1. NAME OF THE MEDICINAL PRODUCT

Ondexxya 200 mg powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 mg of andexanet alfa*.

After reconstitution, each mL of solution contains 10 mg of andexanet alfa.

* Andexanet alfa is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion

White to off-white lyophilised powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

4.2 Posology and method of administration

Restricted to hospital use only.

Posology
Andexanet alfa is administered as an intravenous bolus at a target rate of approximately 30 mg/min over 15 minutes (low dose) or 30 minutes (high dose), followed by administration of a continuous infusion of 4 mg/min (low dose) or 8 mg/min (high dose) for 120 minutes (see Table 1).

Table 1: Dosing regimens

	Initial intravenous bolus	**Continuous intravenous infusion**	**Total number of 200 mg vials needed**
Low dose	400 mg at a target rate of 30 mg/min	4 mg/min for 120 minutes (480 mg)	5
High dose	800 mg at a target rate of 30 mg/min	8 mg/min for 120 minutes (960 mg)	9

Reversal of apixaban
The recommended dose regimen of Ondexxya is based on the dose of apixaban the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose of apixaban

(see Table 2). If the strength of the last dose of anticoagulant or the interval between the last dosage and the bleeding episode are unknown, no dose recommendation is available. Measurement of baseline anti-FXa-level could support the clinical decision of starting treatment (if level is available in an acceptable timeframe).

Table 2: Summary of dosing for reversal of apixaban

FXa inhibitor	**Last dose**	**Timing of last dose before Ondexxya initiation**	
		< 8 hours	**≥ 8 hours**
Apixaban	≤ 5 mg	Low dose	Low dose
	> 5 mg	High dose	

Reversal of rivaroxaban
The recommended dose regimen of Ondexxya is based on the dose of rivaroxaban the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose of rivaroxaban (see Table 3). If the strength of the last dose of anticoagulant or the interval between the last dosage and the bleeding episode are unknown, no dose recommendation is available. Measurement of baseline anti-FXa-level could support the clinical decision of starting treatment (if level is available in an acceptable time frame).

Table 3: Summary of dosing for reversal of rivaroxaban

FXa inhibitor	**Last dose**	**Timing of last dose before Ondexxya initiation**	
		< 8 hours	**≥ 8 hours**
Rivaroxaban	≤ 10 mg	Low dose	Low dose
	> 10 mg	High dose	

Restarting antithrombotic therapy
Following administration of Ondexxya and cessation of a major bleed, re-anticoagulation should be considered to prevent thrombotic events due to the patient's underlying medical condition. Antithrombotic therapy can be re-initiated as soon as medically indicated following treatment if the patient is clinically stable and adequate haemostasis has been achieved. A normal degree of anticoagulation from FXa inhibitors (i.e. apixaban, rivaroxaban) or low molecular weight heparin (i.e. enoxaparin) can be expected after 4 hours following end of infusion of Ondexxya based on PK/PD modelling (see section 5.1). Medical judgement should balance the benefits of anticoagulation with the risks of re-bleeding (see section 4.4).

Special populations
Elderly patients (aged 65 years and over): No dose adjustment is required in elderly patients (see section 5.2).

Renal impairment: The effect of renal impairment on andexanet alfa exposure levels has not been evaluated. Based on the existing data on clearance, no dose adjustment is recommended.

Hepatic impairment: Based on the existing data on clearance of andexanet alfa, no dose adjustment is recommended. The safety and efficacy have not been studied in patients with hepatic impairment (see section 5.2).

Paediatric population: The safety and efficacy of andexanet alfa in children and adolescents have not been established. No data are available.

Method of administration

Intravenous use
After an appropriate number of vials of Ondexxya has been reconstituted, the reconstituted solution (10 mg/mL) without further dilution is transferred to sterile large volume syringes in case a syringe pump is used for administration or to suitable empty intravenous bags comprised of polyolefin (PO) or polyvinyl chloride (PVC) material (see section 6.6). Prior to administration by IV infusion a 0.2 or 0.22 micron inline polyethersulfone (PES) or equivalent low protein-binding filter should be used.

Ondexxya is administered as an IV bolus at a target rate of approximately 30 mg/min over 15 minutes (low dose) or 30 minutes (high dose), followed by administration of a continuous infusion of 4 mg (low dose) or 8 mg (high dose) per minute for 120 minutes (see Table 1).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any other ingredients listed in section 6.1.

Known allergic reaction to hamster proteins.

4.4 Special warnings and precautions for use

Limitations of use
Andexanet alfa is not suitable for pre-treatment of urgent surgery. Use for edoxaban or enoxaparin-reversal is not recommended due to lack of data. Andexanet alfa will not reverse the effects of non-FXa inhibitors (see section 5.1).

Treatment monitoring should be based mainly on clinical parameters indicative of appropriate response (i.e. achievement of haemostasis), lack of efficacy (i.e. re-bleeding), and adverse events (i.e. thromboembolic events). Treatment monitoring of andexanet alfa should not be based on anti-FXa-activity. Commercial anti-FXa-activity assays are unsuitable for measuring anti-FXa activity following administration of andexanet alfa as these assays result in erroneously elevated anti-FXa activity levels, thereby causing a substantial underestimation of the reversal activity of andexanet alfa.

