Andexanet alfa
(acute major bleeding)

Benefit assessment according to §35a SGB V[1]
(expiry of the decision)

EXTRACT

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IQWiG thanks the medical and scientific advisor for her 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 one person.

IQWiG thanks the respondent and the patient organization 'Bundesverband Gemeinnützige Schlafapnoe Deutschland e. V.' for participating in the written exchange and for their support. The respondent and the 'Bundesverband Gemeinnützige Schlafapnoe Deutschland e. V.' were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse event of special interest
EMA	European Medicines Agency
FDA	Food and Drug Administration
FXa	factor Xa
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GCS	Glasgow Coma Scale
ICU	intensive care unit
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mRS	the modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
SOC	System Organ Class
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 1 July 2025.

The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. That dossier was sent to IQWiG on 30 August 2019. In that procedure, the G-BA issued a resolution on 20 February 2020 to limit the period of validity of the resolution to 1 November 2023. By resolution dated 21 September 2023 and most recently by resolution dated 4 July 2024, the period of validity of the resolution dated 20 February 2020, which was originally due to expire on 1 November 2023, was extended until 1 July 2025.

According to the justification for the resolution of 20 February 2020, the reason for the time limit was that no directly comparative data from a randomized controlled trial (RCT) of andexanet alfa versus the appropriate comparator therapy (ACT) were available at the time of the benefit assessment. As part of the conditional marketing authorization of andexanet alfa, the company was required by the European Medicines Agency (EMA) to submit directly comparative data on andexanet alfa versus standard of care treatment. In accordance with this EMA requirement, the ANNEXA-I study was conducted and completed in August 2023. For the reassessment after the deadline, the results of the study of direct comparison of andexanet alfa versus standard treatment required by the EMA were to be presented in the dossier. The period of validity of the resolution of 20 February 2020, which was originally limited until 1 November 2023, was extended until 1 July 2025 at the company's request to await the completion of the assessment procedure at the EMA, which may result in larger and substantial changes to the summary of product characteristics (SmPC). In the June 2025 version, information on the ANNEXA-I study was added to the SmPC.

Research question

The aim of this report is 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 reversal of anticoagulation is needed due to life-threatening or uncontrollable bleeding.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

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

Therapeutic indication	**ACT**[a]
Adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrollable bleeding[b]	Individualized treatment[c, d] with a choice of: ▪ prothrombin complex concentrates ▪ BSC[e, f]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that patients in both arms received optimal intensive care.
c. The term 'individualized treatment' is used instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
d. Both a single-comparator study with prothrombin complex concentrates and a multi-comparator study with a choice of the above-mentioned treatment options may be suitable for the implementation of the ACT. However, the choices should always include prothrombin complex concentrates. If the implementation takes the form of a multi-comparator study, the individualized treatment decision regarding the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).
e. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
f. According to the G-BA, it is assumed that fluid replacement and the administration of plasma expanders or blood products, if indicated, are carried out as part of BSC in the event of severe or life-threatening bleeding. The location of the life-threatening or uncontrollable bleeding (e.g. cerebral haemorrhage, gastrointestinal haemorrhages) is also a criterion for the appropriate therapy in each case.

ACT: appropriate comparator therapy; BSC: best supportive care; EU: European Union; FXa: Factor Xa; G-BA: Federal Joint Committee; HTA: health technology assessment

The G-BA last modified the ACT on 11 June 2025, shortly before the dossier was submitted by the company, to that shown in Table 2. In its dossier, the company referred to the ACT specified in the consultation meeting with the G-BA on 24 February 2023, treatment of physician's choice. The company stated that treatment of physician's choice can include prothrombin complex concentrates in particular, but also fluid replacement, blood products or plasma expanders. It added that patients should also receive optimal intensive care treatment. The resulting definition of the comparator therapy by the company concurred with the current ACT defined by the G-BA on 11 June 2025. This benefit assessment was conducted in comparison with the current ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit.

Study pool and study design

The RCT ANNEXA-I was used for this benefit assessment. The ANNEXA-I study is a completed, multicentre, open-label RCT comparing andexanet alfa versus standard treatment. The study included adult patients with acute intracerebral haemorrhage receiving an oral factor Xa (FXa) inhibitor. To be eligible for enrolment, the bleeding had to be confirmed by a computed

tomography of the head or magnetic resonance imaging within 2 hours prior to randomization and have an estimated blood volume between 0.5 mL and 60 mL. The last dose of an oral FXa inhibitor (apixaban, rivaroxaban or edoxaban) must have been given within 15 hours prior to randomization. A longer time interval between the last FXa inhibitor dose and randomization was only allowed if the local anti-FXa activity was> 100 ng/mL and the measurement was < 2 hours prior to consent. Patients with a National Institutes of Health Stroke Scale (NIHSS) score > 35 or a Glasgow Coma Scale (GCS) score < 7 were excluded from participation in the study.

A total of 530 patients were included in the study and randomly assigned in a 1:1 ratio to treatment with andexanet alfa (N = 263) or standard treatment (N = 267). For the benefit assessment, the company presented analyses of the subpopulation of those patients who were included in the study under therapy with apixaban or rivaroxaban (N = 241 in the intervention arm and N = 233 in the comparator arm).

Treatment with andexanet alfa was largely carried out according to the SmPC with an initial intravenous bolus, followed by a continuous intravenous infusion. For andexanet alfa treatment, patients received either a high dose or a low dose, based on the amount of the most recent FXa inhibitor dose and the time between the most recent use of the FXa inhibitor and the start of the study medication. Deviating from the SmPC, a high dose of andexanet alfa was also planned in the study for patients whose last dose of the FXa inhibitor was > 15 hours before randomization or for whom the time of the last dose was unknown. Overall, 21.2% of patients in the relevant subpopulation received a high dose of andexanet alfa. It was not clear from the study documents how many of these patients received the last dose of the FXa inhibitor > 15 hours before randomization or for how many the time of the last dose was unknown. The resulting uncertainty did not call into question the suitability of the ANNEXA-I study, but was taken into account in the assessment of the certainty of conclusions.

The primary outcome of the study was effective haemostasis 12 hours post-randomization as determined by the blinded adjudication committee. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, and side effects.

Implementation of the ACT

The G-BA specified individualized treatment with a choice of prothrombin complex concentrates and best supportive care (BSC) as the ACT. In ANNEXA-I, standard therapy was used in the comparator arm, which allowed any treatment other than andexanet alfa, including no treatment, administered within 3 hours post-randomization. Overall, it was assumed that the standard treatment used in ANNEXA-I represented a sufficient implementation of individualized treatment with a choice of prothrombin complex concentrates and BSC.

Risk of bias and certainty of conclusions

The risk of bias across outcomes was assessed as low for the ANNEXA-I study.

The risk of bias of the results for the outcomes overall survival, invasive intracranial procedures and the specific adverse events (AEs) thrombotic events (serious AEs [SAEs]), ischaemic stroke (Preferred Term [PT], SAEs) and cardiac disorders (System Organ Class [SOC], SAEs) was assessed as low. The risk of bias of the results for the outcome functional impairment (the modified Rankin Scale [mRS]) was assessed as high due to the lack of blinding in subjective recording of outcomes. For the outcome SAEs, the risk of bias of the results was assessed as high due to the uncertainty regarding the selection of potentially disease-related events. The risk of bias of the results for the outcome of discontinuation due to AEs was increased because of lack of blinding in subjective decisions regarding treatment discontinuation.

The vast majority of patients in the ANNEXA-I study were followed up for 30 days. The extent to which the effects observed in the ANNEXA-I study were transferable to patients with a bleeding event that occurred > 30 days previously remained unclear. In addition, for an unclear proportion of patients in the intervention arm, the dosage of andexanet alfa deviated from the specifications in the SmPC. The certainty of conclusions of the study results for the given research question was therefore reduced overall. Based on the available information from the ANNEXA-I study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented.

