# Cost-effectiveness of andexanet alfa versus prothrombin complex concentrate is likely for the treatment of factor Xa inhibitor–related major bleeds in the Netherlands

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## Introduction

- Factor Xa (FXa) inhibitors such as rivaroxaban and apixaban, which are commonly used for the prevention of thrombosis, are associated with a small risk of major, potentially life-threatening bleeding[1]
- Andexanet alfa specifically reverses the anticoagulation effects of rivaroxaban or apixaban in adults with such life-threatening or uncontrolled bleeding[2]
- Prior to the availability of andexanet alfa, management of FXa-associated major bleeding was primarily supportive and included prohemostatic agents, such as (off-label) prothrombin complex concentrates (PCCs), which contain high concentrations of different clotting factors and were originally developed to reverse coagulation factor deficiency induced by vitamin K antagonists (eg, warfarin)
- In the ANdexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors (ANNEXA-4) multicenter, open-label, single-arm study, andexanet alfa rapidly reversed anticoagulation in patients with FXa inhibitor–associated acute major bleeding, with 80% of patients achieving effective hemostasis[3]
- The European Medicines Agency conditionally authorized andexanet alfa for use throughout the European Union in 2019[2]; however, the cost-effectiveness of andexanet alfa has not been fully characterized

## Objective

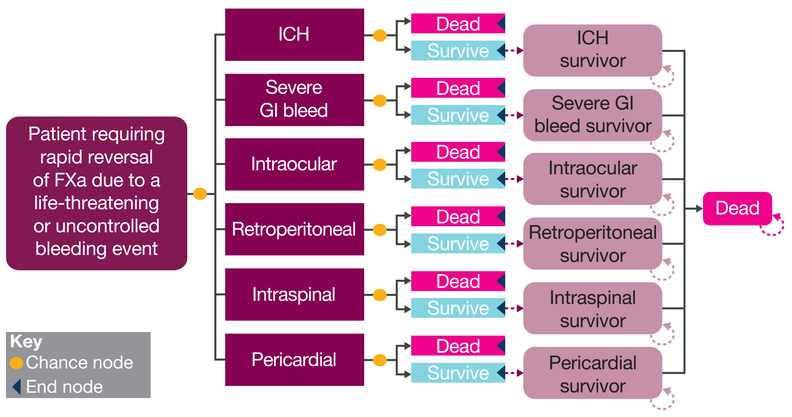
- To assess the cost-effectiveness of andexanet alfa compared to 4-factor PCC (4F-PCC) across rivaroxaban and apixaban users with life-threatening major bleeds from a Dutch perspective

## Methods

### Modeling Framework

- A decision analytic model was used and included a decision tree in the short term and a Markov model in the long term (**Figure 1**)
  - Patients entering the decision tree were assigned to health states according to their bleed type. The decision tree reflected initial bleed management and the 30-day mortality risk
  - Following the 30-day period, a Markov structure was used to capture long-term risk of mortality, morbidity, and costs for survivors over a lifetime horizon, using a monthly cycle length

**Figure 1: Model Structure**




ICH, intracranial hemorrhage; GI, gastrointestinal.

- Andexanet alfa was compared to 4F-PCC across rivaroxaban and apixaban users with life-threatening or uncontrolled bleeding
- A lifetime horizon was applied, and a societal perspective was taken

