ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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.

Excipient with known effect
Each vial of Ondexxya contains 2 mg of polysorbate 80.

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). Posology of andexanet alfa is based upon PK/PD-modelling and simulation exercises (see sections 5.1 and 5.2).

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 should support the clinical decision of starting treatment (if level is available in an acceptable timely frame).

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 should support the clinical decision of starting treatment (if level is available in an acceptable timely 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. The time to when a normal degree of anticoagulation from antithrombotic therapy can be expected has not yet been established.

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 in-line 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
Clinical efficacy is based upon reversal of anti-FXa-activity in healthy volunteers and achievement of haemostatic efficacy in bleeding patients dosed with apixaban or rivaroxaban. Clinical benefit in terms of reduced morbidity or mortality has not been demonstrated (see section 5.1). 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.

Dosage recommendation is based upon data-modelling in healthy volunteers. Data from bleeding

patients are limited and validation has not been successful, yet. Data suggest higher risk of thrombosis for patients receiving the higher dose of andexanet alfa and patients on rivaroxaban.

In clinical studies, intracranial haemorrhage (ICrH) patients (GCS > 7 and haematoma volume ≤ 60 mL) have been included. Treatment of patients with more severe ICrH with andexanet alfa has not been studied.

Thrombotic events
Serious arterial and venous thromboembolic events have been reported following treatment with andexanet alfa, including frequent reports of early manifestation (within 72 hours) after reversal. Patients with prior history of stroke, myocardial infarction or heart failure may be at higher risk of thrombotic events (see section 4.8 and 5.1). Patients being treated with FXa inhibitor therapy have underlying disease states that predispose them to thrombotic events. 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 an additional risk of developing thrombosis. The duration of this effect in bleeding patients 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, while no thrombotic events were reported, 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. These markers were not measured in patients enrolled in studies 14-505 and 18-513, but thromboembolic events have been observed (see sections 4.8 and 5.1). Monitoring for signs and symptoms of thrombosis is therefore strongly recommended and should be started early after treatment.

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.

Excipient with known effect
This medicinal product contains 2 mg of polysorbate 80 in each vial. Polysorbates may cause allergic reactions.

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 heparinisation has been reported to cause unresponsiveness to heparin (see section 4.4). 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 most frequently observed adverse reactions in healthy volunteers 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 clinical studies including patients with acute major bleeding and who were under treatment with a FXa inhibitor (apixaban or rivaroxaban), the most frequently observed adverse reactions were pyrexia (8.8%), ischaemic stroke (6.7%), and myocardial infarction (4.6%).

Tabulated list of adverse reactions
Table 4 provides the list of adverse reactions from clinical studies in bleeding patients 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 bleeding patients

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

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100
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 stroke 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
Arterial and venous thrombotic events including ischaemic stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, arterial systemic embolism and transient ischaemic attack have been observed in clinical trials, with frequent reports of early manifestation (within 72 hours) following treatment with andexanet alfa (see section 4.4 and 5.1).

Reversing FXa inhibitor therapy exposes patients to the thrombotic risk of their underlying disease. In addition, anti-FXa-independent procoagulant effects of andexanet alfa may pose an additional risk of developing thrombosis after treatment.

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 the national reporting system listed in Appendix V.

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 mechanism of action includes 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.

Immunogenicity
Anti-drug antibodies (ADA) were rarely detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed. However, data are still limited.

Population pharmacokinetic/pharmacodynamic (PK/PD) modelling and simulation
PK/PD modelling and simulations rely on the interplay between andexanet alfa and FXa inhibitor PK and on the relationships between biomarkers, here anti FXa-activity, TFPI-activity, and ETP. There remain uncertainties regarding the differing effect of the anticoagulant apixaban or rivaroxaban, the duration of the reversal effect dependent on the anti-TFPI-effect, and on the necessity of continuous infusion. Precision of simulations in bleeding patients is less than that within healthy volunteers due to the high inter-individual variability.

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).

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.

