compares treatment with andexanet alfa with the current standard of care in patients treated with a direct FXa inhibitor who experience intracranial bleeding. This study was a requirement of the European regulatory authority for the conditional approval of andexanet alfa; it will presumably be completed in 2023.

2.4 Results on added benefit

In its dossier, the company presented no suitable data for the assessment of andexanet alfa in comparison with the ACT. This resulted in no hint of an added benefit of andexanet alfa versus the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The company presented no suitable data for the assessment of the added benefit of andexanet alfa. An added benefit of andexanet alfa in comparison with the ACT is therefore not proven.

Table 5 summarizes the results of the assessment of the added benefit of andexanet alfa in comparison with the ACT.

Table 5: 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 events	Optimized standard therapy[b] of the life-threatening or uncontrollable bleeding events	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: The standard therapy can, for instance, comprise blood products, fluid substitution, plasma expanders or prothrombin concentrates. FXa: Factor Xa; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived an indication of non-quantifiable added benefit.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company did not present any relevant data for the benefit assessment.

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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