Results

Mortality

Overall survival

No statistically significant difference between treatment groups was found for the outcome overall survival. There is no hint of an added benefit of andexanet alfa in comparison with standard treatment; an added benefit is therefore not proven.

Morbidity

Invasive intracranial procedures and functional impairment (mRS)

No statistically significant difference between treatment groups was found for the outcomes invasive intracranial procedures and functional impairment recorded using the mRS. In each case, there is no hint of an added benefit of andexanet alfa in comparison with standard treatment; an added benefit is therefore not proven.

Neurological symptoms (NIHSS) and health status (EQ-5D VAS)

No suitable data were available for the outcomes of neurological symptoms recorded using the NIHSS and health status recorded using the EQ-5D visual analogue scale (VAS). In each

case, there is no hint of an added benefit of andexanet alfa in comparison with standard treatment; an added benefit is therefore not proven.

Health-related quality of life

Relevant outcomes on health-related quality of life were not recorded in the included study.

Side effects

SAEs, thrombotic events (SAEs), ischaemic stroke (SAEs) and cardiac disorders (SAEs)

For each of the outcomes SAEs, thrombotic events (SAEs), ischaemic stroke (SAEs) and cardiac disorders (SAEs), there was a statistically significant difference between the treatment groups to the disadvantage of andexanet alfa. There is a hint of greater harm of andexanet alfa in comparison with standard treatment in each case.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm of andexanet alfa in comparison with standard treatment; greater or lesser harm is therefore not proven.

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:

The ANNEXA-I study predominantly included patients with intracerebral haemorrhage (91.4% in relation to the relevant subpopulation of patients treated with apixaban or rivaroxaban). Only a few patients had a different intracranial haemorrhage. Patients with life-threatening or uncontrollable extracranial haemorrhage were not included in the ANNEXA-I study. Based on the available data, conclusions can therefore only be drawn on the added benefit of andexanet alfa versus the ACT in patients with intracerebral haemorrhage. For all other patients in the therapeutic indication, an added benefit is not proven. In addition, on the basis of the available data, conclusions could only be drawn about the shortened observation period of 30 days considered in the ANNEXA-I study.

[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].

Overall, only negative effects of andexanet alfa versus the ACT were shown for adult patients with intracerebral haemorrhage treated with an FXa inhibitor (apixaban or rivaroxaban). For the overall rate of SAEs and the outcome of thrombotic events, there is a hint of greater harm of minor extent in each case. In addition, for 2 specific AEs in the category of serious/severe side effects, there is a hint of greater harm of major extent.

In summary, there is a hint of a lesser benefit of andexanet alfa versus the ACT in adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to intracerebral haemorrhage.

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

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrollable bleeding[b]	Individualized treatment[c, d] with a choice of: ▪ prothrombin complex concentrates ▪ BSC[e, f]	▪ Patients with intracerebral haemorrhage: hint of a lesser benefit[g] ▪ All other patients in the therapeutic indication: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that patients in both arms received optimal intensive care.
c. The term 'individualized treatment' is used instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
d. Both a single-comparator study with prothrombin complex concentrates and a multi-comparator study with a choice of the above-mentioned treatment options may be suitable for the implementation of the ACT. However, the choices should always include prothrombin complex concentrates. If the implementation takes the form of a multi-comparator study, the individualized treatment decision regarding the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).
e. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
f. According to the G-BA, it is assumed that fluid replacement and the administration of plasma expanders or blood products, if indicated, are carried out as part of BSC in the event of severe or life-threatening bleeding. The location of the life-threatening or uncontrollable bleeding (e.g. cerebral haemorrhage, gastrointestinal haemorrhages) is also a criterion for the appropriate therapy in each case.
g. The subpopulation of the ANNEXA-I study relevant for this benefit assessment also includes a small proportion (9%) of patients with other intracranial haemorrhages.

ACT: appropriate comparator therapy; BSC: best supportive care; EU: European Union; FXa: Factor Xa; G-BA: Federal Joint Committee; HTA: health technology assessment

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is 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 reversal of anticoagulation is needed due to life-threatening or uncontrollable bleeding.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

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

Therapeutic indication	**ACT**[a]
Adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrollable bleeding[b]	Individualized treatment[c, d] with a choice of: ▪ prothrombin complex concentrates ▪ BSC[e, f]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that patients in both arms received optimal intensive care.
c. The term 'individualized treatment' is used instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
d. Both a single-comparator study with prothrombin complex concentrates and a multi-comparator study with a choice of the above-mentioned treatment options may be suitable for the implementation of the ACT. However, the choices should always include prothrombin complex concentrates. If the implementation takes the form of a multi-comparator study, the individualized treatment decision regarding the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).
e. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
f. According to the G-BA, it is assumed that fluid replacement and the administration of plasma expanders or blood products, if indicated, are carried out as part of BSC in the event of severe or life-threatening bleeding. The location of the life-threatening or uncontrollable bleeding (e.g. cerebral haemorrhage, gastrointestinal haemorrhages) is also a criterion for the appropriate therapy in each case.

ACT: appropriate comparator therapy; BSC: best supportive care; EU: European Union; FXa: Factor Xa; G-BA: Federal Joint Committee; HTA: health technology assessment

The G-BA last modified the ACT on 11 June 2025, shortly before the dossier was submitted by the company, to that shown in Table 4. In its dossier, the company referred to the ACT specified in the consultation meeting with the G-BA on 24 February 2023, treatment of physician's choice [3]. The company stated that treatment of physician's choice can include prothrombin complex concentrates in particular, but also fluid replacement, blood products or plasma expanders. It added that patients should also receive optimal intensive care treatment. The resulting definition of the comparator therapy by the company concurred with the current ACT defined by the G-BA on 11 June 2025. This benefit assessment was conducted in comparison with the current ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit. This concurred with the company’s inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on andexanet alfa (status: 14 April 2025)
- Bibliographical literature search on andexanet alfa (last search on 14 April 2025)
- Search of trial registries/trial results databases for studies on andexanet alfa (last search on 14 April 2025)
- Search on the G-BA website for andexanet alfa (last search on 14 April 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on andexanet alfa (last search on 17 July 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies. In Section 4.4 of Module 4 A, the company also presented the results of the pivotal single-arm study ANNEXA-4, but did not take them into account for its derivation of the added benefit. A description of the ANNEXA-4 study can be found in dossier assessment A19-76 [4].