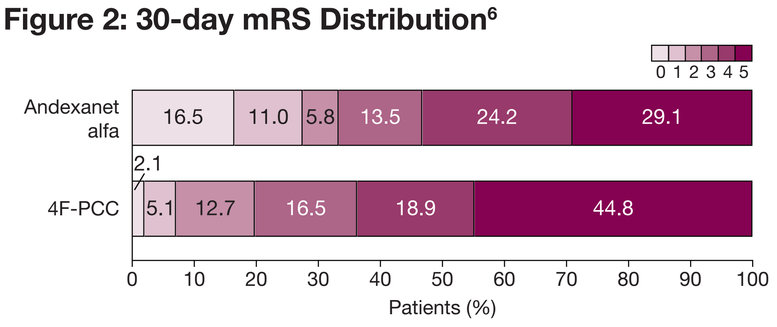
### Model Inputs

- Bleed type distribution was based on ANNEXA-4,[4] with the majority of patients being treated for ICH (65%) and GI bleeds (25%)
- In the absence of a randomized controlled trial to compare the efficacy of andexanet alfa directly to 4F-PCC, indirect treatment comparisons were required to inform comparative efficacy in the model. The ANNEXA-4/ORANGE propensity score–matched comparison was used to inform 30-day mortality[5] and the propensity score–adjusted ANNEXA-4/RETRACE comparison informed modified Rankin Scale (mRS) outcomes after an ICH[6] (**Table 1**; **Figure 2**)
  - The ORANGE study was a UK multicenter, prospective, observational study that enrolled patients (N = 145) on an oral anticoagulant with an acute major bleed[7]
  - RETRACE-II was a German multicenter, retrospective, observational study of patients with oral anticoagulant–associated ICH[8]
  - Due to limited patient numbers for other major bleeds, it was assumed that mortality risk reductions for retroperitoneal and pericardial bleeds were 25% compared to usual care. Moreover, it was assumed that no patient would die due to intraocular or intraspinal bleeds in either treatment arm
- Long-term survival (>30 days) after ICH was estimated by fitting parametric survival curves onto published Kaplan-Meier curves for each mRS category.[9] Transition probabilities to the death state were calculated each month by weighting the probability of survival from the survival curves by the distribution of mRS scores for ICH survivors
- GI and other major bleed survivors were assumed to have no increased long-term mortality risk resulting from their bleed event, and their mortality probability was estimated from Dutch national life tables, multiplied by a standardized mortality ratio of 1.3 to correct for underlying comorbidities in this population[10]
- Quality-of-life inputs were sourced from the literature. Acute utilities (first 30 days) and long-term utilities after GI, retroperitoneal, and pericardial bleeds were assumed equal between treatment arms. For ICH survivors, a long-term utility (>90 days) difference of 0.10 was applied, reflecting the difference in survivors' mRS outcomes[11]
- Due to the paucity of data in ANNEXA-4 for intraspinal and intraocular bleeds, it was assumed that treatment with andexanet alfa would also lead to a reduction in associated morbidities (eg, paralysis and blindness). Therefore, long-term utility improvements of 0.04 and 0.01 were assumed for intraspinal and intraocular bleed survivors treated with andexanet alfa, respectively
- Costs were derived from the literature and national list prices
  - The average acquisition cost of andexanet alfa was estimated at €17,945 per patient, assuming 85% of patients required a low-dose regimen and including the cost of vial wastage
  - The average acquisition cost of 4F-PCC was estimated at €1,553.74 per patient, based on 22.5 to 25 UI/kg dosing as observed in the ORANGE study

**Table 1: 30-day Outcomes Within the Decision Tree**

| | Andexanet alfa | 4F-PCC |
|---|---|---|
| 30-day mortality by bleed type,[5] % | | |
| ICH | 15.3 | 50.0 |
| Severe GI bleed | 12.2 | 25.0 |
| Intraocular bleed | 0 | 0 |
| Intraspinal bleed | 0 | 0 |
| Retroperitoneal bleed | 9.4 | 12.5 |
| Pericardial bleed | 9.4 | 12.5 |

**Figure 2: 30-day mRS Distribution[6]**




Redistributed to exclude death.

## Results

- Treatment with andexanet alfa was associated with a gain in quality-adjusted life years (QALYs) of 1.099 and incremental costs of €31,195, resulting in an incremental cost-effectiveness ratio (ICER) of €28,385/QALY (**Table 2**)
  - Assuming a health care perspective resulted in an ICER of €29,929/QALY (**Table 2**)

**Table 2: Cost-effectiveness Results**

| | Total costs (€) | Total QALYs | ΔCosts | ΔQALYs | ICER |
|---|---|---|---|---|---|
| **Societal perspective** | | | | | |
| 4F-PCC | 72,655 | 2.290 | 31,195 | 1.099 | 28,385 |
| Andexanet alfa | 103,849 | 3.389 | | | |
| **Health care perspective** | | | | | |
| 4F-PCC | 64,606 | 2.290 | 32,891 | 1.099 | 29,929 |
| Andexanet alfa | 97,498 | 3.389 | | | |

Δ represents the difference between andexanet alfa and 4F-PCC.