Thrombotic events
Thrombotic events have been reported following treatment with andexanet alfa. Patients being treated with FXa inhibitor therapy have underlying disease states that predispose them to thrombotic events. Patients with prior history of stroke, myocardial infarction or heart failure may be at higher risk of thrombotic events (see section 4.8). Reversing FXa inhibitor therapy exposes patients to the thrombotic risk of their underlying disease. In addition, independent pro-coagulant effect of andexanet alfa, mediated by inhibition of tissue factor pathway inhibitor (TFPI), has been demonstrated, which may pose a risk of developing thrombosis. Duration of this effect in subjects with

bleeds is not known. Laboratory parameters as anti-FXa activity, endogenous thrombotic potential (ETP), or markers of thrombosis might not be reliable for guidance. To reduce this risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate after completion of treatment (see section 4.2).

In healthy volunteers, dose-dependent increases in coagulation markers F1+2, TAT, and D-dimer, and dose-dependent decreases in TFPI, after administration of andexanet alfa were observed, but no thromboembolic events were reported. These markers were not measured in patients enrolled in study 14-505 and 18-513, but thromboembolic events have been observed (see section 4.8 and 5.1). Monitoring for signs and symptoms of thrombosis is therefore strongly recommended.

Use of andexanet alfa in conjunction with other supportive measures
Andexanet alfa can be used in conjunction with standard haemostatic supportive measures, which should be considered as medically appropriate.

The safety of andexanet alfa has not been evaluated in patients who received prothrombin complex concentrates, recombinant factor VIIa, or whole blood within seven days prior to the bleeding event, as they were excluded from clinical studies. Pro-coagulant factor treatments (e.g. 3- or 4-factor prothrombin complex concentrate (PCC)/activated PCC, recombinant factor VIIa, fresh frozen plasma) and whole blood should be avoided unless absolutely required, due to lack of data in combination with these treatments.

Interaction with heparin
Use of andexanet alfa prior to heparinisation e.g. during surgeries or procedures should be avoided as andexanet alfa causes unresponsiveness to heparin. Use of andexanet alfa as an antidote for heparin or low-molecular weight heparin has not been evaluated and is not recommended (see section 4.5).

Infusion-related reactions
In case of mild or moderate infusion reactions, careful observation may be sufficient. For moderate symptoms, consideration may be given to a brief interruption or slowing of the infusion with resumption of the infusion after symptoms subside. Diphenhydramine may be administered.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with andexanet alfa have been performed.

In vitro data suggest interaction of andexanet alfa with the heparin- anti-thrombin III (ATIII) complex and neutralisation of the anticoagulant effect of heparin. Off-label use of andexanet alfa pre-surgery, intra-operatively, or during procedures requiring heparinization has been reported to cause unresponsiveness to heparin (see section 4.4). Based on PK/PD modelling, the anticoagulant activity of low molecular weight heparin may be affected up to 4 hours following end of infusion with andexanet alfa (see section 5.1). Use of andexanet alfa as an antidote for heparin or low-molecular weight heparin has not been evaluated and is not recommended.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no data from the use of andexanet alfa in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Andexanet alfa is not recommended during pregnancy or in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether andexanet alfa is excreted in human milk. A risk to newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with andexanet alfa.

Fertility

There are no data on the effects of andexanet alfa on human fertility.

4.7 Effects on ability to drive and use machines

Andexanet alfa has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of andexanet alfa has been evaluated in clinical studies including 417 healthy subjects administered an FXa inhibitor, as well as in the Phase IIIb/IV study 14-505 (ANNEXA-4) including 419 patients who had acute major bleeding and were under treatment with an FXa inhibitor (apixaban and rivaroxaban), and in the Phase IV study 18-513 (ANNEXA-I) including 262 andexanet alfa-treated patients presenting with acute intracranial haemorrhage (ICrH) and under treatment with apixaban, rivaroxaban or edoxaban (see section 5.1).

In clinical studies in healthy subjects who were administered a FXa inhibitor and then received andexanet alfa, the frequency of adverse reactions was similar in the andexanet alfa-treated group (16.8%) and in the placebo treated group (12.2%). The most frequently observed adverse reactions were mild or moderate infusion-related reactions comprising symptoms such as flushing, feeling hot, cough, dysgeusia, and dyspnoea occurring within a few minutes to a few hours of the infusion. Among the healthy subjects studied, women experienced more adverse reactions (mainly infusion-related reactions) than men.

In ANNEXA-4, the most commonly reported adverse reactions were pyrexia, deep vein thrombosis, and ischaemic stroke. In ANNEXA-I, the most commonly reported adverse reactions were pyrexia and ischaemic stroke. The safety profile of andexanet alfa was overall consistent across the studies.