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: andexanet alfa vs. individualized treatment

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
ANNEXA-I	No	Yes	No	Yes [5,6]	Yes [7,8]	Yes [9]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for this benefit assessment consists of the RCT ANNEXA-I and corresponds to the study pool of the company.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: andexanet alfa vs. standard treatment (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ANNEXA-I	RCT, open-label, parallel	adult patients with acute intracerebral[b] haemorrhage[c] (confirmed by CT or MRI ≤ 2 hours before randomization) and ▪ ≤ 15 hours before randomization[d] treated with an oral FXa inhibitor[e] ▪ Onset of symptoms ≤ 6 hours[f] prior to the baseline imaging scan ▪ NIHSS score ≤ 35 and GCS score ≥ 7	andexanet alfa (N = 263) Standard treatment[g] (N = 267) Relevant subpopulation thereof[h]: andexanet alfa (N = 241) Standard treatment[g] (N = 233)	Screening: < 1 day Treatment: < 1 day Observation: ▪ 30 days ▪ Patients with antibody formation against andexanet alfa up to 120 days after randomization	131 centres in Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, United Kingdom, United States 6/2019–8/2023 (study stopped early) Data cuts ▪ 1st data cut[i]: ND ▪ 2nd data cut: 18 Sep 2023[j]	Primary: effective haemostasis (all of the following criteria must be met): ▪ 12 hours after randomization ▫ No haematoma expansion > 35% ▫ No increase in the NIHSS score of ≥ 7 points ▪ No rescue therapy 3–12 hours after randomization Secondary: mortality, morbidity, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: andexanet alfa vs. standard treatment (multipage table)

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

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. As of Amendment 1 of 15 April 2020; previously, patients with acute intracranial haemorrhage, defined as a blood volume of any extent acutely observed radiographically within the skull, were included, according to the original study protocol of 2 July 2018.
c. Defined as an estimated blood volume ≥ 0.5 mL to ≤ 60 mL acutely observed radiographically within the cerebrum (under Amendment 1 of 15 April 2020, patients with an estimated blood volume > 0 mL to ≤ 60 mL were included); patients could have extracerebral or extracranial bleeding additionally, but the intracerebral haemorrhage had to be the most clinically significant bleed at the time of enrolment.
d. The last dose of an oral FXa inhibitor could also be > 15 hours prior to randomization (or at an unknown time) if the following criteria were met: 1) local anti-FXa activity > 100 ng/mL, and 2) the local anti-FXa activity level was obtained within 2 hours prior to consent (before Amendment 1, patients with unknown timepoint of the last dose of the FXa inhibitor were not enrolled).
e. Apixaban, rivaroxaban or edoxaban.
f. As of Amendment 1 of 15 April 2020; according to the original study protocol of 2 July 2018: onset of symptoms < 12 prior to the baseline imaging scan.
g. Any treatment other than andexanet alfa, including no treatment, administered within 3 hours post-randomization that the investigators and/or treating physicians considered to be appropriate.
h. Patients who were included under therapy with edoxaban (N = 53) or enoxaparin (N = 3) are excluded from the analysis and are no longer shown in the following tables.
i. Prespecified interim analysis, planned after 50% of the patients had been adjudicated with regard to the primary outcome; at this time, 224 patients were included in the intervention arm and 228 in the comparator arm. Based on the results of this analysis (superiority of andexanet alfa in the primary outcome), it was decided on 31 May 2023 to stop the study.
j. Final analysis on efficacy (sensitivity analyses) and safety; includes all patients enrolled, including those who were enrolled during and after the interim analysis until the end of the study.

AE: adverse event; CT: computed tomography; FXa: Factor Xa; GCS: Glasgow Coma Scale; MRI: magnetic resonance imaging; n: relevant subpopulation; N: number of randomized patients; ND: no data; NIHSS: National Institutes of Health Stroke Scale; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: andexanet alfa vs. standard treatment (multipage table)

Study	Intervention	Comparison
ANNEXA-I	andexanet alfa[a] ▪ Low-dose regimen: ▫ Bolus: 400 mg IV (30 mg/min as an infusion of approx. 15 min) ▫ Then 480 mg IV as a continuous infusion (4 mg/min as a 120-minute infusion) ▪ High-dose regimen: ▫ Bolus: 800 mg IV (30 mg/min as an infusion of approx. 30 min) ▫ Then 960 mg IV as a continuous infusion (8 mg/min as a 120-minute infusion)	Standard treatment[b]
	Criteria for the choice of the dose regimen[c]: ▪ <u>Low-dose regimen for</u> ▫ rivaroxaban 10 mg or apixaban ≤ 5 mg, each ≤ 15 hours before initiation of andexanet alfa ▫ rivaroxaban > 10 mg or apixaban > 5 mg, each ≥ 8 hours and ≤ 15 hours before initiation of andexanet alfa ▪ <u>High-dose regimen for</u> ▫ rivaroxaban > 10 mg or apixaban > 5 mg, each < 8 hours before initiation of andexanet alfa ▫ rivaroxaban and apixaban at all doses, each > 15 hours or at an unknown time[d] before initiation of andexanet alfa	
	Allowed prior treatment ▪ Red blood cell and platelet concentrates **Disallowed prior treatment** ▪ andexanet alfa ▪ ≤ 7 days prior to enrolment ▫ Vitamin K antagonists ▫ dabigatran ▫ Prothrombin complex concentrate products, recombinant factor VIIa, anti-inhibitor coagulant complex, fresh frozen plasma, or whole blood ▪ Other investigational products within 30 days prior to enrolment **Allowed concomitant treatment** ▪ Red blood cell and platelet concentrates ▪ Anticoagulants and platelet aggregation inhibitors[e] ▪ Procoagulant blood products and whole blood[f, g, h] ▪ Antifibrinolytics and other haemostatic agents[f, g, h] ▪ Diagnostic and therapeutic procedures for bleeding[g, h] ▪ Planned minimally invasive surgical procedures not directly related to treatment of the bleeding[i] **Disallowed concomitant treatment** ▪ Planned surgical procedures (including Burr holes for haematoma drainage) ≤ 12 hours after randomization	

Table 7: Characteristics of the intervention – RCT, direct comparison: andexanet alfa vs. standard treatment (multipage table)

Study	Intervention	Comparison
a. Treatment should be initiated no later than 30 minutes after randomization and preferably within 2 hours of the baseline brain imaging scan. b. Any treatment other than andexanet alfa, including no treatment, administered within 3 hours post-randomization that the investigators and/or treating physicians considered to be appropriate. c. The dosing regimen was based on the last dose and the timing of the last dose of the previously used FXa inhibitor. d. The last dose of an oral FXa inhibitor could also be > 15 hours prior to randomization (or at an unknown time) if the following criteria were met: 1) local anti-FXa activity > 100 ng/mL, and 2) the local anti-FXa activity level was obtained within 2 hours prior to consent. e. Anticoagulation could be restarted at the investigator's discretion. f. In the intervention arm, administration of procoagulant blood products, whole blood and haemostatic agents could be considered if a patient had haematoma expansion (a > 35% increase in haematoma volume). Treatment for other reasons was strongly discouraged, though not prohibited, during the 30-day observation period. g. Administration of procoagulant blood products, whole blood, systemic haemostatic agents (with the exception of tranexamic acid) and unplanned rescue surgery or an interventional procedure (to treat the primary bleeding in case of clinical deterioration) between 3 and 12 hours after randomization led to an assessment of effective haemostasis as 'poor' or 'none'. h. A review by the EAC was conducted if there was misadministration of procoagulant blood products (including andexanet alfa in the comparator arm), administration of haemostatic agents or surgery or interventional procedures to treat the primary bleeding within 3 hours after randomization. Unplanned rescue procedures or surgery which could impact haematoma volume were also reviewed by the EAC. i. Since Amendment 1 of the study protocol of 15 April 2020, only procedures that were not expected to significantly affect haematoma volume		

EAC: Endpoint Adjudication Committee; FXa: Factor Xa; IV: intravenous; min: minute; RCT: randomized controlled trial

The ANNEXA-I study is a completed, multicentre, open-label RCT comparing andexanet alfa versus standard treatment. Standard treatment was any treatment (other than andexanet alfa, but including no treatment) administered within 3 hours post-randomization that the investigators and/or treating physicians considered to be appropriate. The study included adult patients with acute intracerebral haemorrhage receiving an oral factor Xa (FXa) inhibitor. Until Amendment 1 of the study protocol, patients with another acute intracranial bleeding episode were also included. To be eligible for enrolment, the bleeding had to be confirmed by a computed tomography of the head or magnetic resonance imaging within 2 hours prior to randomization and have an estimated blood volume between 0.5 mL and 60 mL. The last dose of an oral FXa inhibitor (apixaban, rivaroxaban or edoxaban) must have been given within 15 hours prior to randomization. A longer time interval between the last FXa inhibitor dose and randomization was only allowed if the local anti-FXa activity was> 100 ng/mL and the measurement was < 2 hours prior to consent. Patients with a National Institutes of Health Stroke Scale (NIHSS) score > 35 or a Glasgow Coma Scale (GCS) score < 7 were excluded from participation in the study.