- Although the results were most sensitive to long-term costs and utilities post-ICH (**Figure 3**), they were generally consistent across sensitivity analyses
- Under a willingness-to-pay threshold of €50,000/QALY, andexanet alfa had an 87% probability of being cost-effective (**Figure 4**)

**Figure 3: Tornado Diagram**

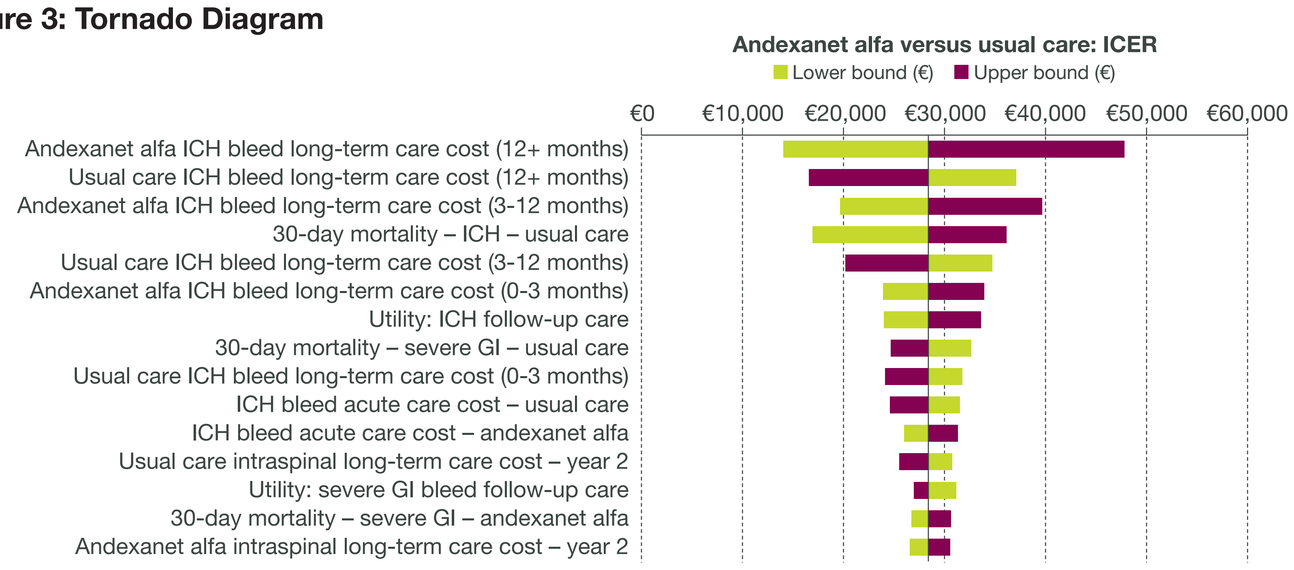
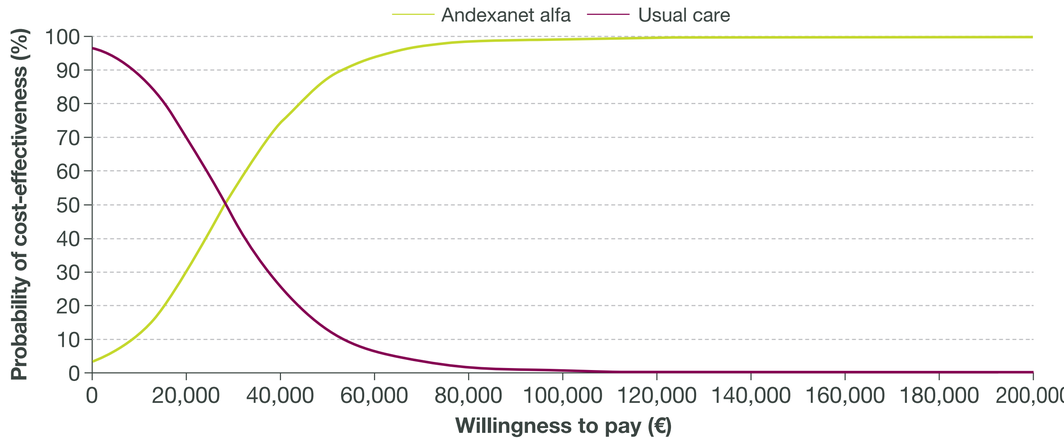



**Figure 4: Cost-effectiveness Acceptability Curve**




## Discussion

- There is an ongoing need for an approved treatment for FXa inhibitor–associated major bleeds to standardize practice and improve patient outcomes
- Recently, high-level results from the ANNEXA-I clinical trial[12] confirmed the hemostatic efficacy of andexanet alfa compared to usual care in a population with (predominantly) intracerebral bleeds, with a similar proportion of deaths between treatment groups at day 30. Further investigation is required to understand implications on cost-effectiveness in the overall population

## Conclusion

- This analysis indicates that andexanet alfa is likely to be a cost-effective treatment option for patients with FXa inhibitor–related major bleeds in the Netherlands

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### Disclosures

**ML**, **CH**, **EC**, and **LG** are employees of FIECON, which received payment from AstraZeneca to develop the model used in this work. **NW**, **SN**, and **HvH** are employees of AstraZeneca.

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