Andexanet alfa in the treatment of acute major bleeding related to apixaban and rivaroxaban: a profile of its use in the USA

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Abstract
Andexanet alfa (Andexxa®), a first-in-class recombinant modified factor Xa protein, is currently the only specific agent available to reverse life-threatening or uncontrolled bleeding with the factor Xa inhibitors apixaban and rivaroxaban. Andexanet alfa acts as a decoy and competes with endogenous factor Xa to bind factor Xa inhibitors, thereby reversing the anticoagulant effects of factor Xa inhibitors, and restoring the activity of endogenous factor Xa. In adults with major bleeding associated with the use of apixaban or rivaroxaban, intravenous administration of andexanet alfa effectively and rapidly reduces anti-factor Xa levels, with reduced levels being maintained during continued treatment. The tolerability profile of andexanet alfa in patients is generally similar to that reported of other approved anticoagulation reversal agents. With the known increased risk of thromboembolic events following andexanet alfa treatment, anticoagulant therapy should be resumed as soon as medically appropriate.

Adis evaluation of andexanet alfa in the treatment of apixaban- and rivaroxaban-associated major bleeding

| Currently the only available specific reversal agent for the treatment of apixaban- and rivaroxaban-associated bleeding |
| Rapidly reverses the anticoagulant effects of apixaban and rivaroxaban, and provides sustained reductions in anti-factor Xa activity |
| Not indicated for the treatment of bleeding event related to any other factor Xa inhibitors |
| Associated with a risk of thromboembolic events; resume anticoagulation therapy as soon as medically appropriate |

What is the rationale for developing andexanet alfa as a reversal agent for apixaban and rivaroxaban?

Thromboembolism is a leading cause of preventable hospital death, with elderly patients being at a particularly high risk [1]. Warfarin (an oral vitamin K antagonist) has long been the mainstay for the treatment and prevention of thromboembolism, as well as for stroke prevention in atrial fibrillation. However, warfarin has several limitations, including its narrow therapeutic index, the need for frequent blood testing, and the potential for multiple drug interactions [1]. With the emergence of more convenient anticoagulants, such as direct thrombin inhibitors (e.g. dabigatran) and factor Xa inhibitors (e.g. apixaban, rivaroxaban, edoxaban, and betrixaban), these newer anticoagulants are increasingly being used in lieu of warfarin [1–3]. Direct thrombin and factor Xa inhibitors provide anticoagulant efficacy similar to that of warfarin. Moreover, these anticoagulants have many advantages over warfarin, including their wide therapeutic index, fixed dosing regimen without the need for frequent blood testing, rapid onset of action, and relatively low risk of drug interactions [1–3].

The major safety concern with anticoagulants is bleeding [1, 2, 4]. Although direct thrombin and factor Xa inhibitors show a better bleeding risk profile (e.g. a lower incidence of intracranial bleeding) than warfarin, all anticoagulants are
associated with the risk of major hemorrhagic complications [3–6]. A rapid reversal of the anticoagulant effect is desirable as anticoagulant-associated hemorrhagic complications often lead to substantial use of healthcare resources [1, 2, 5]. Specific reversal agents for warfarin [e.g. prothrombin complex concentrates (PCC) and fresh frozen plasma (FFP)] and dabigatran (i.e. idarucizumab) are available for the management of major hemorrhagic complications [6]. Unlike warfarin and dabigatran, however, factor Xa inhibitor-associated major bleeding events have been managed with nonspecific reversal agents (e.g. PCC, FFP, and activated recombinant factor VIIa) due to lack of a specific reversal agent for factor Xa inhibitors [3, 6]. The development of such a specific reversal agent may potentially promote the more widespread use of factor Xa inhibitors [6].

Andexanet alfa [coagulation factor Xa (recombinant), inactivated-zhzo; Andexxa®] is a first-in-class recombinant modified factor Xa protein that has been developed with the goal of becoming an agent to reverse anticoagulant effects of direct and indirect factor Xa inhibitors [7]. This review focuses on the use of intravenously administered andexanet alfa as a specific reversal agent for apixaban and rivaroxaban as approved in the USA [8].

How does andexanet alfa work?

Andexanet alfa is a genetically modified variant of human factor Xa protein that acts as a decoy and competes with endogenous factor Xa to bind factor Xa inhibitors [7, 9]. The affinity of andexanet alfa for factor Xa inhibitors is thought to be similar to that seen with endogenous factor Xa; however, it is not catalytically active, and is not capable of assembling into the prothrombinase complex [9]. Andexanet alfa sequesters factor Xa inhibitors and reverses anticoagulant effects, whilst showing minimal intrinsic anticoagulant or procoagulant properties, [7].