A total of 530 patients were included in the study and randomly assigned in a 1:1 ratio to treatment with andexanet alfa (N = 263) or standard treatment (N = 267). Randomization was stratified by the investigator's intended-standard treatment (prothrombin complex concentrate versus other) as well as time from symptom onset to baseline imaging scan (< 180 minutes versus ≥ 180 minutes). For the benefit assessment, the company presented analyses of the subpopulation of those patients who were included in the study under therapy with apixaban or rivaroxaban (N = 241 in the intervention arm and N = 233 in the comparator arm). The study also included 53 patients under therapy with edoxaban and 3 patients under therapy with enoxaparin. As these patients are not covered by the approved therapeutic indication, the exclusion of these patients for this benefit assessment was appropriate.

Treatment with andexanet alfa was largely carried out according to the summary of product characteristics (SmPC) [10] with an initial intravenous bolus, followed by a continuous intravenous infusion. For andexanet alfa treatment, patients received either a high dose (800 mg IV as a 30-minute bolus infusion, followed by 960 mg IV as a 120-minute continuous infusion) or a low dose (400 mg IV as a 15-minute bolus infusion, followed by 480 mg IV as a 120-minute continuous infusion), based on the amount of the most recent FXa inhibitor dose and the time between the most recent use of the FXa inhibitor and the start of the study medication. According to the SmPC, the high-dose regimen is used if the last dose of the FXa inhibitor was given < 8 hours ago, and the last dose of apixaban was > 5 mg or the last dose of rivaroxaban was > 10 mg [10]. Deviating from this, a high dose of andexanet alfa was also planned in the study for patients whose last dose of the FXa inhibitor was > 15 hours before randomization or for whom the time of the last dose was unknown. Overall, 21.2% of patients in the relevant subpopulation received a high dose of andexanet alfa. It was not clear from the study documents how many of these patients received the last dose of the FXa inhibitor > 15 hours before randomization or for how many the time of the last dose was unknown. The resulting uncertainty did not call into question the suitability of the ANNEXA-I study, but was taken into account in the assessment of the certainty of conclusions (see Section I 4.2).

The primary outcome of the study was effective haemostasis 12 hours post-randomization as determined by the blinded adjudication committee. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, and side effects.

Implementation of the ACT

The G-BA specified individualized treatment with a choice of prothrombin complex concentrates and best supportive care (BSC) as the ACT. The G-BA further specified the implementation of individualized treatment in its additional notes. The G-BA assumed that fluid replacement and the administration of plasma expanders or blood products, if indicated, are carried out as part of BSC in the event of severe or life-threatening bleeding. The location

of the life-threatening or uncontrollable bleeding is also a criterion for the appropriate therapy in each case.

In ANNEXA-I, standard treatment was used in the comparator arm, which allowed any treatment other than andexanet alfa, including no treatment, administered within 3 hours post-randomization. In the comparator arm of the ANNEXA-I study, 87.6% of patients received prothrombin complex concentrates, 10.3% of patients did not receive any haemostatic therapy and 2 patients received another haemostatic therapy not defined in detail in the study documents. It is unclear why 10.3% of patients in the comparator arm did not receive haemostatic therapy or whether prothrombin complex concentrates would have been a relevant option for these patients. It is also not clear from the study documents to what extent these patients received treatment in terms of BSC. However, treatment with platelet or red blood cell concentrates was permitted at any time during the study. Overall, it was assumed that the standard treatment used in ANNEXA-I represented a sufficient implementation of individualized treatment with a choice of prothrombin complex concentrates and BSC.

Data cuts

Two data cuts were available for the ANNEXA-1 study:

- Prespecified interim analysis planned after 50% of patients were adjudicated with regard to the primary outcome
- Final analysis on efficacy and safety from 18 September 2023

The ANNEXA-I study was stopped prematurely due to the results of the interim analysis. The exact time of the first data cut-off for the interim analysis was unclear. In its dossier, the company stated this date as 31 May 2023. However, this is the date on which the Data Safety Monitoring Board recommended the termination of the study.

In its dossier, the company presented results for the relevant subpopulation at the final 18 September 2023 data cut-off. This data cut included all patients enrolled, including those who were enrolled during and after the interim analysis until the end of the study. The results of the final data cut-off of 18 September 2023 were used for this benefit assessment.

Uncertainties of the ANNEXA I study – shortened observation period

Most patients included in ANNEXA-I were patients with intracerebral haemorrhage. A small proportion of patients in the study (approx. 9%) had another intracranial haemorrhage. The variability of neurological and functional impairment as a result of bleeding episodes requires long-term observation of the patients. Accordingly, clinical studies in patients with intracerebral haemorrhage generally require an observation period of at least 3 months [11-13]. The European Medicines Agency (EMA) also recommends a minimum study duration of 3 months for studies involving patients with acute stroke [14].

Patients included in ANNEXA-I were observed for a total of 30 days. Only patients with anti-andexanet alfa antibodies on Day 30 had additional follow-up up to 120 days post-randomization. However, this only affected 1 patient in the intervention arm and 3 patients in the comparator arm. An observation period of 30 days appeared to be too short in this therapeutic indication to fully capture a deterioration or improvement in patient morbidity following the bleeding episode. It was also assumed that the risk of death in the patients included in the study was increased beyond the period considered in the study. It was therefore unclear whether the effects observed in the ANNEXA-I study persisted to the same extent beyond the 30-day period. The resulting uncertainty did not completely call into question the suitability of the ANNEXA-I study, but was taken into account in the assessment of the certainty of conclusions (see Section I 4.2).

Characteristics of the study population

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: andexanet alfa vs. standard treatment

Study **Characteristic** **Category**	**andexanet alfa** **N[a] = 241**	**Standard treatment** **N[a] = 233**
ANNEXA-I		
Age [years], mean (SD)	79 (8)	79 (9)
Sex [F/M], %	46/54	49/51
Geographical region, n (%)		
Europe	212 (88)	206 (88)
North America	29 (12)	27 (12)
Systolic blood pressure (mmHg), mean (SD)	160.8 (26.4)[b]	158.1 (27.5)[b]
Primary bleeding location, n (%)		
Intracerebral	215 (89)	218 (94)
Intraventricular	2 (< 1)	1 (< 1)
Subarachnoid	10 (4)	8 (3)
Subdural	13 (5)	5 (2)
Missing	1 (< 1)	1 (< 1)
Haematoma volume at baseline [mL], mean (SD)	18.8 (22.7)	17.3 (21.8)
ICH score at baseline, mean (SD)	1.4 (1.1)	1.3 (1.1)
Previous FXa inhibitor, n (%)		
apixaban	162 (67)	158 (68)
rivaroxaban	79 (33)	75 (32)
Time from symptom onset to treatment [hours], mean (SD)	4.4 (2.0)	4.6 (2.1)
Time from last FXa inhibitor dose to randomization [hours], mean (SD)	10.0 (4.7)	10.1 (4.5)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)[c]	77 (32)	64 (28)

a. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Discrepant data between Module 4 A and the CSR; the data from the CSR are shown.
c. Frequent reasons for study discontinuation in the intervention arm vs. the control arm (percentages refer to randomized patients): AEs (24% vs. 21%), disease progression (3% vs. 4%), withdrawal of consent (2% vs. 1%).

