

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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion

White to off-white lyophilized 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).

Table 2: Summary of dosing for reversal of apixaban

FXa inhibitor	Last dose	Timing of last dose before Ondexxya initiation	
		< 8 hours or unknown	≥ 8 hours
Apixaban	≤ 5 mg	Low dose	Low dose
	> 5 mg/ Unknown	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).

Table 3: Summary of dosing for reversal of rivaroxaban

FXa inhibitor	Last dose	Timing of last dose before Ondexxya initiation	
		< 8 hours or unknown	≥ 8 hours
Rivaroxaban	≤ 10 mg	Low dose	Low dose
	> 10 mg/ Unknown	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. 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) is transferred to a suitable empty intravenous bag comprised of polyolefin (PO) or polyvinyl chloride (PVC) material without further dilution (see section 6.6) prior to administration by IV infusion using a 0.2 or 0.22 micron in-line polyethersulfone (PES) or equivalent low protein-binding filter.

Ondexxya is administered as an IV bolus at a target rate of approximately 30 mg/min over 15 to 30 minutes, 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 dosed with apixaban or rivaroxaban. 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).

Although determination of anti-FXa-activity in emergency situations is increasingly recommended, no recommendation for adapted andexanet alfa dosage is available. Therefore, 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).

Dosage recommendation is based upon data-modelling in healthy volunteers. Validation has not been successful, yet. Data from bleeding patients are limited. Preliminary data suggest higher risk of thrombosis for patients receiving the higher dose of andexanet, previous lower dose of the anti-FXa inhibitor, and patients on rivaroxaban.

In ANNEXA-4, intracranial haemorrhage (ICH) patients (GCS > 7 and haematoma volume < 60 mL) have been included. Treatment of patients with more severe ICH with andexanet alfa has not been studied.

Thrombotic events

Thrombotic events have been reported following treatment with andexanet alfa (see sections 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-thrombotic effect of andexanet alfa cannot be ruled out. 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.

In healthy volunteers, dose-dependent increases in coagulation markers F1+2, TAT, and D-dimer after administration of andexanet alfa were observed, but no thromboembolic events were reported. These markers were not measured in patients enrolled in the ANNEXA-4 study, but thromboembolic events have been observed (see section 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 trials. 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with andexanet alfa have been performed.

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 has been evaluated in clinical trials including 247 healthy subjects administered an FXa inhibitor, as well as in 352 patients in a Phase IIIb/IV trial (ANNEXA-4), who had acute major bleeding and were under treatment with an FXa inhibitor (mostly apixaban and rivaroxaban).

In the clinical trials in healthy subjects administered an FXa inhibitor and then receiving andexanet alfa, no serious or severe adverse reactions were reported. The most frequently observed adverse reactions were mild or moderate infusion-related reactions (see table 4) 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 the healthy subject trials, 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. Clinical relevance in the target population (patients with uncontrolled or life-threatening bleeding who are anticoagulated due to high to very high risk of thrombosis) is unknown.

Tabulated list of adverse reactions

Table 4 provides the list of adverse reactions from clinical studies of healthy subjects treated with andexanet alfa. The second column provides the list of adverse reactions from the interim results of the Phase IIIb/IV ANNEXA-4 study, including 352 patients with acute major bleeding treated with andexanet alfa. The adverse reactions are classified by system organ class (SOC) and frequency, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); or not known (cannot be estimated from available data).

Table 4: List of adverse reactions in healthy subjects and bleeding patients

System organ class/ Preferred term	Frequency in healthy volunteers	Frequency in bleeding patients
Immune system disorders		
Urticaria	common	
Nervous system disorders		
Cerebral infarction		uncommon
Cerebrovascular accident		uncommon
Dizziness postural	common	
Headache	common	
Ischaemic stroke		common
Transient ischaemic attack		uncommon
Cardiac disorders		
Acute myocardial infarction		uncommon
Cardiac arrest		uncommon
Myocardial infarction		uncommon
Palpitations	common	
Vascular disorders		
Deep vein thrombosis		uncommon
Iliac artery occlusion		uncommon
Respiratory, thoracic and mediastinal disorders		
Cough	common	
Dyspnoea	common	
Pulmonary embolism		uncommon