In the healthy subject studies, elevations > 2 x ULN in D-dimer and prothrombin fragments F1+2 were frequently observed. These elevations were maintained between several hours to a few days following administration, but no thrombotic events were reported.

In patients with major bleedings, thrombosis-markers have not been investigated since bleeding can interfere with the thrombosis marker results. Thromboses and thromboembolic events have

commonly been documented.

Tabulated list of adverse reactions

Table 4 provides the list of adverse reactions from clinical studies in subjects with bleeds treated with andexanet alfa. The adverse reactions are classified by system organ class (SOC) and frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); or not known (cannot be estimated from available data).

Table 4: List of adverse reactions from clinical studies in subjects with bleeds

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100
Nervous system disorders	Ischaemic stroke[b]	Transient ischaemic attack
Cardiac disorders	Myocardial infarction[c]	Cardiac arrest
Vascular disorders	Deep vein thrombosis	Embolism arterial[d]
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	
General disorders and administrative site conditions	Pyrexia	
Injury, poisoning and procedural complications		Infusion related reaction[a]

[a]Reported signs/symptoms (rigors, chills, hypertension, oxygen desaturation, agitation and confusion) were transient and mild to moderate in severity.
[b] Ischaemic strokes includes, e.g. the preferred terms: cerebrovascular accident, cerebellar stroke and cerebral infarction.
[c] Myocardial infarction includes, e.g. the preferred term: acute myocardial infarction.
[d] Embolism arterial includes, e.g. the preferred terms: iliac artery occlusion, renal infarct and femoral artery embolism.

Description of selected adverse reactions

Thrombotic events
Study 14-505 (ANNEXA-4)
In study 14-505, 45/419 (11%) patients experienced one or more of the following thromboembolic events: cerebrovascular accident (CVA) (19/45; 42%), deep venous thrombosis (11/45; 24%), myocardial infarction (MI) including acute myocardial infarction and myocardial ischaemia (9/45; 20%), pulmonary embolism (PE) (5/45; 11%), and transient ischaemic attack (TIA) (1/45; 2%). The median time to first thromboembolic event was 10 days. A total of 38% of patients with thromboembolic events (17/45) experienced the thromboembolic event during the first three days. Of the 419 subjects who received andexanet alfa, 266 received at least one anticoagulation dose within 30 days after treatment as a prophylactic measure. Of these 266 subjects, 14 subjects (5%) had a thrombotic event after resumption of anticoagulation; while of the 153 subjects who did not receive anticoagulation as a prophylactic, 31 (20.3%) had a thrombotic event (see section 4.4).

Study 18-513 (ANNEXA-I)

In the ANNEXA-I study, adjudicated thrombotic events through 30 days post-randomisation were reported in 27 patients (10.3%) in the andexanet alfa group and 15 patients (5.7%) in the usual care group. The difference in rate of thrombotic events between the treatment groups across the pre-defined patient subgroups was generally consistent with the overall population.

When considering underlying disease history, patients in the andexanet alfa group with a prior history of stroke or myocardial infarction, or history of heart failure, were found to have a numerically higher rate of thrombotic events, compared with patients without a history of these underlying diseases. Of the 78 patients who had a prior history of stroke or myocardial infarction, 10 patients (12.8%) had a thrombotic event, compared with 17 of 184 patients (9.2%) without this medical history. In the 46 patients who had a history of heart failure, 8 patients (17.4%) had a thrombotic event, compared with 19 of 216 patients (8.8%) without this medical history (see section 4.4).

Patients in the andexanet alfa group and usual care group experienced one or more of the following adjudicated thrombotic events, respectively: ischaemic stroke (6.5% versus 1.5%), myocardial infarction (4.2% versus 1.5%), pulmonary embolism (0.4% versus 2.3%), arterial systemic embolism (1.1% versus 0.8%) and deep vein thrombosis (0.4% versus 0.8%). The median time to thrombotic event was 3 and 14 days in the andexanet alfa and usual care group, respectively. In the andexanet alfa group, 14 patients had a thrombotic event during the first 3 days, compared with 1 patient in the usual care group. None of these patients had received any dose of anticoagulant prior to the thrombotic event. Adjudicated thrombotic events leading to death were reported in 6 patients (2.3%) in the andexanet alfa group and 2 patients (0.8%) in the usual care group.

Overall, 199 patients (76.0%) in the andexanet alfa group and 192 patients (72.5%) in the usual care group were restarted with any anticoagulant within 30 days post randomisation. Of those, 183 patients (92.0%) in the andexanet alfa group and 187 patients (97.4%) in the usual care group received at least one dose of any anticoagulant as a prophylactic measure. In this population, a similar rate of thrombotic events (4.9% and 4.8%) was observed in the andexanet alfa and usual care group, respectively. In the 79 patients in the andexanet alfa group who did not receive any anticoagulation as a prophylactic measure, 18 patients (22.8%) had a thrombotic event, compared with 6 of 78 patients (7.7%) in the usual care group (see section 4.4).