AE: adverse event; F: female; ICH: intracerebral haemorrhage; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the patients were largely balanced between both treatment arms of the ANNEXA I study. The mean age of the patients was 79 years. In both treatment arms, a small majority of the study population were men (54% and 51% respectively). The vast majority of patients had an intracerebral haemorrhage at the time of inclusion in the study. Patients in

the intervention arm had a mean haematoma volume of 18.8 mL versus a mean haematoma volume of 17.3 mL in the comparator arm. Around two-thirds of the patients in both treatment arms had previously received treatment with apixaban. The number of study discontinuations was comparable between the arms (32% vs. 28%).

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: andexanet alfa vs. standard treatment

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
ANNEXA-I	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was assessed as low for the ANNEXA-I study. Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company stated that ANNEXA-I fulfilled essential requirements for the transferability of the study results to the German health care context. It explained that ANNEXA-I primarily included patients from European study centres and more than a third from study centres in Germany. In the company's view, the age and weight distribution of the study population, the distribution of apixaban- and rivaroxaban-treated patients and the standard treatment in the comparator arm were also consistent with the German health care context. It added that the comparator arm in the ANNEXA-I study fulfilled the criteria of the ACT and thus allowed an appropriate comparison with treatment of physician's choice.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Invasive intracranial procedures
  - Neurological symptoms, recorded with the National Institutes of Health Stroke Scale (NIHSS)
  - Functional impairment, recorded with the modified Rankin Scale (mRS)
  - Health status, recorded with the visual analogue scale (VAS) of the EQ-5D
- Health-related quality of life
- Side effects
  - Serious adverse events (SAEs)
  - Discontinuation due to AEs
  - Thrombotic events (AEs)
  - Other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4).

Table 10 shows for which outcomes data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: andexanet alfa vs. standard treatment

Study	Outcomes										
	Overall survival	Invasive intracranial procedures[a]	Neurological symptoms (NIHSS)	Functional impairment (mRS)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs[b]	Discontinuation due to AEs	Thrombotic events[c] (SAEs)	Ischaemic stroke (PT, SAEs)	Cardiac disorders (SOC, SAEs)
ANNEXA-I	Yes	Yes	No[d]	Yes	No[d]	No[e]	Yes	Yes	Yes	Yes	Yes

a. Defined as any surgery or interventional procedure performed to manage the haematoma or its complications, including Burr holes, craniotomies and placement of intraventricular catheters.
b. Unclear proportion of potentially disease-related events; see text below for an explanation.
c. The AE of special interest recorded by the company in the study is considered (including arterial systemic embolism, deep vein thrombosis, myocardial infarction, pulmonary embolism, stroke and transient ischaemic attack); see text below for an explanation.
d. No suitable data available; see text below for explanation.
e. Relevant outcomes in this category were not recorded.

AE: adverse event; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Primary outcome 'effective haemostasis'

The outcome 'effective haemostasis' presented by the company was made up of the following 3 components:

- No haematoma expansion > 35% 12 hours after randomization
- No rescue therapy between 3 and 12 hours after randomization
- No neurological deterioration 12 hours after randomization

All 3 components had to be fulfilled for the outcome to be reached. Effective haemostasis was assessed in the study by a blinded adjudication committee. The company presented results for the outcome 'effective haemostasis' as well as the results for the individual components. The results on the outcome 'effective haemostasis' and on the individual components were not suitable for this benefit assessment. This is justified below.

No haematoma expansion > 35% 12 hours after randomization

The patient relevance of the component 'no haematoma expansion > 35% 12 hours after randomization', which was determined by means of imaging (computed tomography or magnetic resonance imaging), was unclear. It was not clear from the available information to what extent an increase in haematoma volume represented tangible symptoms for the patient. Various studies have shown no association between an effect on haematoma expansion and long-term patient impairment in patients with intracerebral haemorrhage [13,15-17]. Symptoms due to an increase in haematoma volume should be reflected in other patient-relevant outcomes, however. In addition, it was unclear to what extent the threshold value of 35% used in the ANNEXA-I study was suitable for assessing haematoma expansion. Both relative and absolute threshold values have been discussed in the scientific literature [18-20]. To be able to assess the influence of an increase in haematoma volume on the long-term impairment of patients, the location of the haemorrhage must also be taken into account [18]. It should also be noted that the individual component 'no haematoma expansion > 35% 12 hours after randomization' notably influenced the result of the outcome 'effective haemostasis', as an increase in haematoma volume > 35% was the most common reason why the outcome was not achieved (in 29.0% of patients in the intervention arm and 42.1% of patients in the comparator arm, the increase in haematoma volume was > 35% 12 hours after randomization). Irrespective of the unclear patient relevance, it was also uncertain whether a recording at 12 hours after randomization covered a sufficiently long period of time to ensure that an increase in the volume of the haematoma by the threshold value of 35% used in the study was recorded.

No rescue therapy between 3 and 12 hours after randomization

One of the criteria of why the primary outcome 'effective haemostasis' was considered not achieved was the need for rescue therapy or (new) haemostatic treatment between 3 and 12 hours after randomization to address continued or recurrent bleeding. This could involve the administration of procoagulant blood products (e.g. prothrombin complex concentrates), whole blood, or medical haemostatic therapy, as well as surgery for haematoma treatment.

The distinction between study medication and rescue therapy or subsequent treatment based solely on a time criterion (3 to 12 hours after randomization) was not appropriate. A (repeated) administration of haemostatic treatment later than 3 hours after randomization was also to be considered part of the standard treatment in the comparator arm. In addition, as already described above, it was unclear whether the recording of rescue therapy up to 12 hours after randomization covered a sufficiently long period. It is conceivable, for example, that treatment with andexanet alfa merely delays the haemorrhage, and haemostatic treatment is required again at a later timepoint, which would then not be included in the analysis. It was also unclear what criteria the investigators used to decide whether rescue therapy had to be initiated. Although the decision to initiate rescue therapy had to be based

on an increase in haematoma volume > 35%, the patient relevance of this was unclear, as already described. It was not clear from the study documents to what extent other criteria were taken into account by the investigators when initiating rescue therapy. Overall, the outcome 'no rescue therapy between 3 and 12 hours after randomization' was therefore not suitable for the benefit assessment.

'Neurological symptoms' – no deterioration 12 hours after randomization

The single component 'no neurological deterioration 12 hours after randomization' was defined as no increase in NIHSS of ≥ 7 points at 12 hours after randomization. An increase of 7 points concurs with 15% of the scale range of the instrument (0 to 42 points). Avoiding neurological deterioration is generally considered relevant for patients. In the given therapeutic indication, however, the period of 12 hours considered was too short to show any longer-term impairment of patients. It should also be noted that in this therapeutic indication, a neurological deterioration is both an expression of the primary bleeding episode and a representation of possible side effects of the treatment, in particular the occurrence of ischaemic strokes. An assessment of neurological symptoms, which also include neurological symptoms resulting from side effects (e.g. ischaemic strokes) that occurred during the course of the study, requires a recording of the outcome over the entire study period of 30 days.

In addition to the analysis of neurological symptoms as part of the primary outcome, the company presented analyses of the change in NIHSS over the period up to 72 hours after randomization. As already described, it was unclear to what extent the short-term changes in neurological symptoms reflected a longer-term impairment of the patients. Overall, there were therefore no suitable data available for the 'neurological symptoms' outcome for the purpose of the benefit assessment. The data for the period up to 72 hours after randomization are presented as supplementary information; there was no relevant effect.

