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CADTH Reimbursement Recommendation

Andexanet Alfa (Ondexxya)

Indication: For adult patients treated with factor Xa inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding
Sponsor: AstraZeneca Canada Inc.
Final recommendation: Do not reimburse



Summary

What Is the CADTH Reimbursement Recommendation for Ondexxya?

CADTH recommends that Ondexxya should not be reimbursed by public drug plans for adult patients treated with factor Xa (FXa) inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial (ANNEXA-4) demonstrated that Ondexxya treatment could reduce the activity of FXa inhibitors in the blood and improve imaging and laboratory markers of bleeding; however, without a control group, there is uncertainty in how much the observed benefits were due to Ondexxya treatment rather than chance. Clinical outcomes such as neurologic status and mortality were also uncertain.
- No evidence was submitted at the time of the review that directly compared Ondexxya to usual care for managing bleeding related to an FXa inhibitor. Observational evidence comparing Ondexxya and prothrombin complex concentrate, which is part of the usual care, was uncertain due to limitations of study design and analysis.
- Based on the evidence reviewed, the CADTH Canadian Plasma Protein Product Expert Committee (CPEC) was not convinced that treatment with Ondexxya would achieve outcomes that are clinically important to patients or meet needs not already addressed by other available treatments.

Additional Information

Why Is a Treatment to Reverse the Effects of FXa Inhibitor Needed? Some patients with cardiovascular disease receive FXa inhibitors (apixaban and rivaroxaban) to prevent formation of blood clots; however, FXa inhibitors are associated with an increased risk of bleeding. A treatment to reverse the effects of an FXa inhibitor is needed in these patients during a serious bleed to reduce the risk of complications and death.

Unmet Needs in the Management of Major Bleeding Related to FXa Inhibitor Use

Although there is an existing treatment for managing patients with major bleeding while receiving FXa inhibitor treatment, it has not been approved by Health Canada. There is an unmet need for a rapid and effective treatment that could reverse the effects of FXa inhibitors in these patients.





Summary

How Much Does Ondexxya Cost?

Treatment with Ondexxya is expected to cost the public drug plan approximately \$26,787 per patient (assuming 1 reversal treatment per patient).

Andexanet Alfa (Ondexxya)



Recommendation

The CADTH Canadian Plasma Protein Product Expert Committee (CPEC) recommends that and exanet alfa not be reimbursed for adult patients treated with factor Xa (FXa) inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

Rationale for the Recommendation

Evidence available to CPEC at the time of the review did not sufficiently demonstrate comparable therapeutic effects of and exanet alfa relative to the usual care, which may include prothrombin complex concentrate (PCC). Evidence from 1 phase IIIb/IV, open-label, single-arm study (ANNEXA-4, N = 477) suggested that and exanet alfa treatment resulted in reduced anti-FXa activity and achieved "good" or "excellent" hemostatic efficacy at 12 hours after infusion based on radiological and laboratory findings for adult patients with acute major bleeding who received FXa inhibitor treatments. The median percent change from baseline in anti-FXa activity at on-treatment nadir was -93.3% (95% confidence interval [CI], -94.2% to -92.5%) in apixabantreated patients and -94.1% (95% CI, -95.1% to -93.0%) in patients treated with rivaroxaban-treated. "Good" or "excellent" hemostatic efficacy at 12 hours after infusion was achieved in 80.0% (95% CI, 75.3% to 84.1%) of patients. However, it is uncertain whether the observed effects could be attributed to and exanet alfa due to the absence of a control group. Use of hemostatic agents and blood products, rebleeding, neurologic status assessments, 30-day mortality, and length of hospital stay were assessed descriptively and were exploratory in nature. Neurologic status outcomes were also associated with uncertainty due to a large amount of missing data, a risk of reporting bias due to the open-label study design, and exclusion of patients without elevated anti-FXa levels at baseline from the analyses. Generalizability of results was limited by the exclusion of patients with severe intracranial hemorrhage (ICH) and patients with an expected survival less than 1 month.

Direct evidence comparing and exanet alfa to PCC, the currently used first-line treatment, was not identified for this review. Comparative evidence was limited to observational studies associated with uncertainty that precluded determination of the relative efficacy of and exanet alfa compared with PCC. These studies suggested that treatment with and exanet alfa may be associated with a lower 30-day mortality rate compared with treatment with PCC; however, limitations prevented conclusions from being drawn about the direction and magnitude of treatment effects.

Patients identified a need for a rapid and effective reversal treatment of FXa inhibitors in patients with major bleeding. CPEC concluded that there was insufficient evidence to demonstrate that and exanet alfa achieves outcomes that are clinically important to patients or meets needs not already addressed by other available treatments for the management of FXa inhibitor-related major bleeding.