Infusion related reactions
Based on data from 419 patients from the Phase IIIb/IV study 14-505 (ANNEXA-4) treated with apixaban and rivaroxaban and experiencing an acute major bleeding episode, two patients (0.5%) experienced an infusion-related reaction neither of which was assessed as severe (1 moderate; 1 mild). In study 18-513 (ANNEXA-I), no events of infusion related reactions were reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no clinical experience with overdose of andexanet alfa. No dose-limiting toxicities have been observed during clinical studies.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products, antidotes. ATC code: V03AB38

Mechanism of action
Andexanet alfa is a recombinant form of human FXa protein that has been modified to lack FXa enzymatic activity. The active site serine was substituted with alanine, rendering the molecule unable to cleave and activate prothrombin, and the gamma-carboxyglutamic acid (Gla) domain was removed to eliminate the ability of the protein to assemble into the prothrombinase complex, thus removing any anti-coagulant effects.

Andexanet alfa is a specific reversal agent for FXa inhibitors. The predominant mechanism of action is the binding and sequestration of the FXa inhibitor. In addition, andexanet alfa has been observed to bind to, and inhibit tissue factor pathway inhibitor (TFPI). Inhibition of TFPI activity can increase tissue factor-initiated thrombin generation inducing a pro-coagulant effect.

Pharmacodynamic effects
The effects of andexanet alfa can be measured through pharmacodynamic markers, including free fraction of available FXa inhibitor as well as through restoration of thrombin generation. In addition, andexanet alfa has been shown to inhibit TFPI-activity.

Commercial anti-FXa-activity assays are unsuitable for measuring anti-FXa activity following administration of andexanet alfa. Due to the reversible binding of andexanet alfa to the FXa inhibitor, the high sample dilution currently used in these assays leads to dissociation of the inhibitor from andexanet alfa, resulting in detection of erroneously elevated anti-FXa activity levels, thereby causing a substantial underestimation of the reversal activity of andexanet alfa.

In prospective, randomised, placebo-controlled, dose-ranging studies in healthy subjects, the dose and dose regimen of andexanet alfa required to reverse anti-FXa activity and restore thrombin generation for FXa inhibitors (apixaban or rivaroxaban) were determined with modified assays that are not commercially available.

The maximal reversal of anti-FXa activity was achieved within two minutes of completing the bolus administration. Administration of andexanet alfa as a bolus followed by continuous infusion resulted in a sustained decrease in anti-FXa activity. The anti-FXa activity returned to the placebo levels and above approximately two hours after the end of a bolus or infusion dependent on dosage.

When andexanet alfa was administered as a bolus followed by a continuous infusion, the maximum decrease in unbound FXa inhibitors was rapid (within two minutes of the end of the bolus) and was sustained over the course of the infusion then gradually increased over time, reaching a maximum at approximately two hours following the end of infusion.

Restoration of thrombin generation following administration was dose- and dose-regimen-dependent and did not correlate with anti-FXa-activity beyond approximately four hours (see below, “restoration of thrombin generation”).

Plasma TFPI activity has been shown to be inhibited completely from 2 minutes to 14.5 hours after andexanet alfa bolus-administration in healthy subjects, and returned to baseline within 3 days. Tissue-factor (TF)-initiated thrombin generation immediately increased above the baseline (prior to anticoagulation) and remained elevated for > 20 hours in contrast to placebo. Plausibility of a pro-coagulant effect of TFPI-inhibition is supported by consecutive and sustained slopes of D-Dimers, TAT, and F1+2.

PK/PD models were used to characterise the anti-FXa effect of low molecular weight heparin (enoxaparin 40 mg) introduced for re-anticoagulation after reversal of FXa inhibition by andexanet alfa. In these simulations, regardless of previous anticoagulant dose, the anti-FXa response to enoxaparin was not affected by andexanet alfa beyond 4 hours post-infusion (see section 4.2). This time interval is consistent with the half-life of andexanet alfa (see section 5.2) and the return to pre-infusion levels of anti-FXa activity shown in the clinical studies 14-503 and 14-504 (see Figure 1). The remaining amount of andexanet alfa is not sufficient to reverse the anticoagulation caused by either the initial oral FXa inhibitor or a subsequent anticoagulant (regardless of oral FXa inhibitor or low molecular weight heparin).

Clinical efficacy and safety

The efficacy and safety of andexanet alfa have been evaluated in the following: 1) randomised, placebo-controlled, Phase II dose-ranging studies with healthy volunteers administered FXa inhibitors to establish doses required for reversal; 2) two Phase III studies, one with apixaban and the other with rivaroxaban, to confirm the efficacy of the high and low dose regimens; 3) a global, multicentre, prospectively defined, open-label Phase IIIb/IV study (ANNEXA-4) in patients with an acute major bleeding episode requiring urgent reversal of FXa anticoagulation; and 4) a randomised, open-label, Phase IV study (ANNEXA-I) in patients presenting with acute intracranial haemorrhage (ICrH) within 6 hours of symptom onset to baseline scan and within 15 hours of taking an oral FXa inhibitor.