Through this mechanism of action, andexanet alfa dose-dependently reversed the anti-factor Xa activity of apixaban and rivaroxaban in vitro, as well as in various animal models of bleeding [10–12]. Likewise, in a number of dose-ranging phase 2 trials in healthy volunteers who were pre-treated with apixaban [13] or rivaroxaban [14], andexanet alfa dose-dependently reversed the anticoagulation effects of these factor Xa inhibitors. Relative to placebo, andexanet alfa rapidly (≤ 2 min after administration) decreased unbound plasma concentrations of apixaban and rivaroxaban, reduced anti-factor Xa activity, and restored normal thrombin generation [13, 14]. Anti-factor Xa levels decreased during andexanet alfa treatment, with levels returning to placebo levels ≈ 2 h after end of treatment [13, 14], which is consistent with the short pharmacodynamic half-life of andexanet alfa of ≈ 1 h [15].

Andexanet alfa may also modulate tissue factor-initiated thrombin generation by binding to and inhibiting the activity of tissue factor pathway inhibitor, an endogenous inhibitor of factor Xa [8, 16]. In vitro, andexanet alfa transiently increased markers of thrombin formation (i.e. prothrombin 1 and 2) and fibrinolysis (i.e. plasmin-antiplasmin complexes and D-dimer), with such transient increase in coagulation markers also being consistently seen in clinical studies in healthy volunteers [16].

For whom is andexanet alfa indicated?

Andexanet alfa is approved in the USA for use in adults treated with rivaroxaban and apixaban, when reversal of anticoagulant effects is required in the event of life-threatening or uncontrolled bleeding [8]. The dose of andexanet alfa administered intravenously is based on the specific FXa inhibitor associated with the bleeding event (i.e. apixaban or rivaroxaban), the dose of FXa inhibitor received (i.e. ≤ 5 mg or > 5 mg/unknown for apixaban, and ≤ 10 mg or > 10 mg/unknown for rivaroxaban), and the time since the last dose of the FXa inhibitor (< 8 h/unknown or ≥ 8 h) [8]. See Table 1 and local prescribing information for further information on the use of andexanet alfa.

What is the efficacy of andexanet alfa as a reversal agent for apixaban and rivaroxaban?

In healthy older adult volunteers

Andexanet alfa was effective in reversing the anticoagulant effects of apixaban and rivaroxaban in healthy volunteers aged 50–75 years in two randomized, double-blind, placebo-controlled phase 3 trials (ANNEXA-A and ANNEXA-R) [15]. In ANNEXA-A, volunteers received oral apixaban 5 mg twice daily for 3.5 days; in ANNEXA-R, volunteers received oral rivaroxaban 20 mg once daily for 4 days. Once steady-state plasma levels of apixaban and rivaroxaban were achieved on day 4, those enrolled in ANNEXA-A and ANNEXA-R were randomized to andexanet alfa or placebo [15]. In both trials, andexanet alfa was administered as an intravenous bolus (part 1), or as an intravenous bolus followed by a continuous infusion (part 2). The discussion focuses on the efficacy of andexanet alfa in part 2, in which the drug was administered using the approved infusion regimen in the USA (Table 2) [8].

In ANNEXA-A and ANNEXA-R, andexanet alfa effectively reversed the anticoagulant activity of apixaban and rivaroxaban, with significantly (p < 0.001) greater reductions from baseline to nadir in anti-factor Xa activity with...
andexanet alfa relative to with placebo (primary endpoint; Table 2) [15]. Andexanet alfa rapidly reduced anti-factor Xa activity within 2–5 min of administration, with the reduction sustained during treatment. Furthermore, all andexanet alfa recipients experienced at least 80% reversal of anti-factor Xa activity (Table 2); anti-factor Xa levels returned to placebo levels 1–2 h after the end of the infusion [15].

Within 2–5 min of administration, andexanet alfa also significantly ($p < 0.001$) decreased unbound concentrations of apixaban and rivaroxaban compared with placebo (Table 2) [15]. This reduction was sustained during andexanet alfa treatment, and unbound concentrations of apixaban and rivaroxaban returned to placebo levels within 1–3 h after the infusion. Moreover, thrombin generation was restored in a significantly higher proportion of andexanet alfa than placebo recipients (Table 2). Prothrombin fragments 1 and 2, thrombin-antithrombin complex, and d-dimer were transiently elevated in andexanet alfa recipients; within 24–72 h, these levels returned to the normal range [15].