Discussion Points

- During the initial and reconsideration meetings, CPEC acknowledged that a specific antidote for FXa inhibitors is currently not available and that PCC, which is part of usual care for the management of patients with FXa inhibitor-related major bleeding, is a widely used treatment. CPEC noted that there remains an unmet need for patients on FXa inhibitors who have a major bleed and require emergency management with a safe and effective therapy because of the high levels of morbidity and mortality in this population. However, CPEC noted there is substantial uncertainty about whether andexanet alfa could meet these needs without direct comparative evidence submitted at the time of the review supporting that andexanet alfa provides similar or added clinical benefits compared with usual care.
- During the reconsideration meeting, CPEC acknowledged that new data were recently released from a
 postmarketing phase IV randomized controlled trial (RCT), ANNEXA-I, that compared andexanet alfa
 with usual care in adult patients with ICH who have received oral FXa inhibitors. This new evidence
 could not be accepted or considered by CPEC during the reconsideration process for andexanet alfa
 in accordance with the *Procedures for CADTH Reimbursement Reviews*. Without a comprehensive
 appraisal of the new evidence from CADTH, CPEC noted that it remains unclear if andexanet alfa
 could meet the unmet needs.
- During the initial and reconsideration meetings, CPEC discussed the clinical relevance of outcomes assessed in the ANNEXA-4 trial. The committee noted that the clinical relevance of the coprimary end point of change from baseline in anti-FXa activity to be limited. This is based on the clinical experts' input that anti-FXa activity is not routinely measured in clinical practice in the management of FXa inhibitor-related bleeding and that anti-FXa activity level is not known to reliably predict clinical outcomes. CPEC also discussed the results of the 30-day mortality and neurologic status analyses, which are clinical outcomes important to patients and clinicians, and noted that they were assessed descriptively and were exploratory in nature. Additionally, neurologic status outcomes were uncertain due to a large amount of missing data, potential report bias, and exclusion of patients without elevated baseline anti-FXa levels from the analyses. CPEC noted that these limitations add to the uncertainty of the treatment effect of andexanet alfa on clinical outcomes.
- CPEC discussed evidence from 3 weighted comparative observational studies and 6 comparative observational studies submitted by the sponsor assessing the comparative efficacy of andexanet alfa versus PCC for the reversal treatment of patients with FXa inhibitor-related major bleeding. CPEC considered the important methodological limitations of these studies, including selection bias, heterogeneity in inclusion and exclusion criteria between included studies, and inadequate adjustment for prognostic factors and effect modifiers, which limit interpretation of the relative efficacy of andexanet alfa and PCC.
- Patients expressed a need for an effective reversal treatment of FXa inhibitors in patients without major bleeding who require urgent surgery. However, CPEC noted that evidence to support the use of



and exanet alfa in this patient population was not provided in the submission given that this patient population is not included in the Health Canada-approved indication.

Background

Serious bleeding is a major risk associated with anticoagulant treatment and could manifest as gastrointestinal (GI) bleeding, ICH, and bleeding at a critical site (e.g., intraocular, pericardial). It is estimated that rivaroxaban and apixaban, which belong to a class of anticoagulants called FXa inhibitors, are used in approximately 900,000 patients in Canada and are associated with an annual risk of major bleeding of 2% to 4%. FXa inhibitor-related major bleeding is associated with an increased risk of death, with 30-day mortality estimates of 9% to 45%. To date, there is no available antidote in Canada that specifically reverses the anticoagulant effect of FXa inhibitors in the event of major bleeding. The usual care is PCC, an off-label, plasma-derived product that provides nonspecific supplementation of exogenous coagulation factors, although it does not directly reverse FXa inhibitor activity. Clinical trial evidence for PCC in treating FXa inhibitor-related bleeding is lacking, and its use is primarily informed by observational studies.

Andexanet alfa has been approved by Health Canada for adult patients treated with FXa inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Andexanet alfa is a recombinant modified human FXa protein without procoagulant or anticoagulant activity that acts as an antidote for apixaban and rivaroxaban. It is available as a 200 mg powder for solution for IV infusion. The product monograph recommends andexanet alfa administered at a low dose of 400 mg via IV bolus at a target rate of 30 mg per minute, followed by an IV infusion at 4 mg per minute for 120 minutes, or at a high dose of 800 mg via IV bolus at a target rate of 30 mg via Selected based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase IIIb/IV, single-arm trial; 3 weighted comparative observational studies; and 6 comparative observational studies in adult patients treated with FXa inhibitors who had acute major bleeding
- patients perspectives gathered by 2 patient groups, including the Canadian Venous Thromboembolism Research Network (CanVECTOR) and the HeartLife Foundation
- input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with acute major bleeding
- input from 5 clinician groups, including Thrombosis Canada, Thrombosis and Anticoagulation Team at Dalhousie University, faculty members at McMaster University in hematology and



thromboembolism, Canadian Stroke Consortium, and a journal club comprising local emergency medicine physicians in Peel region

- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the Request for Reconsideration (described subsequently).

Stakeholder Perspectives

Patient Group Input

Two patient groups, the CanVECTOR Patient Partners and the HeartLife Foundation, submitted input for this review. The input from CanVECTOR was informed by 33 interviews with patients with lived experience with venous thromboembolism and varied treatment experience, including warfarin, direct oral anticoagulants (DOACs), and low-molecular-weight heparin for anywhere from 1 to 6 months to long-term treatment (over 3 years; n = 16).

According to the input by CanVECTOR, patients receiving treatment for venous thromboembolism have to find a balance between the risk of another clot and actual or potential side effects of treatment. Patients expressed that bleeding is the most concerning potential side effect of venous thromboembolism treatments and they may live with a fear of bleeding that can impact life choices and daily activities, guality of life, and mental health. The input noted that a variety of personal factors affect a patient's treatment preferences. Many patients described the burden of treatment with warfarin (the inconvenience of blood monitoring, restrictions on diet or alcohol intake), or with low-molecular-weight heparin injections (pain, bruising, discomfort with self-injections) and some had later switched to a DOAC. The input noted that there were fewer burdens described with DOACs, but the lack of a reversal agent was seen as a concern by patients, for example "However much I have my misgivings on warfarin, it had one benefit. It was reversible. It had all the other things that were not attractive to it, but if you could make some of those things more attractive, or certainly if the new drug that would come on the market to replace or be an alternative to apixaban, if it had a reversibility aspect to it, I think would be attractive." The HeartLife Foundation noted that the use of an FXa inhibitor can increase the risk of bleeding; as well, patients with heart failure may require invasive surgeries, which put them at risk of surgical bleeds. The group expressed a need for a treatment that can rapidly and effectively reverse the anticoagulant effect of an FXa inhibitor to prevent further bleeding and ensure the best possible outcome in patients who require urgent surgery or are experiencing life-threatening bleeds. This was echoed by the input by CanVECTOR which highlighted that patients were concerned that the absence of a reversal agent for DOAC could prevent them from undergoing a surgery in case of an emergency: "If an accident happened and the surgery is almost immediate, a reversal agent can help me with it to be going into the emergency surgery safely." CanVECTOR also highlighted that some patients with a high risk of another clot will be prescribed blood thinners for the rest of their lives and the experience could be daunting for a young person with decades of treatment ahead.



Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of acute major bleed in patients receiving a FXa inhibitor.

Unmet Needs

The clinical experts noted that there is currently a lack of a specific reversal agent for FXa-related bleeding. They noted that currently available hemostatic agents (i.e., PCC) do not always achieve a rapid response. This can be a concern in patients with time-sensitive major bleeding, such as patients with bleeding within the central nervous system, high-risk GI bleeding, trauma in need of urgent operative intervention, and, in rare instances, patients with acute kidney injury who experience prolonged anticoagulant effects of an FXa inhibitor. The clinical experts also noted that PCC and blood products are not universally available in all clinical settings. In addition, the risk of thrombosis with existing treatments is unclear per the clinical experts.

Place in Therapy

The clinical experts noted that andexanet alfa is a specific reversal agent of FXa inhibitors and may act more rapidly than other reversal agents currently available. The clinical expert anticipated that andexanet alfa would have the same place in therapy as PCC (i.e., as an alternative option to PCC) in the treatment of acute major bleed in patients receiving a FXa inhibitor; however, it is unclear if andexanet alfa or PCC should be the preferred therapy based on available evidence and suggested this should be based on clinical presentation. The clinical experts noted that in addition to clinical evidence, practical factors such as treatment access (e.g., via hospital transfusion medicine laboratories versus hospital pharmacy) and cost could also affect adoption of treatment. Therefore, it is challenging to conclude with certainty whether andexanet alfa has the potential to cause a shift in the current treatment paradigm.

Patient Population

The clinical experts noted that patients receiving an FXa inhibitor who have acute major bleeding are potential candidates for andexanet alfa treatment. According to the clinical experts, this patient population would most commonly include (but not limited to) older patients who are adherent with their FXa inhibitor treatment and present to the emergency department with brisk non-variceal upper GI bleeding or head trauma resulting in intracranial bleeding that is believed to be worsening or at risk of worsening. The clinical experts also noted that patients who receive FXa inhibitor treatment and require urgent surgery (e.g., patients with hip fractures who could benefit from early operative intervention) may also be candidates for andexanet alfa, although this patient population was not studied in the pivotal trial.



The clinical experts noted that the definition of major bleed by the International Society on Thrombosis and Hemostasis is most commonly used by clinicians in Canada. According to the clinical experts, patients with major bleeding who require reversal of the anticoagulant effect of an FXa inhibitor would be identified primarily based on assessments of the clinical status of patients (severity, bleed location, and response to nonspecific supportive measures) in clinical practice. Laboratory markers such as prothrombin time are not sensitive measures of anticoagulant activity. Establishing when the last dose of an anticoagulant was taken would be a more reliable indicator of whether anti-FXa activity is still present per the clinical experts. The clinical experts noted that FXa assays could help inform treatment decisions if done in a timely fashion (turnaround time of less than 1 hour); however, this is not realistic outside of a few treatment centres in Canada.

The clinical experts noted that patients with minor bleeding would not be suitable for and exanet alfa treatment because nonmajor bleeds are expected to resolve on their own without the need for a reversal agent and with minimal patient harm.

Assessing the Response to Treatment

The clinical experts noted that, in general, response to treatment is assessed based on hemostatic stability, hemostatic control (i.e., cessation of bleeding), need for blood transfusion, survival, and health-related quality of life (HRQoL). Stabilization of vital signs, improvement or normalization in laboratory markers (e.g., serial hemoglobin and lactate measures, coagulation profile), and cessation of bleeding (e.g., based on findings on endoscopy) are typical indicators of achievement of hemostatic control, according to the clinical experts. The clinical experts noted that continuous monitoring of hemostatic control, transfusion needs, and survival is typically done for the first 72 hours after admission. Absence of thrombosis (ideally assessed at 5 days and at 1 month posttreatment) and improvement of HRQoL (ideally assessed at 1 month posttreatment) would also be indicative of a positive response to treatment, although timing of assessment could differ between patients.

Prescribing Considerations

The clinical experts noted that the vast majority of emergency department physicians would be comfortable to prescribe andexanet alfa in consultation with a hematologist, thrombosis physician, or transfusion medicine specialist. However, the clinical experts indicated that access to a hematologist, thrombosis physician, or transfusion medicine specialist is limited in remote and rural areas and could potentially become a barrier to timely administration of a reversal agent in an emergency situation. Therefore, the clinical experts noted it may be reasonable to allow prescribing by clinicians who have expertise in the management of acute major bleeding.

The clinical experts noted it would be appropriate to prescribe and exanet alfa in a hospital setting (e.g., emergency department, inpatient ward, or operating room).

The clinical experts noted that redosing of reversal treatment is rare in clinical practice, and the pharmacology of andexanet alfa suggests that redosing is not necessary. Redosing is associated with



increased thrombotic risk and should only be done in exceptional circumstances under the guidance of a transfusion medicine specialist, thrombosis physician, or hematologist.

Clinician Group Input

The clinician group input was obtained from 5 clinician groups, including Thrombosis Canada represented by 2 clinicians, members of the Thrombosis and Anticoagulation Team at Dalhousie University represented by 3 clinicians, faculty members at McMaster University in hematology and thromboembolism represented by 5 clinicians, Canadian Stroke Consortium represented by 5 clinicians, and a journal club comprising local emergency medicine physicians in Peel region represented by 5 clinicians.

The clinician groups noted that PCC, which is currently the reversal treatment of choice for DOAC-related major bleeding, has a nonspecific mechanism of action and is an off-label drug with no robust clinical data supporting its efficacy or safety. They noted PCC may promote prothrombotic state and may not be safe to use in patients who have a history of heparin-induced thrombocytopenia and thrombosis because a small amount of heparin may be present in PCC.