Reversal of anticoagulation in healthy subjects aged 50-75 (Studies 14-503 and 14-504)

In a prospective, randomised, placebo-controlled study, healthy subjects with a median age of 56.5 years on apixaban 5 mg twice daily received andexanet alfa (n=24) administered as a 400 mg IV bolus immediately followed by a 4 mg per minute IV infusion for 120 minutes (480 mg) or placebo (n=8).

In a similar study, subjects with a median age of 57 years on rivaroxaban 20 mg daily received andexanet alfa (n=26) administered as an 800 mg IV bolus immediately followed by an 8 mg per minute IV infusion for 120 minutes (960 mg) or placebo (n=13).

Reduction in anti-FXa activity

The primary endpoint for both Study 14-503 (apixaban) and Study 14-504 (rivaroxaban) was the percent change in anti-FXa activity from baseline to post-infusion nadir.

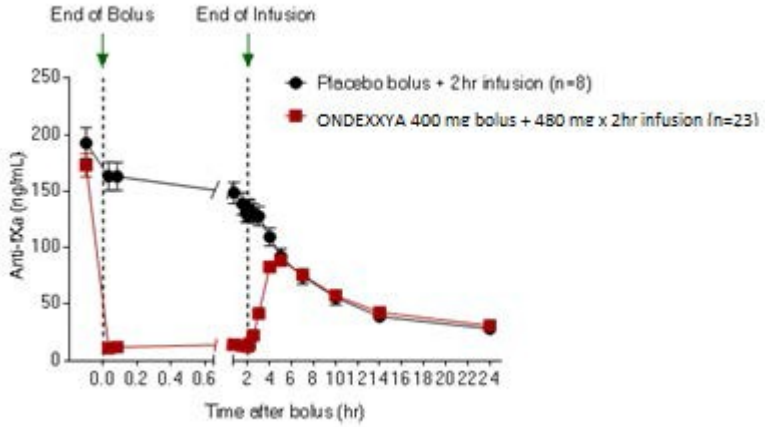
Among the apixaban-treated subjects in Study 14-503, the percent change [± standard deviation (SD)] in anti-FXa activity was -92.34% (± 2.809%) for the andexanet alfa group and -32.70% (± 5.578%) for the placebo group ($p < 0.0001$), the latter reflecting the intrinsic clearance of the anticoagulant.

Among the rivaroxaban-treated subjects in Study 14-504, the percent change (± SD) in anti-FXa activity was -96.72% (± 1.838%) for the andexanet alfa group and -44.75% (± 11.749%) for the placebo group ($p < 0.0001$), the latter reflecting the intrinsic clearance of the anticoagulant.

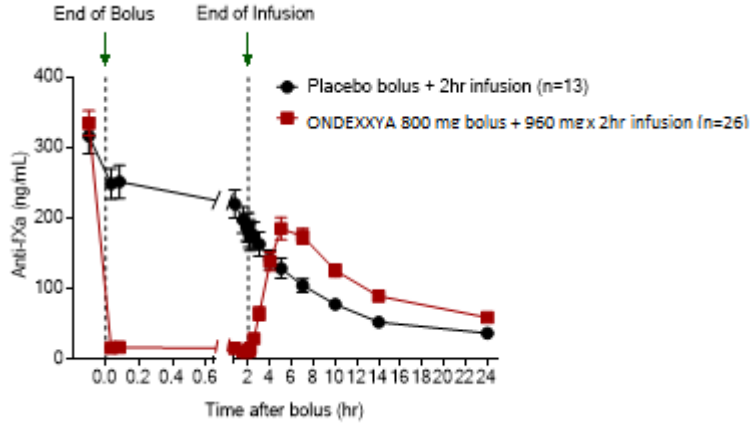
The time courses of anti-FXa activity before and after andexanet alfa administration are shown in Figure 1. Reduction in anti-FXa activity correlates with restoration of thrombin generation. The anti-FXa activity thresholds for normalisation of thrombin generation (defined by mean ETP and standard deviations) were estimated to be 44.2 ng/mL (within one standard deviation of normal ETP) based on pooled data from Studies 14-503 and 14-504, as indicated in the figure.

Figure 1: Change in anti-FXa activity (ng/mL) in healthy subjects anticoagulated with apixaban (A) and rivaroxaban (B)

(A)



(B)



Restoration of thrombin generation

In both Study 14-503 and Study 14-504, treatment with andexanet alfa also resulted in a statistically significant increase in thrombin generation in healthy subjects anticoagulated with apixaban or rivaroxaban versus placebo ($p < 0.0001$). Restoration of thrombin generation to within normal ranges (defined as one standard deviation from baseline levels) within two minutes and maintained for 20 hours was achieved with bolus only and bolus plus infusion for low-dose andexanet alfa in subjects on apixaban. For subjects on rivaroxaban, high-dose andexanet alfa (bolus plus infusion) resulted in increased thrombin generation above two standard deviations. No clinical evaluation for apixaban-treated subjects with high-dose andexanet alfa and no evaluation for rivaroxaban-treated subjects with low-dose andexanet alfa was performed in these studies.