Invasive intracranial procedures

The outcome 'invasive intracranial procedures' was defined as any surgery or interventional procedure performed to manage the haematoma or its complications. The invasive intracranial procedures performed in the study included Burr holes for implanting a ventricular catheter or for drainage of the haematoma as well as craniectomy/craniotomy for the drainage of the haematoma. Burr holes and craniectomy/craniotomy were considered patient-relevant events. For this benefit assessment, the analyses presented by the company on the proportion of patients with at least one invasive intracranial procedure after randomization were used.

Glasgow Coma Scale

In Module 4 A, the company presented analyses of the change in the Glasgow Coma Scale over the period up to 72 hours after randomization. The validity of the scale was not verified, as

the results presented by the company could not be used for the assessment. One reason for this was that the observation period of 72 hours was too short to draw a conclusion about the entire study period based on the results. Another reason was that the response rates in both study arms were < 70% at all timepoints of recording after baseline.

Functional impairment (mRS)

In the ANNEXA-I study, the functional impairment of patients was recorded using the mRS. The scale covers a range from 0 to 6 points (0: no symptoms; 6: death). In the study, the recording of functional impairment was planned at baseline and at the end of the study on Day 30. If recording was not possible during screening, the corresponding value could be collected retrospectively. A relative, care giver or legal representative could also be interviewed for this purpose. The value at baseline had to reflect the patient's status before the acute bleeding episode. It is not clear from the study documents how the recording of the mRS was actually conducted. For example, it was unclear whether a structured interview guideline was used for the recording.

The outcome 'functional impairment' recorded using mRS is generally a patient-relevant outcome and was used despite the uncertainty in the recording. The score at Day 30 was taken into account for the benefit assessment. The value recorded at baseline was unsuitable for the benefit assessment, as it represented the condition of the patients before the disease-related event and was also at least partially recorded retrospectively.

Length of initial hospitalization

The length of initial hospitalization was defined as the period in days from the start of the initial hospitalization for the qualifying bleeding event until the initial hospital discharge. In addition to the analysis of the length of initial hospitalization, the company presented analyses of the total time admitted to the intensive care unit (ICU) during the initial hospitalization as well as the length and proportion of patients with rehospitalization. Total time admitted to the ICU was already included in the analysis of the length of initial hospitalization. A rehospitalization was operationalized as a new hospitalization ≥ 6 hours after the first discharge from the ICU or from an inpatient non-ICU or – regardless of the time interval – as a new hospitalization after discharge due to the primary bleeding episode from home care, home hospice, long-term care hospital, intermediate care facility, outpatient treatment or another facility. The company did not provide any justification for the time limit of 6 hours to define renewed hospitalization. In addition, the company did not explain why the time limit of 6 hours was applied if the discharge location was an ICU or an inpatient non-ICU, but not if the discharge was from another facility. It was also unclear in which cases a discharge due to the primary bleeding episode occurred from another, non-inpatient facility.

Irrespective of this, it remained unclear whether the duration of the initial hospitalization was a sufficient representation of the seriousness of the symptoms as a result of the primary bleeding episode. Furthermore, patient-relevant events that led to the patient's rehospitalization during the course of the study, for example due to a thrombotic event, were not captured by the length of the initial hospitalization. The outcome 'length of initial hospitalization' was therefore not suitable for the benefit assessment.

Health status (EQ-5D VAS)

In the ANNEXA-I study, health status was recorded using the EQ-5D VAS. In Module 4 A of the dossier, the company did not present any analyses for the outcome health status, however. It justified this by stating that no values were recorded in the study at baseline. Recording of the EQ-5D VAS was only planned on Day 30 of the study. The clinical study report contained analyses of the mean difference between the 2 treatment arms at Day 30 only for those patients who were enrolled in the study up to the data cut-off of the interim analysis. Analyses including patients who were enrolled during or after the interim analysis until the end of the study were not available. There were therefore suitable data for the health status outcome for this benefit assessment.

Outcomes in the category of side effects

SAEs and discontinuation due to AEs

In Module 4 A of the dossier, the company presented analyses on side effects without disease-related events. It stated that the events haematoma expansion, intracerebral haemorrhage and associated neurological deterioration that occurred within 12 hours of randomization were considered disease-related events and not AEs or SAEs, unless there was a causal relationship between the therapy received and the event. Neurological deterioration can be both a symptom of haemorrhage and a side effect of treatment in this therapeutic indication. From the information available, it remained unclear which specific neurological events were considered disease-related and were therefore not included in the analyses. It was also assumed that disease-related events could still occur later than 12 hours after randomization. For example, the Preferred Term (PT) cerebral haemorrhage was included in the analysis of the overall rate of SAEs. The negative effects of andexanet in the side effects category were likely to have a tendency to be underestimated due to the inclusion of the PT cerebral haemorrhage (more events in the control arm). In the given situation, where differentiating between side effects and disease-related events was complex and no suitable outcome for recording haemorrhages was collected, a precise list of the events assessed as disease-related would be necessary, regardless of the time of occurrence.

Overall, however, it was not assumed in this data scenario that the company's approach to the selection of potentially disease-related events had any conclusion-relevant effects on the benefit assessment. It was taken into account that in this therapeutic indication it is difficult

to differentiate between clearly disease-related events and side effects. The overall rates of SAEs and discontinuation due to AEs were used for this benefit assessment. However, the uncertainty regarding the selection of potentially disease-related events was taken into account in the assessment of the risk of bias.

Thrombotic events

Thrombotic events are relevant AEs in this therapeutic indication. The outcome thrombotic events was prespecified as an adverse event of special interest (AESI) in the ANNEXA-I study. There was no prespecified list of symptoms that were to be recorded as thrombotic events. However, potential thrombotic events in the study were submitted for adjudication based on prespecified criteria by a blinded adjudication committee. The outcome was to include the events arterial systemic embolism, deep vein thrombosis, ischaemic stroke, myocardial infarction, pulmonary embolism and transient ischaemic attack. With the exception of myocardial infarction, the events included in the outcome were diagnosed in the study on the basis of symptoms in combination with imaging techniques or lung function tests. The diagnosis of myocardial infarction was based on evidence of cardiac biomarkers in combination with symptoms of myocardial ischaemia and/or imaging techniques. It was unclear whether all myocardial infarctions that occurred were accompanied by tangible symptoms and thus represented patient-relevant events. In the given data scenario, the outcome thrombotic event was nonetheless considered with sufficient certainty to be patient relevant and was used for the benefit assessment. In Module 4 A of its dossier, the company presented analyses of any thrombotic events, SAEs and severe AEs that occurred. For the outcome thrombotic events, the SAEs were used for this benefit assessment.

I 4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: andexanet alfa vs. standard treatment

Study		Outcomes										
	Study level	Overall survival	Invasive intracranial procedures[a]	Neurological symptoms (NIHSS)	Functional impairment (mRS)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs[b]	Discontinuation due to AEs	Thrombotic events[c] (SAEs)	Ischaemic stroke (PT, SAEs)	Cardiac disorders (SOC, SAEs)
ANNEXA-I	L	L	L	–[d]	H[e]	–[d]	–[f]	H[g]	H[h]	L	L	L

a. Defined as any surgery or interventional procedure performed to manage the haematoma or its complications, including Burr holes, craniotomies and placement of intraventricular catheters.
b. Unclear proportion of potentially disease-related events; see Section I 4.1 for an explanation.
c. The AE of special interest recorded by the company in the study is considered (including arterial systemic embolism, deep vein thrombosis, myocardial infarction, pulmonary embolism, stroke and transient ischaemic attack). For an explanation, see Section I 4.1.
d. No suitable data available; see Section I 4.1 for the reasoning.
e. Lack of blinding in subjective recording of outcomes.
f. Relevant outcomes in this category were not recorded.
g. For an explanation, see Section I 4.1.
h. Lack of blinding in the presence of subjective decision on treatment discontinuation.