The clinician groups noted that andexanet alfa, being the only specific reversal treatment available to patients who are on an FXa inhibitor, would be used as a first-line treatment in patients who require urgent anticoagulant reversal in the setting of serious, life-threatening bleeding or need for urgent surgery. One clinician group noted that PCCs would likely to be used for an "average patient" who needs DOAC reversal, whereas andexanet alfa would be used in selected patients with life-threatening bleeding that does not respond to supportive management (i.e., fluids, packed red cells), critical site bleeding (intracranial, spinal, pericardial), and a need for emergency (within 6 to 8 hours) or urgent (within 12 to 24 hours) surgery. They noted that there is no established threshold for clinically significant hemostatic impairment, and most centres do not have FXa inhibitor drug assays available, so treatment is usually considered based on timing of the last dose, drug half-life, patient's kidney or liver function, examination findings (e.g., hypotension), radiographic findings (e.g., CT scans), and clinician judgment. They also noted that patients who would be less suitable would be those who last took their dose of FXa inhibitor more than 1 to 2 days previously (in the presence of normal renal function), who have bleeding that is not life-threatening, or those who can have surgery delayed for 1 to 2 days after their last dose of FXa inhibitor.

Outcomes to assess response to treatment deemed important by the clinician groups included achievement of excellent or good hemostatic efficacy, thrombotic events, decreased mortality, decrease in hemoglobin or hematocrit by less than 20% compared to baseline, improvement of symptoms, reduction in hematoma expansion in ICH, survival to discharge, disability score on discharge, and measurement of anti-FXa levels before and after drug administration (not widely available). They noted that length of hospital stay may also be a surrogate marker. The clinical groups noted that criteria for discontinuation would include unexpected allergic or infusion reactions or thromboembolic events.

The clinical groups also supported the use of andexanet alfa in the hospital setting including the emergency department, critical care unit, or operating room, tertiary trauma centres and stroke or neurosurgical referral centres, by specialists such as in emergency medicine, anesthesiologists, and internal medicine or surgical



specialists depending on the site of bleeding (e.g., neurologist or neurosurgeon for intracranial hemorrhage or gastroenterologists for gastrointestinal bleeding).

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH Reimbursement Review process. The following were identified as key factors that could potentially affect the implementation of a CADTH recommendation for and examet alfa:

- considerations for initiation of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of Studies

One pivotal phase IIIb/IV, open-label, single-arm trial (ANNEXA-4, N = 477) was included in the sponsor's submission. The study assessed change in anti-FXa activity from baseline and whether hemostatic efficacy was reached with andexanet alfa treatment in adult patients with acute major bleeding while receiving FXa inhibitor treatment. Patients with features of severe ICH (i.e., Glasgow Coma Scale [GCS] score less than 7 or intracerebral hematoma volume above 60 cc) and those with expected survival of less than 1 month were excluded from the study. Percent change from baseline in anti-FXa activity to on-treatment nadir and achievement of hemostatic efficacy at 12 hours postinfusion (coprimary end points), rebleeding, use of non-study-prescribed blood products and/or hemostatic agents, red blood cell (RBC) transfusion, change in neurologic status scores in patients with ICH (exploratory end points), and mortality (safety end point) were assessed. At baseline, patients had a mean age of 77.9 (SD = 10.66) years; 54.3% identified as being male while 45.7% identified as female. The majority of patients indicated they were white (86.8%), while 6.1% of patients identified as being Black and 5.2% identified as being of other race. Most patients received apixaban (51.4%) or rivaroxaban (36.5%) anticoagulation, with the remaining patients receiving edoxaban (7.5%) or enoxaparin (4.6%), and had ICH bleed (69.0%) or GI bleed (22.9%).

Two pivotal phase III, double-blind RCTs (ANNEXA-A, N = 68; ANNEXA-R, N = 80) comparing the efficacy of andexanet alfa versus placebo in reversing apixaban (ANNEXA-A) or rivaroxaban (ANNEXA-R) anticoagulation in healthy volunteers were submitted by the sponsor. Because the study populations do not align with the indicated population of andexanet alfa, they were considered to have limited relevance to this review by the CADTH review team in consultation with the clinical experts and are not summarized here.



Efficacy Results: ANNEXA-4

All efficacy end points were assessed in the efficacy population, except for rebleeding, use of non-studyprescribed blood products and hemostatic agents, and RBC transfusion which were assessed in the safety population. The efficacy population consisted of 347 of 477 enrolled patients (73%) who met the International Society on Thrombosis and Haemostasis (ISTH)-based criteria for bleeding severity and with baseline anti-FXa activity greater than the prespecified threshold (at least 75 ng/mL for patients treated with apixaban or rivaroxaban, at least 40 ng/mL for patients treated with edoxaban, or at least 0.25 IU/mL for patients treated with enoxaparin). The safety population consisted of all 477 enrolled patients who received andexanet alfa treatment.

Change From Baseline in Anti-FXa Activity (Coprimary End Point)

In the primary analysis, the median percent change from baseline in anti-FXa activity at on-treatment nadir (i.e., minimum value between end of bolus and end of infusion) was -93.3% (95% Cl, -94.2% to -92.5%) for patients treated with apixaban and -94.1% (95% Cl, -95.1% to -93.0%) for patients treated with rivaroxaban in the efficacy population. Subgroup analysis showed results consistent with the primary analysis across bleed types; however, subgroup analysis by estimated glomerular filtration rate (eGFR) is not available. Results in the safety population showed results consistent with the primary analyses.

Achievement of Hemostatic Efficacy (Coprimary End Point)

In the primary analysis of hemostatic efficacy, 80.0% (95% CI, 75.3% to 84.1%) of the efficacy population achieved "good" or "excellent" hemostatic efficacy. The lower bound of the 95% CI was greater than the predefined threshold of 50%, which is sufficient to reject the null hypothesis at the 0.05 level. Three sensitivity analyses were conducted to assess the effect of including patients rated as "nonevaluable for administrative reason," among all patients with available baseline anti-FXa levels, and in patients otherwise evaluable but with a baseline anti-FXa level below the prespecified threshold. Results of all sensitivity analyses and estimates within the subgroups of interest (by bleed type and eGFR) were consistent with primary analysis.