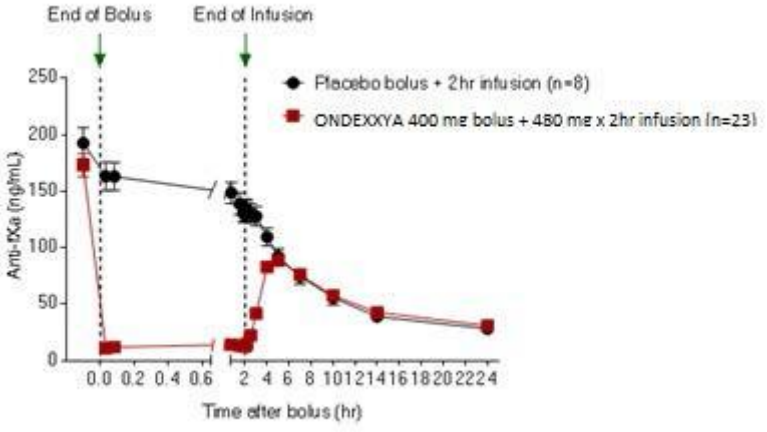
Among the apixaban-treated subjects in Study 14-503, the percent change [± standard deviation (SD)] in anti-FXa activity was -92.34% (± 2.809%) for the andexanet alfa group and -32.70% (± 5.578%) for the placebo group ($p < 0.0001$), the latter reflecting the intrinsic clearance of the anticoagulant.

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.

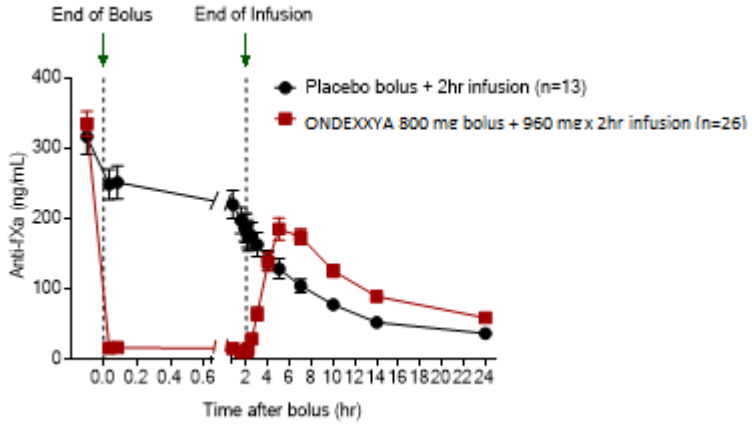
The time courses of anti-FXa activity before and after andexanet alfa administration are shown in Figure 1. Reduction in anti-FXa activity correlates with restoration of thrombin generation. The anti-FXa activity threshold for normalisation of thrombin generation (defined by mean ETP and standard deviations) was 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.

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.

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, andexanet alfa 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 intracranial haemorrhage (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 rated as good or excellent in 79% of 169 patients taking apixaban and in

80% of 127 patients taking rivaroxaban.

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

Anti-TFPI-effect
An 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).

Deaths
In the safety population (n=419), 75 patients (18%) died. 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. 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.

Thromboembolic events
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 based on clinical judgment.

Haemostatic efficacy and reversal of FXa activity in patients with ICrH (study 18-513)
Study 18-513 (ANNEXA-I) was a randomised, open-label Phase IV study with blinded adjudication on primary efficacy and safety endpoints, to determine the efficacy and safety of andexanet alfa 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.

The primary endpoint was to evaluate the effect of andexanet alfa versus usual care on the rate of effective haemostasis, which was assessed at 12 hours after randomisation and defined as a composite of $\leq 35\%$ increase in haematoma volume compared to baseline AND a less than 7-point change from baseline NIHSS score points AND no receipt of rescue therapies within 3 to 12 hours after randomisation. The secondary endpoint was percent change from baseline to nadir in anti-FXa activity during the first 2 hours post-randomisation.

In ANNEXA-I, eligible patients were randomised 1:1 to andexanet alfa or usual care. In total, 530 patients were enrolled, of whom 320 (60.4%) had received apixaban and 154 (29.1%) had received rivaroxaban. These formed the extended population used for safety and sensitivity analyses. Efficacy was assessed in an interim analysis that included 452 patients (primary efficacy population), of whom 275 (60.8%) had received apixaban and 129 (28.5%) had received rivaroxaban. In the extended population, the median age was 80 years, 52.3% were male, and 93.3% of the patients were white. The most common indication for FXa inhibitors was atrial fibrillation (84.0%).

Overall, 76.8% and 21.2% of patients in the andexanet alfa group received the low and high dose regimen, respectively. In the usual care group, 87.6% of patients were treated with PCC, 10.3% of patients received no haemostatic treatment (platelets or packed red blood cells were allowed) and 0.9% of patients were treated with other therapy.