AE: adverse event; H: high; L: low; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results for the outcomes overall survival, invasive intracranial procedures and the specific AEs thrombotic events (SAEs), ischaemic stroke (PT, SAEs) and cardiac disorders (SOC, SAEs) was assessed as low.

The risk of bias of the results for the outcome functional impairment (mRS) was assessed as high due to the lack of blinding in subjective recording of outcomes.

For the outcome SAEs, the risk of bias of the results was assessed as high due to the uncertainty regarding the selection of potentially disease-related events. The risk of bias of the results for the outcome of discontinuation due to AEs was increased because of lack of blinding in subjective decisions regarding treatment discontinuation.

Summary assessment of the certainty of conclusions

As already described in Section I 3.2, the vast majority of patients in the ANNEXA-I study were followed up for 30 days. The extent to which the effects observed in the ANNEXA-I study were

transferable to patients with a bleeding event that occurred > 30 days previously remained unclear. In addition, for an unclear proportion of patients in the intervention arm, the dosage of andexanet alfa deviated from the specifications in the SmPC (see Section I 3.2). The certainty of conclusions of the study results for the given research question was therefore reduced overall. Based on the available information from the ANNEXA-I study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented.

I 4.3 Results

Table 12, Table 13 and Table 14 summarize the results of the comparison of andexanet alfa versus standard treatment in adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrollable bleeding. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Tables on common AEs and common SAEs are presented in I Appendix B of the full dossier assessment. A Kaplan-Meier curve for the time-to-event analysis of the outcome overall survival was not available in the company's dossier.

Table 12: Results (morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: andexanet alfa vs. standard treatment

Study Outcome category Outcome	andexanet alfa N	andexanet alfa Patients with event n (%)	Standard treatment N	Standard treatment Patients with event n (%)	andexanet alfa vs. standard treatment RR [95% CI]; p-value[a]
ANNEXA-I					
Morbidity (Day 30)					
Invasive intracranial procedures[b]	239	16 (6.7)	232	20 (8.6)	0.78 [0.41; 1.46]; 0.432
Health status (EQ-5D VAS)	No suitable data[c]				
Health-related quality of life	Relevant outcomes in this category were not recorded				
Side effects (Day 30)					
AEs (supplementary information)[d]	239	205 (85.8)	232	190 (81.9)	–
SAEs[d]	239	111 (46.4)	232	86 (37.1)	1.25 [1.01; 1.55]; 0.039
Discontinuation due to AEs	239	0 (0)	232	0 (0)	NC
Thrombotic events[e] (SAEs)	239	24 (10.0)	232	12 (5.2)	1.94 [0.99; 3.79]; 0.047
Ischaemic stroke (PT, SAEs)	239	12 (5.0)	232	1 (0.4)	11.65 [1.53; 88.87]; 0.002
Cardiac disorders (SOC, SAEs)	239	21 (8.8)	232	4 (1.7)	5.10 [1.78; 14.62]; < 0.001

a. Mantel-Haenszel method.
b. Defined as any surgery or interventional procedure performed to manage the haematoma or its complications, including Burr holes, craniotomies and placement of intraventricular catheters.
c. For an explanation, see Section I 4.1.
d. Unclear proportion of potentially disease-related events; see Section I 4.1 for an explanation.
e. The AE of special interest recorded by the company in the study is considered (including arterial systemic embolism, deep vein thrombosis, myocardial infarction, pulmonary embolism, stroke and transient ischaemic attack). For an explanation, see Section I 4.1.

AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Table 13: Results (mortality) – RCT, direct comparison: andexanet alfa vs. standard treatment

Study Outcome category Outcome	andexanet alfa N	andexanet alfa Median time to event in days [95% CI] Patients with event n (%)	Standard treatment N	Standard treatment Median time to event in days [95% CI] Patients with event n (%)	andexanet alfa vs. standard treatment HR [95% CI]; p-value[a]
ANNEXA-I					
Mortality (until Day 30)					
Overall survival	239	NA 67 (28.0)	232	NA 61 (26.3)	1.06 [0.75; 1.50]; 0.729

a. Cox proportional hazards model adjusted for time from symptom onset to baseline imaging scan (< 180 minutes vs. ≥ 180 minutes).

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial

Table 14: Results (morbidity, continuous) – RCT, direct comparison: andexanet alfa vs. standard treatment

Study Outcome category	andexanet alfa			Standard treatment			andexanet alfa vs. standard treatment
Outcome	**N[a]**	**Values at baseline mean (SD)**	**Mean change in the course of the study / value on Day 30 mean (SE)**	**N[a]**	**Values at baseline mean (SD)**	**Mean change in the course of the study / value on Day 30 mean (SE)**	**MD [95% CI]; p-value**
ANNEXA-I							
Morbidity							
Neurological symptoms (NIHSS)	No suitable data[b]						
Neurological symptoms (NIHSS) up to 72 hours after randomization[c] (supplementary information)	*231*	*10.8 (7.10)*	*0.85 (0.35)[d]*	*229*	*10.0 (7.21)*	*1.84 (0.35)[d]*	*−0.98 [−1.95; −0.02]; 0.0450[d]* *SMD: −0.19 [−0.37; −0.00][e]*
Functional impairment (mRS)[c]	218	–	4.2 (1.66)[f]	216	–	4.1 (1.74)[f]	0.10 [−0.22; 0.42]; 0.540[g]

a. Number of patients taken into account in the effect estimation; baseline values may be based on different patient numbers.
b. For an explanation, see Section I 4.1.
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage of the intervention (NIHSS: scale range 0 to 42; mRS: scale range: 0 to 6).
d. MD and SE (per treatment group) as well as MD, CI and p-value (group comparison): MMRM with fixed factors baseline value, time from symptom onset to baseline imaging scan, treatment and timepoint or visit as well as treatment-timepoint interaction; patients as random effect; unstructured covariance matrix; the average change over time is taken into account.
e. As the CI for the SMD is not entirely outside the irrelevance range [−0.2; 0.2], it cannot be inferred that there is a relevant effect.
f. Mean (SD) at Day 30; see Section I 4.1 for an explanation.
g. Effect, CI and p-value: Institute's calculation (t-test).

CI: confidence interval; MMRM: mixed-effects model with repeated measures; mRS: modified Rankin Scale; MD: mean difference; N: number of analysed patients; NIHSS: National Institutes of Health Stroke Scale; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 4.2).

Mortality

Overall survival

No statistically significant difference between treatment groups was found for the outcome overall survival. There is no hint of an added benefit of andexanet alfa in comparison with individualized treatment; an added benefit is therefore not proven.

Morbidity

Invasive intracranial procedures and functional impairment (mRS)

No statistically significant difference between treatment groups was found for the outcomes invasive intracranial procedures and functional impairment recorded using the mRS. In each case, there is no hint of an added benefit of andexanet alfa in comparison with individualized treatment; an added benefit is therefore not proven.

Neurological symptoms (NIHSS) and health status (EQ-5D VAS)

No suitable data were available for the outcomes of neurological symptoms recorded using the NIHSS and health status recorded using the EQ-5D VAS (for an explanation, see Section I 4.1). In each case, there is no hint of an added benefit of andexanet alfa in comparison with individualized treatment; an added benefit is therefore not proven.

Health-related quality of life

Relevant outcomes on health-related quality of life were not recorded in the included study.