Results of hemostatic efficacy analysis in patients with ICH who have high risk of hematoma expansion (exploratory end point) were consistent with the whole ICH subpopulation and the efficacy population.

Rebleeding, Use of Non–Study-Prescribed Blood Products and Hemostatic Agents, and RBC Transfusion (Exploratory End Points)

In the safety population, rebleeding as adjudicated by the end point adjudication committee occurred in 1 (0.4%) of 264 assessed patients, 24.7% of patients received non-study-prescribed blood products and/or hemostatic agents between the start of andexanet alfa treatment and 12 hours after the end of the infusion and 19.5% (95% CI, 16.0% to 23.3%) of patients received RBC transfusion.

Modified Rankin Scale, National Institutes of Health Stroke Scale, and GCS Scores (Exploratory End Point)

The modified Rankin scale (mRS) is an assessment that describes "global disability" on a scale from 0 (perfect health without symptoms) to 6 (death). The proportions of patients with ICH in the efficacy



population who had an mRS score of 0 to 2 at baseline, 1 hour posttreatment, 12 hours posttreatment, and day 30 were 32.2% (95% CI, 26.4% to 38.5%), 22.6% (95% CI, 16.1% to 30.3%), 23.4% (95% CI, 16.8% to 31.2%), and 35.9% (95% CI, 29.6% to 42.7%), respectively.

The National Institutes of Health Stroke Scale (NIHSS) is an assessment that categorizes neurologic deficits after stroke as having no stroke symptoms (score of 0), minor stroke (score of 1 to 4), moderate stroke (scores of 5 to 15), moderate to severe stroke (scores of 16 to 20), and severe stroke (scores of 21 to 42). An overall change of 4 points or more is considered clinically relevant. The mean change from baseline in the NIHSS score at 1 hour posttreatment, 12 hours posttreatment, and day 30 was 0.4 (SD = 2.66), 1.0 (SD = 3.58), and -1.0 (SD = 4.96), respectively, in patients with ICH.

The GCS describes the level of consciousness (i.e., eye opening, verbal response, best motor response) in acute medical and trauma patients on a scale from 3 (deep coma) to 15 (normal) The mean change from baseline in GCS score at 1 hour posttreatment, 12 hours posttreatment, and day 30 was -0.4 (SD = 1.69), -0.6 (SD = 2.06), and 0.2 (SD = 2.23), respectively, in patients with ICH.

ICU Admission, Hospital Length of Stay, HRQoL (Other Outcomes of Interest to This Review) Intensive care unit (ICU) admissions and HRQoL were not measured. Length of hospital stay was not an efficacy outcome of the trials, but the median was reported to be 10.9 days in the safety population.

Harms Results: ANNEXA-4

Treatment-emergent adverse events (TEAEs) were reported in 72.5% of patients. The most common TEAEs were urinary traction infection (10.5%) and pneumonia (8.2%). Serious TEAEs were reported in 41.9% of patients, and the most common were pneumonia (4.2%), respiratory failure (2.5%), and ischemic stroke (2.1%). Four (0.8%) patients discontinued treatment due to TEAEs. Death occurred in 17.0% of patients.

Thromboembolic event was reported in 10.5% of patients, including cerebrovascular accident (4.6%), deep vein thrombosis (2.5%), myocardial infarction (1.9%), pulmonary embolism (1.0%), and transient ischemic attack (0.4%). Infusion-related reaction was reported in 2 (0.4%) patients. There was no report of neutralizing antibodies to FX, FXa, or andexanet alfa.

Critical Appraisal: ANNEXA-4

An important limitation was the noncomparative study design, which precludes conclusions about whether any observed effect could be attributed to andexanet alfa alone due to lack of consideration for potential confounders. The open-label study design could increase uncertainty in neurologic status outcomes (mRS, NIHSS, and GCS) due to potential reporting bias given that these scales involve subjective assessment of clinical parameters by the investigators, although the presence and extent of such bias could not be determined. All end points other than the coprimary end points were exploratory, which precludes definitive conclusions to be drawn from these analyses. Approximately 20% of patients were excluded from the primary efficacy analyses due to baseline anti-FXa activity below the prespecified threshold. The impact of excluding such patients from neurologic status outcomes is unclear because no sensitivity analyses were conducted. There is also potential attrition bias in neurologic status outcomes because there is a large amount of missing data, although the direction and extent of any bias are unclear.



The generalizability of the study population is limited by the exclusion of patients with severe ICH (GCS score less than 7, estimated ICH volume greater than 60 cc) and an expected survival less than 1 month, as well as a younger patient population, which were suggestive of a study population with better prognosis than in general clinical practice based on clinical expert input. Patients without major bleeding but who require FXa inhibitor reversal for emergency surgery and are expected to be reasonable candidates for andexanet alfa according to clinical expert input were not included in the study. The treatment effects in these patients are unknown. According to the clinical experts, the coprimary end points were not as clinically relevant and meaningful to patients and clinicians compared with clinical outcomes such as mortality, morbidity, and functional status, which were assessed as exploratory end points in the study. They noted that anti-FXa activity is not routinely measured in clinical practice during FXa inhibitor reversal treatment nor widely available. Although hemostatic efficacy is a commonly measured outcome in clinical studies of reversal treatments for major bleeding, it is not a patient-important outcome. The absence of direct comparative evidence between andexanet alfa with PCC, the most relevant comparator of andexanet alfa per clinical expert input, represents a gap in evidence.

Studies Addressing Gaps in the Pivotal and RCT Evidence

Weighted Comparative Observational Evidence

Description of Studies

In the absence of direct comparative evidence between andexanet alfa and PCC, the sponsor submitted 3 published observational analyses assessing the comparative effect of andexanet alfa and PCC in patients with major bleeding while receiving apixaban or rivaroxaban anticoagulation based on individual patient's data from the ANNEXA-4 trial and 3 observational cohort studies of PCC in real-world clinical practice, including the ORal ANticoagulant aGEnt-associated bleeding events reporting system (ORANGE) study, the Hartford HealthCare study (HHCS), and the German-Wide Multicenter Analysis of Oral Anticoagulant-Associated Intracerebral Hemorrhage - Part Two (RETRACE-II) study.