System organ class/ Preferred term	Frequency in healthy volunteers	Frequency in bleeding patients
Gastrointestinal disorders		
Abdominal discomfort	common	
Abdominal pain	common	
Dry mouth	common	
Dysgeusia	common	
Nausea	common	
Skin and subcutaneous tissue disorders		
Pruritus	common	
Pruritus generalised	common	
Musculoskeletal and connective tissue disorders		
Back pain	common	
Muscle spasms	common	
General disorders and administrative site conditions		
Flushing	very common	
Feeling hot	very common	
Chest discomfort	common	
Hyperhidrosis	common	
Peripheral coldness	common	
Pyrexia		common
Investigations		
Transient elevations of D-dimer and F1+2 fragments	very common	

Description of selected adverse reactions

Based on data from 352 patients from the Phase IIIb/IV ANNEXA-4 study treated with an FXa inhibitor and experiencing an acute major bleeding episode, one patient experienced a serious or severe infusion-related reaction. Thirty-six of 352 patients with complete 30-day safety follow up (10.3%) had thrombotic events, including venous thromboembolism (VTE), myocardial infarction (MI), and stroke. Ten of 36 (27.8%) patients had restarted antithrombotic therapy at the time of the event, and all 36 patients had been anticoagulated for a prior history of VTE and/or atrial fibrillation at the time of receiving andexanet alfa (see sections 4.4 and 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important, as 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 trials.

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, although there may be a minor contribution from the inhibition of tissue factor pathway inhibitor (TFPI) activity through binding to TFPI. The interaction between andexanet alfa and TFPI has not been fully characterized. Andexanet alfa binds direct FXa inhibitors with high affinity, making them unavailable to exert their anticoagulant effects.

Pharmacodynamic effects

The effects of andexanet alfa can be measured through pharmacodynamic markers, including anti-FXa activity, and free fraction of available FXa inhibitor as well as through restoration of thrombin generation.

Anti-FXa activity correlates poorly to clinical efficacy and safety, making it unsuitable for dosing guidance (see section 4.4 and 5.1)

In prospective, randomized, 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.

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 for 10 to 20 hours following andexanet alfa administration. The clinical relevance of this interaction in terms of maintenance of thrombin generation and the potential for a prothrombotic effect has not been fully elucidated.

PK/PD modelling

Bolus strengths of andexanet alfa being necessary to achieve mean unbound apixaban (400 mg bolus) and unbound rivaroxaban concentrations (800 mg bolus) below the anticipated respective threshold for no anticoagulant effect were twice as high for rivaroxaban (20 mg QD) compared to apixaban (5 mg BID), due to the differential PK characteristics and dose levels of respective FXa inhibitor.

Clinical efficacy and safety

The efficacy and safety of andexanet alfa have been evaluated in the following: 1) randomized, placebo-controlled, Phase II dose-ranging trials 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; and 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.

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

In a prospective, randomized, 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

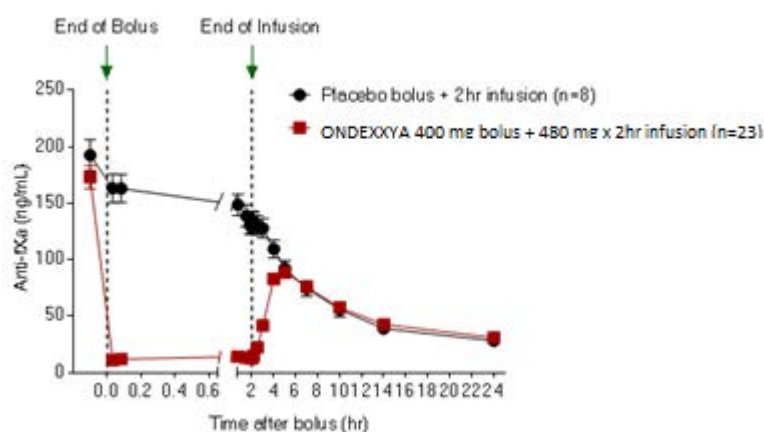
The primary endpoint for both Study 14-503 (apixaban) and Study 14-504 (rivaroxaban) was the percent change in anti-FXa activity from baseline to post-infusion nadir.