The most common bleeding location was intracerebral haemorrhage (91.7%), most bleeds were spontaneous (86.9%) and the median (IQR) haematoma volume at baseline was 9.9 (3.6, 24.5) mL. The median time from symptom onset to treatment was 4.1 hours.

Haemostatic efficacy
In the primary efficacy population, andexanet alfa was statistically superior to usual care in achieving effective haemostasis at 12 hours in acute ICrH in patients receiving a direct oral FXa inhibitor (67.0% versus 53.1%, difference 13.4% [95% CI 4.6%, 22.2%], p=0.0032).

Anti-FXa change from baseline to nadir
In the primary efficacy population, andexanet alfa was statistically superior to usual care in reducing anti-FXa activity from baseline to nadir during the first 2 hours post-randomisation in acute ICrH in patients receiving a direct oral FXa inhibitor (−94.4% versus −27.5% median reduction, $p < 0.0001$). The median on treatment nadir in anti-FXa activity was 5.1 ng/mL in the andexanet alfa group and 80.9 ng/mL in the usual care group. The median (95% CI) reduction from baseline to nadir in anti-FXa activity was −94.1% (-95.1%, -93.3%) versus −20.8% (-28.4%, -13.9%) for patients who had previously taken apixaban and −96.4% (-97.3%, -94.9%) versus −46.8% (-60.6%, -35.5%) for rivaroxaban, in the andexanet alfa and usual care group, respectively.

Thrombotic events
In the ANNEXA-I study, adjudicated thrombotic events through 30 days post-randomisation were reported in 26 patients (10.9%) in the andexanet alfa group and 13 patients (5.6%) in the usual care group.

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 73 patients who had a prior history of stroke or myocardial infarction, 10 patients (13.7%) had a thrombotic event, compared with 16 of 166 patients (9.6%) without this medical history. In the 40 patients who had a history of heart failure, 8 patients (20.0%) had a thrombotic event, compared with 18 of 199 patients (9.0%) without this medical history (see section 4.4). Such numerical increases were not observed in the corresponding sub-groups in the usual care treatment group.

Patients in the andexanet alfa group and usual care group experienced one or more of the following adjudicated thrombotic events, respectively: ischaemic stroke (6.7% versus 1.3%), myocardial infarction (4.6% versus 1.3%), pulmonary embolism (0.4% versus 2.6%), arterial systemic embolism (1.3% versus 0.4%) and deep vein thrombosis (0.4% versus 0.9%). 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 experienced a thrombotic event during the first 3 days, compared to 1 patient in the usual care group. All thrombotic events that occurred within the first 5 days after treatment were arterial events. None of the affected patients had received any dose of anticoagulant prior to the thrombotic event. Adjudicated thrombotic events leading to death were reported in 6 patients (2.5%) in the andexanet alfa group and 2 patients (0.9%) in the usual care group.

Overall, 182 patients (76.2%) in the andexanet alfa group and 168 patients (72.4%) in the usual care group were restarted with any anticoagulant within 30 days post-randomisation based on clinical judgement.

Mortality
In total, 67 patients (28.0%) in the andexanet alfa group and 61 patients (26.3%) in the usual care group died before Day 30 post-randomisation. Overall, there were 54 patients (22.6%) in the andexanet alfa group and 51 patients (22.0%) in the usual care group with in-hospital death. Bleeding-related deaths within 72 hours post-randomisation were reported in 12 patients (5.0%) in the andexanet alfa group and 16 patients (6.9%) in the usual care group.

Functional outcomes
The change from baseline in NIHSS score up to 72 hours post-randomisation was numerically better in the andexanet alfa group compared to the usual care group, with a difference of -1.2, 95% CI (-2.3%, -0.2%) for the average over 72 hours. The effects on neurologic deterioration (NIHSS score increase ≥4 or a GCS score decrease ≥2 at 24 hours post-randomisation), mRS score and GCS scores were similar between both treatment groups. The odds ratio for functional independence (mRS 0-3) at 30 Day when comparing andexanet alfa to usual care was 1.23, 95% CI (0.78, 1.92), with a GCS score difference of 0.1, 95% CI (-0.4, 0.6) for the average over 72 hours.

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 bleeding patients is not known.