### In patients with acute major bleeding

Andexanet alfa also effectively reversed the anticoagulant effects of factor Xa inhibitors in an open-label, multinational phase 3b/4 trial (ANNEXA-4) [17, 18]. Enrolled patients were aged ≥ 18 years, had a high burden of major cardiovascular disease, and presented with acute major bleeding after taking the last dose of a factor Xa inhibitors ≤ 18 h previously [17]. This section focuses on the efficacy of andexanet alfa in managing apixaban- and rivaroxaban-related major bleeding events in ANNEXA-4 [8].

Patients received low- or high-dose regimens of andexanet alfa depending on the strength and the timing of the last dose of apixaban and rivaroxaban, which is consistent with the approved dosing regimens of andexanet alfa in the USA (Table 1) [8]. A pharmacokinetic/pharmacodynamic model of andexanet alfa based on data from healthy volunteers further supported the selected andexanet alfa dosing regimen for this population [19].
Three interim descriptive preliminary analyses of ANNEXA-4 (after 67 [17], 185 [8], and 227 [18] patients were treated) evaluated the efficacy of andexanet alfa in factor Xa inhibitor-treated patients who presented with acute major bleeding [8, 17, 18]. In the most recent interim analysis of ANNEXA-4 (cut-off date 20 October 2017; n = 227), the mean patient age was 77 years, and the mean time from presentation to the initiation of the andexanet alfa treatment was 4.7 h. Most enrolled patients had received anticoagulation treatment for atrial fibrillation (78%) and had intracranial bleeding (61%); 27% of patients had gastrointestinal bleeding [18].

The time course of reversal of anti-factor Xa activity in apixaban- and rivaroxaban-treated patients following andexanet alfa was consistent with that seen in healthy volunteers [8]. In the most recent interim analysis, andexanet alfa rapidly reduced the anti-factor Xa activity from baseline to nadir post-infusion by 91% in patients receiving apixaban (n = 105 evaluable) or rivaroxaban (n = 75 evaluable) [co-primary endpoint] [18]. The reduction of anti-factor Xa activity in the respective groups was sustained during andexanet alfa treatment, and decreased to 35% and 60% at 12 h after the end of the andexanet alfa infusion.

Of the 132 evaluable patients, 83% achieved excellent or good hemostasis 12 h after the andexanet alfa infusion [co-primary endpoint] [18], but the clinical significance of this finding has not been established [8].

### What is the tolerability of andexanet alfa?

Andexanet alfa was generally well tolerated in healthy older adults [15] and patients with factor Xa inhibitor-related bleeding, with a tolerability profile in patients generally similar to that reported for other approved anticoagulant reversal agents [18].

In a pooled analysis of clinical trials, the incidence of treatment-emergent adverse events (TEAEs) in 223 healthy volunteers receiving andexanet alfa was comparable to that in 94 volunteers receiving placebo (54 vs 57%); none of TEAEs were serious or severe [8]. The most common, and the only reaction occurring with a higher incidence with andexanet alfa than with placebo, was infusion-related reactions (18 vs 6% of volunteers). Infusion-related reactions (symptoms including flushing, feeling hot, cough, dysgeusia, and dyspnea) were of mild to moderate intensity, with most (90%) not requiring treatment. The only TEAEs reported in ≥ 5% of patients receiving andexanet alfa were urinary tract infections and pneumonia [8].

Treatment with andexanet alfa treatment has been associated with serious and life-threatening adverse events. The US prescribing information carries a black box warning regarding the increased risk of arterial and venous thromboembolic events, ischemic events (e.g. myocardial infarction, ischemic stroke), cardiac arrest, and sudden death, and precautions should be followed (Table 1) [8]. No thromboembolic events were reported in healthy volunteers [8].

In the most recent interim safety analysis of 227 patients in ANNEXA-4, by day 30 after andexanet alfa treatment, thrombotic events (stroke, deep-vein thrombosis and heart attack) had occurred in 24 patients (11%), and 27 patients (12%) had died, of which 11 deaths were due to cardiovascular reasons [18]. Of those who experienced thrombotic events, nine patients restarted anticoagulation therapy before thrombosis occurred [18].