Change from baseline in free FXa inhibitor concentration at nadir

The mean unbound concentrations of apixaban and rivaroxaban were < 3.5 ng/mL and 4 ng/mL, respectively, after bolus andexanet alfa administration and were maintained throughout the continuous infusion. These levels of unbound FXa inhibitor provide little or no anticoagulant effect.

Reversal of FXa inhibitor anticoagulation in patients with acute major bleeding (study 14-505)

In Study 14_505 (ANNEXA-4), a Phase IIIb/IV multinational, prospective, single-arm, open-label study, Ondexxya was administered to 477 patients on FXa inhibitors, 419 of whom were on apixaban and rivaroxaban, who presented with acute major bleeding. The two co-primary endpoints were: a) percent change in anti_FXa activity from baseline to the nadir between five minutes after the end of the bolus up until the end of the infusion, and; b) rate of good or excellent (compared to poor or none) haemostatic efficacy within 12 hours after infusion, as rated by an independent endpoint adjudication committee.

Approximately half of the patients were male, and the mean age was 77.9 years. Most patients had previously received either apixaban (245/477; 51.4%) or rivaroxaban (174/477; 36.5%), or edoxaban (36/477; 7.5%) or enoxaparin (22/477; 4.6%) and experienced either an ICrH (329/477; 69%) or a gastrointestinal (GI) bleed (109/477; 22.9%). 381/477 (79.9%) received the low-dose regimen of andexanet alfa, while 96/477 patients (20.1%) received the high-dose regimen, accordingly to section 4.2.

Anti-FXa change from baseline to nadir
Of the 477 enrolled patients, 347 (73%) were evaluable for efficacy as they were dosed with andexanet alfa for a confirmed major bleed and had a baseline anti-FXa activity above 75 ng/mL. For these patients, median anti-FXa activity at baseline was 147 ng/mL for patients taking apixaban, and 214 ng/mL for patients taking rivaroxaban. For anti-FXa activity, the median (95% CI) decrease from baseline to nadir in anti-FXa activity for apixaban was -93.3% (-94.2%, -92.5%); and rivaroxaban was -94.1% (-95.1%; -93.0%).

Haemostatic efficacy
Haemostatic efficacy was good or excellent in 79% of 169 patients taking apixaban and in 80% of 127 patients taking rivaroxaban.

Anti-TFPI-effect
Immediate and sustained (for about 3 days post infusion) pro-coagulant anti-TFPI-effect was documented in patients with major bleeding – consistent with respective results from studies in healthy volunteers (14-503, 14-504, 16-508, 19-514).

Analysis of study 14-505 demonstrated that the change in anti-FXa activity (surrogate) was not predictive for achievement of haemostatic efficacy.

Deaths
In the safety population (n=419), 75 patients (18%) died. Of the 75 subjects who died, the bleeding type was intracranial bleeding in 55 (73%), gastrointestinal bleeding in 14 (19%), and other bleeding types in 6 (8%) subjects. The mortality rates were 19.0% (55/289) in patients presenting with ICrH, 14.7% (14/95) with GI bleeding and 17.1% (6/35) with other types of bleeding. The mortality rates were 23.0% (64/278) in patients aged > 75 years old and 7.8% (11/141) in patients aged ≤ 75 years. According to region, death rates were 24.9% (53/213) in patients recruited in the European Union and 11.3% (22/194) in patients recruited in North America. The higher mortality rate in Europe is only present in older patients or patients with heart failure. Compared with patients recruited in North America, EU patients were significantly older (81.0 years vs. 79.0 years), more frequently had ICrH as index event (75.1% vs. 60.3%) and more ICrHs were intraparenchymal (69.3% vs. 42.7%).
Cardiovascular causes of death (n=36) included: haemorrhagic stroke (n=6), ischaemic stroke (n=10), sudden cardiac death (including unwitnessed) (n=6), cardiomechanical/pump failure (n=4), myocardial infarction (n=2), bleeding other than haemorrhagic stroke (n=2), and other cardiovascular causes (n=6).
Non-cardiovascular deaths (n=39) included: infection/sepsis (n=11), respiratory failure (n=6), accident/trauma (n=2), cancer (n=2), and other/non-vascular cause (n=18).
The average time to death was 15 days after treatment. All deaths occurred before Day 44.

Haemostatic efficacy and reversal of FXa activity in patients with ICrH (study 18-513)
Study 18-513 (ANNEXA-I) was a randomised 1.1, open-label Phase 4 study with blinded adjudication on primary efficacy (452 patients) and safety endpoints (530 patients), to determine the efficacy and safety of Ondexxya compared to usual care in patients presenting with acute intracranial haemorrhage (ICrH) with a haematoma volume of ≥ 0.5 to ≤ 60 mL, within 6 hours of symptom onset to baseline scan, and within 15 hours of taking an oral FXa inhibitor. In total, 60.4% of patients had received apixaban, 29.1% had received rivaroxaban and 10.0% had received edoxaban.