The ANNEXA-4 versus ORANGE analysis was conducted in patients with any bleed type using propensity score matching. The ANNEXA-4 versus HHCS analysis was conducted in patients with ICH using propensity score overlap weighting. The ANNEXA-4 versus HHCS analysis was conducted in patients with atraumatic ICH based on a propensity score model using the inverse probability treatment weighting approach. Outcomes assessed included 30-day mortality, in-hospital mortality, hemostatic efficacy (or hematoma expansion, which reflects failure to achieve hemostatic efficacy in ICH), mRS score at discharge or at day 30, and thrombotic event at day 5.

ANNEXA-4 Versus ORANGE (Any Bleed Type)

The analysis included 322 patients in the andexanet alfa cohort from the ANNEXA-4 trial and the effective sample size of the PCC cohort from the ORANGE study, which was 88 after propensity score matching. Results of the 30-day mortality analysis estimated results in favour of andexanet alfa in the whole cohort (andexanet alfa versus PCC: relative risk = 0.43, 95% CI, 0.29 to 0.63) and ICH cohort (relative risk = 0.31; 95% CI, 0.20 to 0.48). A reduced risk of 30-day mortality in the GI cohort (relative risk = 0.49; 95% CI, 0.21 to



1.16) and an increased risk with other bleeds (relative risk = 1.29, 95% CI, 0.17 to 9.55) with and exanet alfa were shown, but the results did not show a significant difference between the interventions. Harms were not assessed in this study.

ANNEXA-4 Versus HHCS (ICH Only)

The analysis included 107 patients in the andexanet alfa cohort from the ANNEXA-4 trial and 95 patients in the 4-factor PCC (4F-PCC) cohort from the HHCS study. After weighting, results were in favour of andexanet alfa over 4F-PCC with respect to hemostatic efficacy (weighted odds ratio [OR] = 2.733; 95% CI, 1.163 to 6.421) and 30-day all-cause mortality (weighted OR = 0.355; 95% CI, 0.129 to 0.977). Thromboembolism occurred in 2 (1.9%) patients in the andexanet alfa cohort and 0 patients in the 4F-PCC cohort within 5 days posttreatment.

ANNEXA-4 Versus RETRACE-II (Atraumatic ICH Only)

In the subanalysis of patients receiving and exanet alfa (n = 85) or PCC (n = 73), after weighting, results were in favour of and exanet alfa over PCC with respect to hematoma expansion (risk ratio = 0.443; 95% CI, 0.223 to 0.878) but did not show a difference in in-hospital mortality between the interventions in in-hospital mortality (hazard ratio [HR] = 0.852; 95% CI, 0.397 to 1.827) and mRS score at discharge or 30 days (mean difference = -0.517, 95% CI, -1.146 to 0.113). Harms were not assessed in this study.

Critical Appraisal

Several important limitations were common to the 3 weighted comparative analyses, which preclude definitive conclusions regarding the comparative efficacy of andexanet alfa and PCC. This includes a risk of selection bias for studies included in the analyses given the absence of a systematic literature review or due to lack of reporting in the methods of a systematic literature review. Furthermore, there was evidence of heterogeneity in the inclusion criteria and exclusion criteria between included studies (e.g., definition of major bleeding, recent history of blood product, ICH severity, recent history of thromboembolism, expected survival). There was also potential residual confounding due to inadequate adjustment for prognostic factors or treatment effect modifiers, specifically the studies adjusted for covariates inconsistently and resulting estimates varied widely. The comparative efficacy of andexanet alfa and PCC for mental status, ICU admission, length of hospital stay, and HRQoL, all of which were of interest to the stakeholders, were not assessed.

Comparative Observational Evidence

Description of Studies

In the absence of direct comparative evidence between andexanet alfa and PCC, the sponsor submitted 6 studies summarizing the comparative evidence of andexanet alfa versus PCC in real-world clinical practice. All 6 studies were multicentre, retrospective chart audits conducted in the US. The patient populations for the studies by Coleman et al. (2021), Dobesh et al. (2022), Fermann et al. (2022), and Dobesh et al. (2023) were sourced from the US Hospital Chart Audit, while the populations for the Sutton et al. (2022) and Sutton et al. (2023) studies were sourced from the US Veterans Affairs databases. In all studies, data were captured from electronic medical records. The eligible patient population was adult patients aged 18 years and older



hospitalized for FXa inhibitor-related bleeding. Patients were identified via electronic medical records using the *International Classification of Diseases-Tenth Revision (ICD-10)* billing codes, or administrative claims and pharmacy dispensation information form the Veterans Affairs Informatic and Computing Infrastructure. Outcomes of interest were stratified by bleed type for each reversal or replacement agent (i.e., andexanet alfa and PPC), and included in-hospital mortality, in-hospital 30-day mortality, length of hospital stay, and ICU length of stay.

Study sample size ranged from 255 to 4,395 patients. The average age of patients across the studies ranged from 65.0 years to 70.1 years. The most commonly used FXa inhibitors documented were apixaban (40% to 84.0%) and rivaroxaban (14.7% to 56%). Exposure to andexanet alfa ranged from 11.3% to 48.8% across the studies, while exposure to 4F-PCC ranged from 24.2% to 80.1%.