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

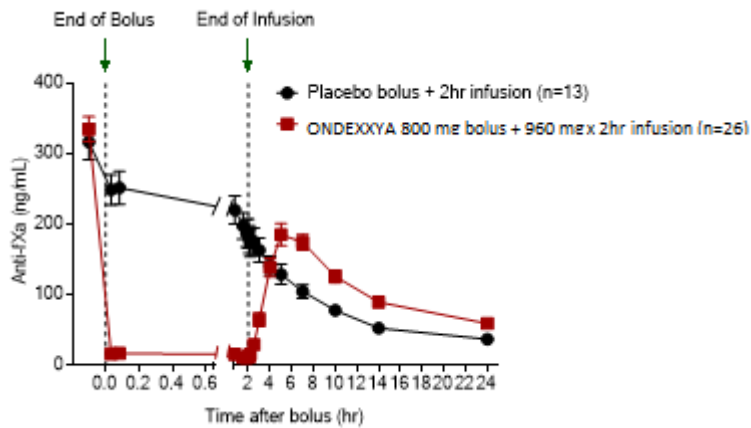
Among the rivaroxaban-treated subjects in Study 14-504, the percent change in anti-FXa activity was -96.72% (\pm 1.838%) for the andexanet alfa group and -44.75% (\pm 11.749%) for the placebo group ($p < 0.0001$), the latter reflecting the intrinsic clearance of the anticoagulant.

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 normalization 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

In Study 14-505 (ANNEXA-4), a Phase IIIb/IV multinational, prospective, single-arm, open-label study, Ondexxya was administered to 352 patients on FXa inhibitors who presented with acute major bleeding. The two co-primary endpoints are: a) percent change in anti-FXa activity from baseline to the nadir between five minutes after the end of the bolus 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.

In an updated interim analysis, data of 352 patients were evaluated.

Approximately half of the patients were male, and the mean age was 77.4 years. Most patients had previously received either apixaban (194/352; 55.1%) or rivaroxaban (128/352; 36.4%), and experienced either an ICH (230/352; 65.3%) or a gastrointestinal (GI) bleed (94/352; 26.7%). 297/352 patients (84.4%) received the low-dose regimen of andexanet, while 55 patients (15.6%) received the high-dose regimen.

Of 352 enrolled patients, 249 (70.7%) were included in the efficacy-analysis. For these patients, median anti-FXa activity at baseline was 149.7 ng/mL for patients taking apixaban, and 211.8 ng/mL for patients taking rivaroxaban. Median change from baseline to nadir in anti-FXa activity was -93.4% (95% CI -94.3%, -92.4%) for apixaban, and -92.5% (95% CI -94.2%, -90.3%) for rivaroxaban. Haemostatic efficacy was good or excellent in 81.9% of 249 patients.

The updated interim analysis demonstrated that the change in anti-FXa activity (surrogate) was not predictive for achievement of hemostatic efficacy in the overall patient population.

Deaths

In the ANNEXA-4 study, of the patients in the safety population completing 30-day follow up (N=351), 54 patients (15.4%) died. The 30-day mortality rates were 16.2% (37/229) in patients presenting with ICH, 12.8% (12/94) with GI bleeding, and 17.9% (5/28) with other types of bleeding. The 30-day mortality rates were 20.1% (44/219) in patients aged > 75 years old and 7.6% (10/132) in patients aged ≤ 75 years. According to region, death rates were 22.1% (31/140) in patients recruited in the European Union and 10.9% (23/211) in patients recruited in North America. Compared with patients recruited in North America, EU patients were significantly older (79.0 years vs. 76.3 years), more frequently had ICH as index event (72.9% vs. 59.0%) and more ICHs were intraparenchymal (54.9% vs. 34.4%). Cardiovascular causes of death (n=27) included: haemorrhagic stroke (n=6), ischaemic stroke (n=5), sudden cardiac death (including unwitnessed) (n=5), cardiomechanical/pump failure (n=4), myocardial infarction (n=2), bleeding other than haemorrhagic stroke (n=1), and other cardiovascular causes (n=4). Non-cardiovascular deaths (n=27) included: respiratory failure (n=5), infection/sepsis (n=5), accident/trauma (n=2), cancer (n=1), and other/non-vascular cause (n=14).

Thromboembolic events

In the ANNEXA-4 study, 36 (10.3%) patients experienced a total of 42 thromboembolic events: cerebrovascular accident (CVA) (15/42; 35.7%), deep venous thrombosis (13/42; 33.1%), acute myocardial infarction (8/42; 19.0%), pulmonary embolism (5/42; 11.9%), and transient ischaemic attack (1/42; 2.4%). The median time to event was nine days. A total of 33.3% of patients with thromboembolic events (12/36) experienced the thromboembolic event during the first three days. Of the 209 patients who were re-anticoagulated prior to a thrombotic event, 10 (4.8%) patients experienced a thromboembolic event. At the time of the event 10/36 (27.8%) patients were on antithrombotic therapy. The occurrence of thromboembolic events was generally comparable between patients > 75 years (11.0%; 24/219) and those ≤ 75 years of age (9.1%; 12/132).