The safety of andexanet alfa has not been evaluated in patients who have experienced thromboembolic events or disseminated intravascular coagulation (DIC) ≤ 2 weeks before the event of life-threatening bleeding, or those who have received PCC, recombinant factor VIIa, or whole blood products ≤ 7 days before the bleeding event [8].

| Outcomes | ANNEXA-A | ANNEXA-R |
|----------|----------|----------|
| No. of volunteers | 23 vs 8 | 26 vs 13 |
| Primary outcome | | |
| Mean change in anti-factor Xa activity from BL to nadir post-infusion (%) | − 92* vs − 33 | − 97* vs − 45 |
| Secondary outcomes | | |
| ≥ 80% reduction in anti-factor Xa activity (% of volunteers) | 100* vs 0 | 100* vs 0 |
| Mean change in unbound inhibitor concentration from BL to nadir (ng/mL) | − 6.5* vs − 3.0 | − 30.3* vs − 12.1 |
| Endogenous thrombin potential > LLN (% of volunteers) | 100* vs 25 | 100* vs 0 |

Prior to randomization, volunteers received apixaban (ANNEXA-A) or rivaroxaban (ANNEXA-R) until steady-state plasma levels were attained. Volunteers randomized to andexanet alfa received an IV bolus of 400 mg, then a continuous infusion of 4 mg/min for 120 min in (ANNEXA-A), or an IV bolus of 800 mg, then a continuous infusion of 8 mg/min for 120 min (ANNEXA-R).

*BL baseline, IV intravenous, LLN lower limit of baseline-derived normal range
*p < 0.001
Does andexanet alfa increase the risk of immunogenicity?

As with all therapeutic proteins, andexanet alfa has a potential for immunogenicity [8]. The pattern of antibody response in bleeding patients was similar to that in healthy volunteers. Among healthy volunteers who were treated with andexanet alfa, 17% of 145 volunteers had low titers of anti-andexanet alfa antibodies. In ANNEXA-4, 6% of 98 andexanet alfa recipients developed antibodies to andexanet alfa, with no patients developing neutralizing antibodies. To date, no antibodies with cross-reactivity to factor X or Xa have been detected in healthy subjects or bleeding patients [8].

What is the current clinical position of andexanet alfa?

All anticoagulants, including direct factor Xa inhibitors, are associated with clinically significant hemorrhagic complications [6]. The number of patients with major bleeding is likely to increase with the more frequent use of factor Xa inhibitors. Andexanet alfa is the first specific reversal agent for apixaban and rivaroxaban approved in the USA [8], fulfilling an unmet need for managing clinically significant hemorrhagic complications associated with apixaban or rivaroxaban.

Andexanet alfa effectively and rapidly reversed the anticoagulant effect of apixaban and rivaroxaban in patients with acute major bleeding [18].

Andexanet alfa was generally well tolerated in healthy older adults and patients with acute major bleeding, with its tolerability profile in patients generally similar to that reported for other anticoagulant reversal agents. For instance, in a clinical trial in warfarin-treated patients with acute major bleeding, 8% of 98 patients had thrombotic events after receiving four-factor-PCC to reverse the anticoagulant effects of warfarin [18]. As patients on anticoagulant therapy are predisposed to thrombotic events due to their underlying medical condition (e.g. atrial fibrillation) [8, 18], it is important to monitor andexanet alfa-treated patients for any symptoms or signs of any thromboembolic events, ischemic events, and cardiac arrest [8]. To reduce the risk of thromboembolic events, anticoagulant therapy should be restarted as soon as medically appropriate following andexanet alfa treatment [8].

Post-marketing and real-world studies, as well as further analysis of ANNEXA-4 with adequate number of patients for statistical power, would be helpful to establish the clinical significance of andexanet alfa in improvement of hemostasis [8], as well as determining the relationship between the reversal of anti-factor Xa activity and clinical hemostatic outcomes [17]. Subpopulation studies to establish the efficacy and safety of andexanet alfa in patients who have experienced thromboembolic events or DIC, or those who have received nonspecific reversal agents ≤ 2 weeks before the event of life-threatening bleeding, would also be of interest.

Data related to the cost effectiveness of andexanet alfa in the real-world setting are currently unavailable. However, real-world data describing the economic burden of major bleeding events among atrial fibrillation patients receiving factor Xa inhibitors are available from 92,949 patients within the MarketScan Commercial and Medicare database [20]. This analysis indicated that, in the absence of specific reversal agent, the total healthcare costs (2014 values) incurred were significantly (p < 0.001) higher in those who experienced major bleeding event than those who did not within 30 days of hospitalization ($US24,686 vs $US14,352; incremental cost burden $US10,334), and well as during the 12 months following hospitalization when adjusted for differences in patient characteristics ($US58,169 vs $US41,241; incremental cost burden $US16,928) [20]. The use of specific reversal agents for factor Xa inhibitors, such as andexanet alfa, may, therefore, reduce the economic burden of hemorrhagic complications associated with anticoagulant therapy.