Side effects

SAEs, thrombotic events (SAEs), ischaemic stroke (SAEs) and cardiac disorders (SAEs)

For each of the outcomes SAEs, thrombotic events (SAEs), ischaemic stroke (SAEs) and cardiac disorders (SAEs), there was a statistically significant difference between the treatment groups to the disadvantage of andexanet alfa. There is a hint of greater harm of andexanet alfa in comparison with individualized treatment in each case.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm of andexanet alfa in comparison with individualized treatment; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account in this benefit assessment:

- Age (< 65 years versus 65 to 74 years versus ≥ 75 years)
- Sex (female versus male)

- Intracerebral haemorrhage (ICH) score at baseline (< 3 versus ≥ 3)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

When applying the above-described methods, the available subgroup results show no effect modifications.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 15).

Table 15: Extent of added benefit at outcome level: andexanet alfa vs. individualized treatment (multipage table)

Outcome category **Outcome**	**andexanet alfa vs. standard treatment** **Median time to event (days) or proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. NA HR: 1.06 [0.75; 1.50]; p = 0.729	Lesser benefit/added benefit not proven
Morbidity		
Invasive intracranial procedures	6.7% vs. 8.6% RR: 0.78 [0.41; 1.46]; p = 0.432	Lesser benefit/added benefit not proven
Neurological symptoms (NIHSS)	No suitable data	Lesser benefit/added benefit not proven
Functional impairment (mRS)	4.2 vs. 4.1[c] MD: 0.10 [-0.22; 0.42]; p = 0.540	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No suitable data	Lesser benefit/added benefit not proven
Health-related quality of life		
Relevant outcomes in this category were not recorded.		

Table 15: Extent of added benefit at outcome level: andexanet alfa vs. individualized treatment (multipage table)

Outcome category **Outcome**	**andexanet alfa vs. standard treatment** **Median time to event (days) or proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
Serious AEs (SAEs)	46.4% vs. 37.1% RR: 1.25 [1.01; 1.55]; RR: 0.80 [0.65; 0.99][d]; p = 0.039 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: minor
Discontinuation due to AEs	0% vs. 0% RR: NC; p = NC	Greater/lesser harm not proven
Thrombotic events[e] (SAEs)	10.0% vs. 5.2% RR: 1.94 [0.99; 3.79]; RR: 0.52 [0.26; 1.01][d]; p = 0.047 Probability: hint	Outcome category: serious/severe side effects Greater harm[f], extent: minor[g]
Ischaemic stroke (SAEs)	5.0% vs. 0.4% RR: 11.65 [1.53; 88.87]; RR: 0.09 [0.01; 0.65][d]; p = 0.002 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% Greater harm, extent: major
Cardiac disorders (SAEs)	8.8% vs. 1.7% RR: 5.10 [1.78; 14.62]; RR: 0.20 [0.07; 0.56][d]; p < 0.001 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% Greater harm, extent: major

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale of the outcome, the effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. Mean value on Day 30.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. The AE of special interest recorded by the company in the study is considered (including arterial systemic embolism, deep vein thrombosis, myocardial infarction, pulmonary embolism, stroke and transient ischaemic attack). For an explanation, see Section I 4.1.
f. The result of the statistical test is decisive for the derivation of the added benefit.
g. Discrepancy between CI and p-value due to different calculation methods; the extent is rated as minor.

Table 15: Extent of added benefit at outcome level: andexanet alfa vs. individualized treatment (multipage table)

Outcome category **Outcome**	**andexanet alfa vs. standard treatment** **Median time to event (days) or proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; CI_L: lower limit of the confidence interval; HR: hazard ratio; mRS: modified Rankin Scale; MD: mean difference; NA: not achieved; NC: not calculated; NIHSS: National Institutes of Health Stroke Scale; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale		

I 5.2 Overall conclusion on added benefit

Table 16 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 16: Positive and negative effects from the assessment of andexanet alfa in comparison with individualized treatment

Positive effects	**Negative effects**
–	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: minor ▪ Thrombotic event (SAEs): hint of greater harm – extent: minor ▪ Ischaemic stroke (SAEs): hint of greater harm – extent: major ▪ Cardiac disorders (SAEs): hint of greater harm – extent: major
No suitable data on the outcomes of neurological symptoms and health status as well as on the outcomes in the category of health-related quality of life	
AE: adverse event; SAE: serious adverse event	

The ANNEXA-I study predominantly included patients with intracerebral haemorrhage (91.4% in relation to the relevant subpopulation of patients treated with apixaban or rivaroxaban). Only a few patients had a different intracranial haemorrhage. Patients with life-threatening or uncontrollable extracranial haemorrhage were not included in the ANNEXA-I study. Based on the available data, conclusions can therefore only be drawn on the added benefit of andexanet alfa versus the ACT in patients with intracerebral haemorrhage. For all other patients in the therapeutic indication, an added benefit is not proven. In addition, on the basis of the available data, conclusions could only be drawn about the shortened observation period of 30 days considered in the ANNEXA-I study.

Overall, only negative effects of andexanet alfa versus the ACT were shown for adult patients with intracerebral haemorrhage treated with an FXa inhibitor (apixaban or rivaroxaban). For the overall rate of SAEs and the outcome of thrombotic events, there is a hint of greater harm of minor extent in each case. In addition, for 2 specific AEs in the category of serious/severe side effects, there is a hint of greater harm of major extent.

It should be noted that for the primary outcome of the study, separate analyses were prespecified for high and low andexanet alfa doses. The andexanet alfa dose was not randomized, but was selected based on the amount of the most recent FXa inhibitor dose and the time between the most recent use of the FXa inhibitor and the start of the study medication. The clinical study report also provided results on the outcomes all-cause mortality on Day 30 (proportion of patients with event in the intervention arm: high dose: 40.4%; low dose: 24.6%) and thrombotic events (any AESI, proportion of patients with event in the intervention arm: high dose: 15.4%; low dose: 9.6%) split according to the andexanet alfa dose. Based on these data, the question arises to what extent the greater harm of andexanet alfa compared with the ACT may depend on the andexanet alfa dose. From the perspective of the Food and Drug Administration (FDA)’s Cellular, Tissue, and Gene Therapies Advisory Committee, there is uncertainty as to whether the currently approved dosage of andexanet alfa is optimized in terms of efficacy and safety [21].

In summary, there is a hint of a lesser benefit of andexanet alfa versus the ACT in adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to intracerebral haemorrhage.

Table 17 summarizes the result of the assessment of the added benefit of andexanet alfa in comparison with the ACT.

Table 17: Andexanet alfa – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrollable bleeding[b]	Individualized treatment[c, d] with a choice of: ▪ prothrombin complex concentrates ▪ BSC[e, f]	▪ Patients with intracerebral haemorrhage: hint of a lesser benefit[g] ▪ All other patients in the therapeutic indication: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that patients in both arms received optimal intensive care.
c. The term 'individualized treatment' is used instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
d. Both a single-comparator study with prothrombin complex concentrates and a multi-comparator study with a choice of the above-mentioned treatment options may be suitable for the implementation of the ACT. However, the choices should always include prothrombin complex concentrates. If the implementation takes the form of a multi-comparator study, the individualized treatment decision regarding the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).
e. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
f. According to the G-BA, it is assumed that fluid replacement and the administration of plasma expanders or blood products, if indicated, are carried out as part of BSC in the event of severe or life-threatening bleeding. The location of the life-threatening or uncontrollable bleeding (e.g. cerebral haemorrhage, gastrointestinal haemorrhages) is also a criterion for the appropriate therapy in each case.
g. The subpopulation of the ANNEXA-I study relevant for this benefit assessment also includes a small proportion (9%) of patients with other intracranial haemorrhages.

ACT: appropriate comparator therapy; BSC: best supportive care; EU: European Union; FXa: Factor Xa; G-BA: Federal Joint Committee; HTA: health technology assessment

The assessment described above deviates from that of the company, which derived an indication of a minor added benefit for patients with intracerebral haemorrhage.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 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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