No thromboembolic events were observed in 223 healthy volunteers who received FXa inhibitors and were treated with andexanet alfa. Dose-dependent increases in coagulation markers F1+2, TAT, and D-dimers after administration of andexanet alfa were observed, but these markers were not measured in patients enrolled in the ANNEXA-4 study, and their relevance in bleeding patients 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, non-neutralizing antibodies to andexanet alfa were detected in approximately 10% (35/345). These antibodies were generally low titre, and no clinical consequences were observed. No neutralising antibodies or antibodies to factor X or FXa were detected. To date, the occurrence of positive, non-neutralizing antibodies to andexanet alfa following treatment in patients in the ANNEXA-4 study (8.5% or 20/236 patients) has been similar to that observed in healthy subjects.

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

Phase II studies of andexanet alfa in the presence of direct FXa inhibitors demonstrated the same dose proportional pharmacokinetics over the intended therapeutic dose range evaluated for both C_{\max} and area under the curve (AUC) with an effective half-life of approximately one hour. The volume of distribution at steady state ($V_{d_{ss}}$) and volume of distribution (V_d) at sub-therapeutic levels decreased with dose, consistent with the saturation of a high-affinity compartment, likely to reflect binding to endothelial cell bound TFPI, the only endogenous molecule known to bind andexanet alfa. FXa inhibitors did not affect andexanet alfa pharmacokinetics at therapeutic levels.

All PK studies were conducted using a former drug substance generation. PK comparability with andexanet alfa in Ondexxya (Generation 2) has not yet been proven.

Distribution

The V_d for andexanet alfa is 5.3 ± 2.6 L, approximately equivalent to the blood volume.

Elimination

Clearance (L/hr) for andexanet alfa is 4.4 ± 1.2 L/hr with low renal elimination. The elimination half-life ranges from four to seven hours. Based on what is known about the disposition kinetics of native FXa, andexanet alfa is likely rapidly broken down in plasma by endogenous proteases, consistent with its relatively short effective half-life (one hour).

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 trials 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 trials 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)

Two years stored at 2°C to 8°C.

Reconstituted medicinal product

Chemical and physical in-use stability have 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 vials.

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 larger) needle.
- Alcohol swabs.
- Large (60 mL or larger) sterile syringe. If a syringe driver is used for administration, multiple syringes should be used to contain the final volume of reconstituted product.
- Intravenous PO or PVC bag (150 mL or larger) to contain the final volume of reconstituted product (if administration is performed with an IV bag).

- Water for injections

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 larger) 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 (60 mL or larger) syringe equipped with a 20 gauge (or larger) 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, air filters, syringe driver) 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 an intravenous bag

1. Once all required vials are reconstituted, withdraw the reconstituted solution from each vial, using the large volume (60 mL or larger) syringe equipped with a 20 gauge (or larger) 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 an IV bag.
4. While it is permissible to combine the bolus and infusion into a single IV bag, it is recommended that the bolus and infusion be split into two separate bags to ensure the correct administration rate.
5. Attach ancillary equipment (i.e., extension tubing, air filters, 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

Portola Netherlands B.V.
Prins Bernhardplein 200
1097 JB Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1345/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 April 2019

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

Portola Netherlands B.V.
Prins Bernhardplein 200
1097 JB Amsterdam
Netherlands

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**

The requirements for submission of periodic safety update reports 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The 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(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further substantiate correlation of the biomarker (antiFXa-activity) with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events, the MAH should submit the results of ANNEXA-4, an interventional non-randomized, multicentre, prospective, open-label, single-group study in patients with acute major bleeding.	Submission of the final CSR by 30 June 2021
In order to further confirm the posology of Ondexxya, the MAH should submit the results of a comparative PK study with Generation 1, process 3, and Generation 2 material (study 19-514). The study should be based on an agreed protocol.	Submission of the final CSR by 30 September 2019
In order to substantiate correlation of the biomarker (antiFXa-activity) with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events, the MAH should submit the results of a global randomised controlled clinical trial to investigate the use of andexanet versus standard of care treatment in patients with intracranial haemorrhage (ICH) taking apixaban, rivaroxaban, or edoxaban (study 18-513).	Submission of the final CSR by 30 June 2023
In order to further confirm the efficacy and safety, the MAH should submit an updated PK/PD model using all previously incorporated data (from studies 11-501, 12-502, 14-503, 14-504, and 14-506) as well as newly incorporated data from study 16-512 (PK-PD study of Generation 2 andexanet versus Generation 1), study 16-508 (PK-PD study of andexanet in individuals of Japanese ethnicity), and study 14-505 (ANNEXA-4).	Submission by 30 September 2019

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(S)

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. METHOD AND ROUTE(S) 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

Portola Netherlands B.V.
Prins Bernhardplein 200
1097 JB Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1345/001

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(S) 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.