The primary endpoint was to evaluate the effect of Ondexxya versus usual care on the rate of effective haemostasis defined as change from baseline NIHSS score increase of < 7 at 12 hours AND ≤ 35% increase in haematoma volume compared to baseline on a repeat CT or MRI scan at 12 hours AND no rescue therapies administered between 3 hours and 12 hours after randomisation.

In the andexanet alfa group, patients received either a low or high dose of Ondexxya based on the specific FXa inhibitor, dose and timing of most recent dose. In the usual care group, 85.4% of patients were treated with PCC, 12.4% of patients received no haemostatic treatment (platelets or packed red blood cells were allowed) and 0.7% of patients were treated with other therapy.

The most common bleeding location was intracerebral haemorrhage (92.2%), most bleeds were spontaneous (87.7%) and the median haematoma volume at baseline was 9.9 mL.

Haemostatic efficacy
In the primary efficacy population, Ondexxya achieved effective haemostasis at 12 hours in acute ICrH in patients receiving a direct oral FXa inhibitor (67.0% versus 53.1% in usual care, difference 13.4% [95% CI 4.6%, 22.2%], p=0.0032). Effective haemostasis was achieved in 70.0% versus 56.3% of patients who had previously taken apixaban, and 56.3% versus 46.2% for rivaroxaban in the andexanet alfa and usual care group, respectively.

With respect to the three components of the primary end point, hematoma volume expansion of 35% or less was observed in 76.7% of patients receiving andexanet and in 64.6% of patients receiving usual care; a change of less than 7 points in the score on the NIHSS was observed in 87.9% and 83.0%, respectively; and no rescue therapy was used in 97.3% and 93.4%.

Mortality
In total, the number of patients who died before Day 30 post randomisation was balanced between the treatment groups: 74 patients (28.2%) in the andexanet alfa group and 70 patients (26.4%) in the usual care group.

Pro-thrombotic laboratory markers
Dose-dependent increases in coagulation markers F1+2, TAT, and D-dimers after administration of andexanet alfa were observed, in 223 healthy volunteers who received FXa inhibitors and were treated with andexanet alfa; no thromboembolic events occurred in these healthy volunteers. F1+2, TAT and D-dimers were not measured in patients enrolled in study 14-505 and 18-513; their relevance in subjects with bleeds is not known.

Immunogenicity
345 andexanet alfa-treated healthy subjects were tested for antibodies cross reacting with andexanet alfa and antibodies to factor X and FXa. Treatment-emergent, anti-andexanet alfa antibodies were detected in approximately 10% (35/345). These antibodies were generally low titre, and no clinical consequences were observed. The occurrence of anti-andexanet alfa antibodies following treatment in patients in the study 14-505 (8% or 22/276 patients) has been similar to that observed in healthy subjects. No neutralising antibodies to andexanet alfa were detected in study 14-505. In study 18-513, 2 patients in the andexanet alfa group tested positive for anti-andexanet alfa antibodies at Day 30.

No neutralising antibodies or antibodies to factor X or FXa have been detected.

Paediatric population
The licensing authority has deferred the obligation to submit the results of studies with andexanet alfa in one or more subsets of the paediatric population in treatment and prevention of FXa inhibitor-associated haemorrhages (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Studies of andexanet alfa in the presence of direct FXa inhibitors in healthy subjects demonstrated dose proportional pharmacokinetics over the intended therapeutic dose range evaluated for both C_{max} and area under the curve (AUC). The pharmacokinetics of andexanet alfa has not been studied in subjects with bleeds due to feasibility reasons.

Table 5: Pharmacokinetic parameters for andexanet alfa bolus-injection of 400 and 800 mg

PK Parameter	400 mg Bolus	800 mg Bolus
$AUC_{0-\infty}$ (hr*µg/mL)	61.3 [43.8, 94.9]	127 [57.5, 209]
Cmax (µg/mL)	61.0 [40.3, 98.5]	118 [50.2, 191]
Clearance (L/hr)	6.52 [4.21, 9.13]	6.29 [3.83, 13.9]
$T_{1/2}$ (hr)	3.78 [2.59, 6.39]	4.24 [2.47, 6.52]
Vss (L)	9.47 [6.08, 15.3]	8.94 [5.36, 23.1]

Source: Study 19-514
Data presented are geometric mean [min, max].

Pharmacokinetics in special populations

Elderly population
In a study comparing andexanet alfa pharmacokinetics in elderly (65-69 years) and younger (26-42 years) healthy subjects who had received apixaban, the pharmacokinetics of andexanet alfa in the elderly subjects were not statistically different than those in the younger subjects.

Renal impairment
No studies have been conducted to investigate the pharmacokinetics of andexanet alfa in renally impaired patients. Based on the available PK data, andexanet alfa has little to no renal clearance, and thus would not require dose adjustment for patients with renal impairment.

Hepatic impairment
No studies have been conducted to investigate the pharmacokinetics of andexanet alfa in patients with hepatic impairment. Biliary and/or faeces elimination of protein therapeutics is not a known route of protein elimination. Therefore, dose adjustment is not considered needed for patients with hepatic impairment.