Data regarding the cost effectiveness of andexanet alfa for the treatment of apixaban- and rivaroxaban-associated major bleeding in the real-world setting would be of interest.

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Compliance with ethical standards

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References

1. Milling TJ Jr, Frontera J. Exploring indications for the use of direct oral anticoagulants and the associated risks of major bleeding. Am J Manag Care. 2017;23(4 Suppl):S67–80.

2. Greinacher A, Thiele T, Selleng K. Reversal of anticoagulants: an overview of current developments. Thromb Haemost. 2015;113(5):931–42.

3. Milling TJ, Clark CL, Feronti C, et al. Management of factor Xa inhibitor-associated life-threatening major hemorrhage: a retrospective multi-center analysis. Am J Emerg Med. 2018;36:396–402.

4. Levy JH, Douketis J, Weitz JI. Reversal agents for non-vitamin K antagonist oral anticoagulants. Nat Rev Cardiol. 2018;15(5):273–81.

5. Dabi A, Koutrouvelis AP. Reversal strategies for intracranial hemorrhage related to direct oral anticoagulant medications. Crit Care Res Pract. 2018;2018(4907164):1–11.

6. Ansell JE. Reversing the effect of oral anticoagulant drugs: established and newer options. Am J Cardiovasc Drugs. 2016;16(3):163–70.

7. Nafee T, Aslam A, Chi G, et al. Andexanet alfa for the reversal of oral anticoagulant activity in patients treated with direct and indirect factor Xa inhibitors. Expert Rev Cardiovasc Ther. 2017;15(4):237–45.

8. Andexxa (coagulation factor Xa (recombinant), inactivated-zhzo) lyophilized powder for solution for intravenous injection: US prescribing information. South San Francisco: Portola Pharmaceuticals, Inc.; 2018.

9. Kaatz S, Bhansali H, Gibbs J, et al. Reversing factor Xa inhibitors: clinical utility of andexanet alfa. J Blood Med. 2017;8:141–9.

10. Lu G, Hollenbach SJ, Baker DC, et al. Preclinical safety and efficacy of andexanet alfa in animal models. J Thromb Haemost. 2017;15(9):1747–56.

11. Lu G, DeGuzman FR, Hollenbach SJ, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med. 2013;19(4):446–51.

12. Grottke O, Akman N, Conley PB, et al. The impact of andexanet alfa in a porcine polytrauma model under apixaban anticoagulation: investigation of hemostatic safety and efficacy [abstract no. 20205]. Circulation. 2017;136(Suppl 1).

13. Siegal D, Lu G, Leeds JM, et al. Safety, pharmacokinetics, and reversal of apixaban anticoagulation with andexanet alfa. Blood Adv. 2017;1(21):1827–38.

14. Mark C, Vandana M, Michael K, et al. A phase 2 randomized, double-blind, placebo-controlled trial demonstrating reversal of rivaroxaban-induced anticoagulation in healthy subjects by andexanet alfa (PRT064445), an antidote for FXA inhibitors [abstract]. Blood. 2013;122(21):3.

15. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373(25):2413–24.

16. Lu G, Lin J, Curnutte JT, et al. Effect of andexanet-tissue factor pathway inhibitor (TFPI) interaction on in vitro clot formation and lysis via different coagulation pathways [slide presentation]. In: International Society on Thrombosis and Haemostasis. 2018.

17. Connolly SJ, Milling TJ Jr, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med. 2016;375(12):1131–41.

18. Connolly S, Milling T, Eikelboom JW, et al. Andexanet alfa in factor Xa inhibitor-associated acute major bleeding [abstract plus slide presentation]. In: American College of Cardiology’s 67th Annual Scientific Session & Expo (ACC18); 2018.

19. Leeds J, Mandema J, Lu G, et al. Pharmacokinetic/pharmacodynamic modeling of andexanet alfa dose in acute major bleeding [abstract no. 33]. Crit Care Med. 2018;46(1 Suppl):17.

20. Deitelzweig S, Neuman W, Lingohr-Smith M, et al. Incremental economic burden associated with major bleeding among atrial fibrillation patients treated with factor Xa inhibitors. J Med Econ. 2017;20(12):1217–23.

21. Heo YA. Andexanet alfa: first global approval. Drugs. 2018;78(10):1049–55.