Paediatric population
The European Medicines Agency 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).

Conditional approval
This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year, and this SmPC will be updated as necessary.

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 bleeding patients 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]
C_{max} (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 and other handling

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 AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1345/001 4 vials
EU/1/18/1345/002 5 vials

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 April 2019
Date of latest renewal: 04 April 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Lonza Biologics Porrino, S.L.
C/ La Relba s/n
Porrino
Pontevedra
36410 Spain

Name and address of the manufacturer responsible for batch release

Alexion Pharma International Operations Limited
Alexion Dublin Manufacturing Facility
College Business and Technology Park
Blanchardstown Rd North
Dublin D15 R925
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.
The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
SOB 1: In order to further characterise the safety of Ondexxya, the adequacy of posology and the pharmacodynamic interaction between Ondexxya and enoxaparin post infusion, the MAH should submit the results of a phase 1 randomised, single-blind placebo-controlled study in healthy volunteers pre-treated with rivaroxaban or apixaban.	Submission of final CSR by December 2026
SOB 2: Considering the results from the imposed phase 1 single-blind, placebo-controlled study, in order to assess the haemostatic effect and the risk of thromboembolic events of Ondexxya, the MAH should conduct a randomised controlled clinical trial in 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, according to an agreed protocol.	Submission study protocol within 3 months of completing SOB 1 Submission of final CSR by December 2031

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ondexxya 200 mg powder for solution for infusion
andexanet alfa

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 200 mg of andexanet alfa.

3. LIST OF EXCIPIENTS

Excipients: Tris base, Tris hydrochloride, L-arginine hydrochloride, sucrose, mannitol, polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion
4 x 1 vial of 200 mg
5 x 1 vial of 200 mg

5. METHOD AND ROUTE OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1345/001 4 vials
EU/1/18/1345/002 5 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Ondexxya 200 mg powder for solution for infusion
andexanet alfa
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg

6. OTHER

Store in a refrigerator.
Do not freeze.
For single use only.
AstraZeneca AB

B. PACKAGE LEAFLET

Package Leaflet: Information for the patient and user

Ondexxya 200 mg powder for solution for infusion
andexanet alfa

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully, because it contains important information for you. Please note this medicine is mainly used in emergency situations, and the doctor will have decided that you needed it.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ondexxya is and what it is used for

Ondexxya contains the active ingredient andexanet alfa. It reverses the effects of certain anticoagulants called factor Xa inhibitors (apixaban or rivaroxaban). Factor Xa inhibitors are given to prevent clots in your blood vessels. Your doctor may decide to give you Ondexxya to rapidly reverse the effects of the anticoagulant in case of a life-threatening or uncontrolled bleeding situation.

2. What you need to know before you receive Ondexxya

Do not use Ondexxya
- if you are allergic to andexanet alfa or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to hamster proteins.
- if you are receiving heparin.

Warnings and precautions
Reversing the effect of a factor Xa inhibitor with Ondexxya may increase the risk of blood clots. After treatment with Ondexxya, your doctor will decide when to restart anticoagulant therapy.

An independent pro-coagulant effect of andexanet alfa may pose an additional risk of developing thrombosis.

If you suffer side effects when you are being given Ondexxya by infusion (drip), your doctor may decide to slow down or pause your treatment. Your doctor may give you an antihistamine medicine to help with any side effects (see section 4).

If a surgery is planned for you which requires anticoagulation with heparin, Ondexxya should be

avoided.

Children and adolescents
There is no information on the use of Ondexxya in children and adolescents.

Other medicines and Ondexxya
Tell your doctor if you are taking, have recently taken, or might take any other medicines.

This medicine has been designed to reverse the effects of factor Xa inhibitor medicines only. It is unlikely that Ondexxya will influence the effect of other medicines or that other medicines will influence Ondexxya.

Ondexxya-treatment should be avoided if anticoagulation with heparin might become necessary. Ondexxya causes unresponsiveness to heparin.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby.

Ondexxya is not recommended during pregnancy or if you have the potential to become pregnant and are not using birth control.

Do not breast-feed your child while you are taking this medicine. It is unknown if andexanet alfa is excreted in human milk.

Driving and using machines
This medicine is unlikely to affect your ability to drive and use machines.