Gender
Based on population pharmacokinetics analysis, gender does not have a clinically meaningful effect on the pharmacokinetics of andexanet alfa.

Paediatric population
The pharmacokinetics of andexanet alfa has not been studied in paediatric patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity studies up to two weeks in rats and monkeys.

Studies to evaluate the mutagenic and carcinogenic potential of andexanet alfa have not been performed. Based on its mechanism of action and on the characteristics of proteins, no carcinogenic or genotoxic effects are anticipated.

Animal reproductive and developmental studies have not been conducted with andexanet alfa.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tris base

Tris hydrochloride

L-arginine hydrochloride

Sucrose

Mannitol

Polysorbate 80

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Vial (unopened)
Five years stored at 2°C to 8°C.

Reconstituted medicinal product
Chemical and physical in-use stability has been demonstrated for 16 hours at 2°C to 8°C in the primary packaging vial. If needed, the reconstituted solution once transferred into the IV bag can be stored for an additional eight hours at room temperature. From a microbiological point of view, once reconstituted, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder in a 20 mL vial (Type I glass) with a stopper (butyl rubber).

Pack size of four or five vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Reconstitution

The following are needed before starting reconstitution:
- Calculated number of vials (see section 4.2).
- Same number of 20 mL (or larger) solvent syringes equipped with a 20 gauge (or smaller in diameter, e.g. 21 gauge) needle.
- Alcohol swabs.
- Large (50 mL or larger) sterile syringe. If a syringe pump is used for administration, multiple syringes should be used to contain the final volume of reconstituted product.
- Intravenous bags of polyolefin (PO) or polyvinyl chloride (PVC) material (150 mL or larger) to contain the final volume of reconstituted product (if administration is performed with IV bag).
- Water for injections.
- 0.2 or 0.22 micron in-line polyethersulfone (PES) or equivalent low protein-binding filter.

Andexanet alfa does not need to be brought to room temperature before reconstitution or administration to the patient. Aseptic technique during the reconstitution procedure should be used.

Each vial is reconstituted according to the following instructions:
1. Remove the flip-top from each vial.
2. Wipe the rubber stopper of each vial with an alcohol swab.
3. Using a 20 mL (or larger) syringe and a 20 gauge (or smaller in diameter, e.g. 21 gauge) needle, withdraw 20 mL of water for injections.
4. Insert the syringe needle through the centre of the rubber stopper.
5. Push the plunger down to slowly inject the 20 mL of water for injections into the vial, directing the stream toward the inside wall of the vial to minimise foaming.
6. Gently swirl each vial, until all of the powder is completely dissolved. DO NOT SHAKE the vials, as this can lead to foaming. The dissolution time for each vial is approximately three to five minutes.
7. The reconstituted solution should be inspected for particulate matter and/or discolouration prior to administration. Do not use if opaque particles or discolouration are present.
8. For the most efficient reconstitution of the needed dose, and to minimise errors, inject each vial needed with 20 mL of water for injections before proceeding to the next step.
9. Use within eight hours after reconstitution when stored at room temperature.

Administration using a syringe pump

1. Once all required vials are reconstituted, the reconstituted solution is withdrawn from each vial, using the large volume (50 mL or larger) syringe equipped with a 20 gauge (or smaller in diameter, e.g. 21 gauge) needle.
2. The bolus and infusion are prepared in separate large volume syringes.
3. Due to the additional volume, the high dose bolus and infusion have to be further separated into additional syringes (two syringes apiece for bolus and infusion).
4. To prevent the inadvertent transfer of air, be careful to hold the syringe needle up, and do not set the syringe down between multiple withdrawals from vials.
5. Attach ancillary equipment (i.e., extension tubing, 0.2 or 0.22 micron in-line polyethersulfone (PES) or equivalent low protein-binding filter, syringe pump) in preparation for administration.
6. Administer the reconstituted solution at the appropriate rate.
7. Discard all used syringes, needles, and vials, including any unused portion of reconstituted solution.

Administration using intravenous bags

1. Once all required vials are reconstituted, withdraw the reconstituted solution from each vial, using the large volume (50 mL or larger) syringe equipped with a 20 gauge (or smaller in diameter, e.g. 21 gauge) needle.
2. Transfer the reconstituted solution from the syringe into an appropriate IV bag.
3. Repeat steps 1 and 2 as necessary to transfer the complete volume of the bolus and the infusion into a PO or PVC IV bags.
4. It is recommended that the bolus and infusion be split into two separate bags to ensure the correct administration rate. Although it is also permissible to use one PO or PVC IV bag for the bolus and infusion, the correct infusion rate must be ensured when switching from the bolus to the infusion.
5. Attach ancillary equipment (i.e., extension tubing, 0.2 or 0.22 micron in-line polyethersulfone (PES) or equivalent low protein-binding filter, IV pump) in preparation for administration.
6. Administer the reconstituted solution at the appropriate rate.

Disposal

All used syringes, needles, and vials, including any unused portion of reconstituted solution, should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited
1 Francis Crick Avenue,
Cambridge,
CB2 0AA,
UK.

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