In-Hospital Mortality

In-hospital mortality for those treated with andexanet alfa was 4% in the Coleman et al. (2021) study; 6% in the Dobesh et al. (2022) and (2023) studies, and 10.6% in the Sutton et al. (2022) study. In-hospital mortality for those treated with 4F-PCC was 10% in the Coleman et al. (2021) study; 8% in Dobesh et al. (2022) study, 10.6% in the Dobesh et al. (2023) study, and 25.3% in the Sutton et al. (2022) study. In the Coleman et al. (2021) study, in-hospital mortality was 11% in those treated with fresh frozen plasma (FFP). In the Fermann et al. (2022) study, in-hospital mortality among patients treated with andexanet alfa was approximately 2.5% among patients with GI bleed and ranged between 9.8% to 16.8% among patients with ICH bleeds. In patients treated with 4F-PCC, in-hospital mortality ranged from 3.2% to 6.0% among patients with GI bleeds and 14.5% to 24.0% in patients with ICH bleeds.

In the adjusted analysis performed by Dobesh et al. (2022), treatment with andexanet alfa was associated with a lower likelihood of death compared with treatment with 4F-PPC (OR = 0.69; 95% CI, 0.49 to 0.98). In the Dobesh et al. (2023) study, treatment with andexanet alfa was also associated with a lower likelihood of in-hospital mortality compared with 4F-PCC across all bleeds (OR = 0.50; 95% CI, 0.39 to 0.65), GI bleeds (OR = 0.49; 95% CI, 0.29 to 0.81) and ICH bleeds (OR = 0.55; 95% CI, 0.39 to 0.76). In the adjusted analysis performed by Fermann et al. (2022), treatment with andexanet alfa was associated with lower odds of in-hospital mortality compared with treatment with 4F-PPC (OR = 0.67; 95% CI, 0.48 to 0.94). In the Sutton et al. (2022) study, treatment with andexanet alfa was associated with a lower hazard of in-hospital mortality compared with treatment with 4F-PPC (IR = 0.31; 95% CI, 0.14 to 0.71).

Thirty-Day Hospital Mortality

Thirty-day hospital mortality was explored in the Sutton et al. (2022) study only. The 30-day mortality rate was 20.0% and 32.4% in patients treated with andexanet alfa and 4F-PCC, respectively. Treatment with andexanet alfa was associated with a lower hazard of 30-day mortality compared with treatment with 4F-PCC (HR = 0.54; 95% CI, 0.30 to 0.98).

ICU Length of Stay

For patients who received and exanet alfa, overall median ICU length of stay was 2 days interquartile range [IQR], 1 to 4 days) in the study by Coleman et al. (2021), 2 days (IQR, 3 days) in the study by Dobesh et al.



(2022), and 1 day (IQR, 0 to 4 days) day in the study by Sutton et al. (2022). In the Sutton et al. (2023) study, the mean ICU length of stay was 4.0 days (SD = 7.1 days). For patients who received 4F-PCC, median ICU stay was 3 days (IQR, 2 to 5 days) in the study by Coleman et al. (2021), 2 days (IQR, 3 days) in the study by Dobesh et al. (2022), and 2 days (IQR, 0 to 5 days) in the study by Sutton et al. (2022). In the Sutton et al. (2023) study, the mean length of ICU stay was 5.0 days (SD = 8.6 days) days. In the study by Coleman et al. (2021), the overall median ICU stay for patients who were treated with FFP was 3 days (IQR, 2 to 5 days).

Hospital Length of Stay

For patients who received andexanet alfa, median hospital length of stay was 5 (IQR, 3 to 6) days in the Coleman et al. (2021) study, 5 days (IQR, 5 days) in the Dobesh et al. (2022) study, and 6 days (IQR, 3 to 10 days) in the Sutton et al. (2022) study. In the Sutton et al. (2023) study, the mean length of stay was 11.3 days (SD = 22.8 days), whereas in the Fermann et al. (2022) study, the mean length of stay ranged from 6.4 days (SD = 4.2 days) to 8.9 days (SD = 6.2 days). For patients who received 4F-PCC, median hospital stay was 5 days (IQR, 4 to 7 days) in the Coleman et al. (2021) study, 5 days (IQR, 5 days) in the Dobesh et al. (2022) study, and 7 days (IQR, 4 to 18 days) in the Sutton et al. (2022) study. In the Sutton et al. (2023) study, the mean length of hospital stay was 12.2 days (SD = 17.5 days), whereas in the Fermann et al. (2022) study, the mean length of hospital stay ranged from 6.3 days (SD = 4.1 days) to 8.3 days (SD = 6.2 days) days. In the Coleman et al. (2021) study, the median length of hospital stay for patients who were treated with FFP was 5 days (IQR, 4 to 8 days).

Critical Appraisal

The nonrandomized comparison of the 6 real-world evidence studies makes interpretation of the efficacy of andexanet alfa compared with 4F-PCC and other reversal or replacement agents challenging. The retrospective nature of the studies means that data collection and entry were dependent on personnel at each medical institution, thus the quality and accuracy of data were dependent on the quality and accuracy of routine documentation. Moreover, the use of *ICD-10* codes for the purpose of clinical research are associated with several limitations. The influence of important patient-level factors (e.g., advanced directives, thrombotic complications after reversal agent administration) — which could not be ascertained from medical records — on the treatment effect of andexanet alfa and 4F-PCC could not be ruled out. Although the studies by Dobesh et al. (2022), Dobesh et al. (2023), Fermann et al. (2022), and Sutton et al. (2022) used covariate adjustment, the possibility of selection bias or residual confounding cannot be ruled out due to the nonrandomized nature of the study designs and a lack of comprehensive literature to assess the relevant confounding variables. As a result, there is uncertainty around the comparative treatment effects of andexanet alfa compared with 4F-PCC due to selection bias and unmeasured and residual confounding that cannot be entirely ruled out.