Ondexxya contains polysorbate 80
This medicine contains 2 mg of polysorbate 80 in each vial which is equivalent to 0.1 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How Ondexxya is used

This medicine is for hospital use only.

Your doctor or nurse will give you this medicine by injection or infusion into a vein.

Your doctor or nurse will work out the dose of this medicine that you need. This is based on the specific anticoagulant medicine you take as well as on the dose and the time since your last dose of anticoagulant medicine.

After you have received Ondexxya, your doctor will decide when to restart your anticoagulant treatment.

Detailed instructions for your doctor or nurse on how to give Ondexxya are given at the end of this package leaflet (see ‘Handling instructions’).

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

List of side effects seen in bleeding people

Common (may affect up to 1 in 10 people)
- Stroke
- Heart-attack
- Blood clot in the leg, arm, lung or brain
- Fever

Uncommon (may affect up to 1 in 100 people)
- Mini stroke
- Cardiac arrest
- Signs/symptoms of infusion related reactions such as chills, high blood pressure, shortness of breath, confusion or agitation.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How Ondexxya is stored

This medicine will be stored in the hospital, and these instructions are intended for hospital staff only.
Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial and the carton after EXP.
The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Once reconstituted, Ondexxya is for immediate use.

6. Contents of the pack and other information

What Ondexxya contains
- The active substance is andexanet alfa.
- The other ingredients are Tris base, Tris hydrochloride, L-arginine hydrochloride, sucrose, mannitol, and polysorbate 80.

What Ondexxya looks like and contents of the pack
Ondexxya is supplied in glass vials as a white to off-white powder for solution for infusion, which is reconstituted (dissolved) before use. The reconstituted solution is a clear, colourless, or slightly yellow solution.

Each pack contains four or five vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
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Manufacturer
Alexion Pharma International Operations Limited
Alexion Dublin Manufacturing Facility
College Business and Technology Park
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in
This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only.

Andexanet alfa has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any FXa inhibitor other than rivaroxaban or apixaban. Also, it will not reverse the effects of non-FXa inhibitors.

Dosage and administration
Andexanet alfa is administered as an intravenous (IV) bolus at a target rate of approximately 30 mg/min over 15 (low dose) or 30 minutes (high dose), immediately 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).

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

Dosage recommendations have been defined from the effects of andexanet alfa in healthy volunteers administered a direct FXa inhibitor and from the ability to reverse the levels of anti-FXa activity. The dosage was used in studies in patients with acute major bleeding.

Reversal of apixaban
The recommended dose regimen of andexanet alfa 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 should support the clinical decision of starting treatment

(if level is available in an acceptable timely frame).

Table 2: Summary of dosing for reversal of apixaban

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

Reversal of rivaroxaban

The recommended dose regimen of andexanet alfa 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 should support the clinical decision of starting treatment (if level is available in an acceptable timely frame).

Table 3: Summary of dosing for reversal of rivaroxaban

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

Patients being treated with FXa inhibitor therapy have underlying disease states that predispose them to thromboembolic events. Reversing FXa inhibitor therapy exposes patients to the thrombotic risk of their underlying disease. To reduce this risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate.

Handling instructions

Andexanet alfa is to be reconstituted and the 10 mg/mL solution then transferred without further dilution to sterile large volume syringes in case a syringe pump is used for administration or to suitable empty IV bags comprised of polyolefin (PO) or polyvinyl chloride (PVC) material. Prior to administration by IV infusion, a 0.2 or 0.22 micron in-line polyethersulfone (PES) or equivalent low protein-binding filter should be used.

For reconstituted solutions, chemical and physical in-use stability have been demonstrated for at least eight hours at 25°C. From a microbiological point of view, once opened, 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.

Reconstitution

Before starting reconstitution, you will need the following:

- Calculated number of vials as given in Table 1.
- 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 administration is done with a syringe pump, 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 done with IV bags).
- Water for injection
- 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. Use aseptic technique during the reconstitution procedure.

Reconstitute each vial 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 injection.
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 andexanet alfa within eight hours after reconstitution when stored at room temperature.

<u>Administration using a syringe pump</u>
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. Prepare the bolus and infusion in separate large volume syringes.
3. Due to the additional volume, the high dose bolus and infusion will need 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.

<u>Administration using intravenous bags</u>
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 appropriate IV bags.
3. Repeat steps 1 and 2 as necessary to transfer the complete volume of the bolus and the infusion into 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.