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
2. What you need to know before you receive Ondexxya
3. How Ondexxya is used
4. Possible side effects
5. How Ondexxya is stored
6. Contents of the pack and other information

1. What Ondexxya is and what it is used for

Ondexxya contains the active ingredientandexanet 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 toandexanet alfa or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to hamster proteins

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.

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).

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.

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.

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.

The most common side effects associated with Ondexxya in clinical trials of healthy people were infusion-related reactions with usually mild symptoms such as flushing or feeling hot (very common side effects which may affect more than 1 in 10 people). Headache, cough, or shortness of breath (common side effects which may affect up to 1 in 10 people) happened within a few minutes to a few hours of the infusion. In clinical trials of patients with life-threatening bleeding, fever and stroke may affect up to 1 in 10 people; transient ischaemic attack (TIA), heart attack, and blood clots in the legs or lungs may affect up to 1 in 100 people (uncommon side effects).

List of possible side effects

Very common (may affect more than 1 in 10 people)

- flushing or feeling hot
- effects on blood clotting markers: some markers which affect blood clotting were increased for a little while and then returned to normal. There were no blood clots in these healthy people.

Common (may affect up to 1 in 10 people)

- hives
- dizziness
- rapid or irregular heartbeat
- stomach pain or discomfort
- dry mouth
- disturbance of taste
- nausea (feeling sick)
- chest discomfort
- feeling cold
- excessive sweating
- itching
- back pain
- muscle spasms

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 vials.

Marketing Authorisation Holder and Manufacturer

Portola Netherlands B.V.
Prins Bernhardplein 200
1097 JB Amsterdam
Netherlands

This leaflet was last revised in Month YYYY.

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 web site:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only.

Andexanet alfa reverses the anticoagulant effect of direct factor Xa (FXa) inhibitor products (apixaban, rivaroxaban) only. Reversal of the effects of other FXa inhibitors (e.g., fondaparinux, unfractionated heparin) with andexanet alfa has not been studied in humans. 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 posology was confirmed in a study 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).

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 or unknown	≥ 8 hours
Apixaban	≤ 5 mg	Low dose	Low dose
	> 5 mg/ Unknown	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).

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 or unknown	≥ 8 hours
Rivaroxaban	≤ 10 mg	Low dose	Low dose
	> 10 mg/ Unknown	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 to a suitable IV bag comprised of polyolefin (PO) or polyvinyl chloride (PVC) material without further dilution prior to administration by IV infusion using a 0.2 or 0.22 micron in-line polyethersulfone (PES) or equivalent low protein-binding filter.

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 larger) needle.
- Alcohol swabs.
- Large (60 mL or larger) sterile syringe. If administration is done with a syringe driver, multiple syringes should be used to contain the final volume of reconstituted product.

- IV PO or PVC bag (150 mL or larger) to contain the final volume of reconstituted product (if administration is done with an IV bag).
- Water for injection

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 larger) 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 discoloration prior to administration. Do not use if opaque particles or discoloration 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.

Administration using a syringe pump

1. Once all required vials are reconstituted, withdraw the reconstituted solution from each vial, using the large volume (60 mL or larger) syringe equipped with a 20 gauge (or larger) 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, air filters, syringe driver) 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 an intravenous bag

1. Once all required vials are reconstituted, withdraw the reconstituted solution from each vial, using the large volume (60 mL or larger) syringe equipped with a 20 gauge (or larger) 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 an IV bag.
4. While it is permissible to combine the bolus and infusion into a single IV bag, to ensure the correct administration rate, it is recommended that the bolus and infusion are split into two separate bags.
5. Attach ancillary equipment (i.e., extension tubing, air filters, 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.

Annex IV
**Conclusions on the granting of the conditional marketing authorisation presented by the
European Medicines Agency**

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.