Economic Evidence

Table 1: Cost and Cost-Effectiveness

Component	Description
Type of economic	Cost-utility analysis
evaluation	Decision tree and Markov model
Target population	Adult patients treated with FXa inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding
Treatment	Andexanet alfa (Ondexxya)
Dose regimen	Andexanet alfa is administered as an IV bolus, with a target rate of 30 mg per minute, followed by continuous infusion for up to 120 minutes. The recommended dosage of andexanet alfa varies between 5 (low dose) to 9 (high dose) 200 mg vials, depending on the rivaroxaban or apixaban dose.
Submitted price	\$4,590.00 per 20 mL vial
Treatment cost	Average total treatment cost per patient is \$26,787 (weighted cost: low dose = \$18,153 and high dose = \$8,634)
Comparators	PCC including human prothrombin complexes Beriplex and Octaplex
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (22 years)
Key data source	 Indirect treatment comparison using patient-level data from single-arm ANNEXA-4 and UK Oral Anticoagulant Agent-Associated Bleeding Events Reporting System (ORANGE) studies to evaluate efficacy.
	 Additional sources include 2 retrospective studies based on real-world evidence and ANNEXA-4 and RETRACE-II studies for long-term mortality.
Key limitations	 Long-term survival for patients with ICH using andexanet alfa is overestimated. Results from the ANNEXA-4 vs. RETRACE-II trial were used to inform the distribution of mRS scores in the ICH survivor clinical population. Feedback obtained from clinical experts consulted by CADTH highlighted that they did not expect a difference in survival or mRS distribution for patients prescribed andexanet alfa compared with those prescribed PCC. The CADTH clinical review notes that the mean difference for mRS at discharge from the ANNEXA-4 vs. RETRACE-II trial was not statistically significant and there is insufficient evidence to justify different mRS distributions between the 2 treatment groups.
	 Comparative clinical effectiveness of andexanet alfa is uncertain. In the absence of direct comparative evidence, the sponsor assumed a 30-day mortality relative risk of 0.43 (95% CI, 0.29 to 0.63) for andexanet alfa. The CADTH clinical review appraisal of the sponsor-submitted ITC noted that several limitations preclude definitive conclusions regarding the comparative efficacy of andexanet alfa and PCC.
	• Comparator pricing is based on publicly available prices. The sponsor's analysis estimated of the cost of PCC using published list prices for Beriplex and Octaplex in the PMPRB basket of 11 comparator countries. Unit prices for Beriplex and Octaplex were only available in 2 and 3 of the 11 countries, respectively. The price of PCC (Beriplex and Octaplex) does not reflect any confidential pricing that may have been negotiated by the CBS; therefore, the estimated drug acquisition costs for PCC are uncertain.



Component	Description
CADTH reanalysis results	 CADTH revised the sponsor's model by setting ICH utilities to be equal in both the andexanet alfa and PCC treatment groups. Additionally, mRS distributions were set to be equal between treatment groups.
	 CADTH's base case: ICER = \$61,865 per QALY gained (incremental cost = \$36,604; incremental QALYs = 0.592). A price reduction of at least 27% would be required to achieve cost-effectiveness at a willingness-to-pay threshold of \$50,000 per QALY gained.

CBS = Canadian Blood Service; CI = confidence interval; FXa = factor Xa; ICER = incremental cost-effectiveness ratio; ICH = intracranial hemorrhage; ITC = indirect treatment comparison; mRS = modified Rankin scale; PCC = prothrombin complex concentrate; PMPRB = Patented Medicine Prices Review Board; QALY = quality-adjusted life-year; RR = relative risk.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: Use of a claims-based approach to estimate market size introduced uncertainty, the proportion of patients eligible for reversal is uncertain and may be overestimated, the cost of treatments paid by CBS is confidential and uncertain, and the market uptake of andexanet alfa is overestimated according to feedback obtained by CADTH from clinical experts.

CADTH did not conduct a base-case analysis because the sponsor's submission provided adequate presentation of the budget impact for andexanet alfa. The sponsor's base case suggested a 3-year budgetary impact of \$106,997,869.

CADTH presented a series of scenario analyses to test the impact of alternative assumptions on the estimated budget impact. Budget impact was sensitive to assumptions about the size of the eligible population, the proportion of patients receiving high- or low-dose and exanet alfa, and the price of and exanet alfa.

Request for Reconsideration

The sponsor filed a Request for Reconsideration for the draft recommendation for adult patients treated with FXa inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. In their request, the sponsor requested that CPEC reconsider their review of andexanet alfa based on the following:

- The sponsor believes that CPEC did not consider life-threatening bleeds associated with FXa inhibitors as an area with significant unmet need. In their opinion, CPEC mischaracterized the current clinical context and thus underestimated the unmet need that exists in life-threatening bleeds associated with FXa inhibitors.
- The sponsor believes that CPEC is holding and exanct alfa to a subjective evidence standard by giving undue weight to methodological limitations of the submitted clinical trial, indirect treatment comparisons, and real-world evidence studies, while showing preference for the lower-quality evidence of PCC, including naive comparisons and clinical experience.
- The sponsor believes that the purpose of the anti-FXa activity coprimary end point is misunderstood.



In the meeting to discuss the sponsor's Request for Reconsideration, CPEC considered the following information:

- feedback from the sponsor
- information from the initial submission related to the issues identified by the sponsor
- feedback from 2 clinical experts with expertise in the diagnosing and treating of patients with acute major bleeding
- feedback from the public drug plans
- feedback from 5 clinician groups: the Dalhousie Emergency Medicine group, the McMaster University academic faculty in hematology and thromboembolism, Canadian Stroke Consortium, the ER Journal Club in the Greater Toronto Area, and Thrombosis Canada
- feedback from 1 patient group: CanVECTOR.

All stakeholder feedback received in response to the draft recommendation from patient and clinician groups and the public drug programs is available on the CADTH website.

CPEC Information

Members of the Committee: Initial Meeting

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Irene Sadek, Dr. Andrew Shih, and Dr. Peter Zed

Initial meeting date: July 26, 2023

Regrets: 3 expert committee members did not attend.

Conflicts of interest: 1 expert committee member did not participate due to considerations of conflict of interest.

Members of the Committee: Reconsideration Meeting

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Andrew Shih, Dr. Edward Xie, and Dr. Peter Zed

Reconsideration meeting date: November 23, 2023

Regrets: 2 expert committee members did not attend.

Conflicts of interest: 1 expert committee member did not participate due to considerations of conflict of interest.



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