Date: 19 January 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

ONDEXXYA

International non-proprietary name: andexanet alfa
Pharmaceutical form: powder for solution for infusion
Dosage strength: 200 mg
Route(s) of administration: i.v.
Marketing Authorisation Holder: Alexion Pharma GmbH
Marketing Authorisation No.: 67759
Decision and Decision date: approved on 02.12.2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
FX	Factor X
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance andexanet alfa of the medicinal product mentioned above.

Temporary authorisation for human medical products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

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.

2.2.2 Approved Indication

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.

2.2.3 Requested Dosage

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.

Table 1: Dosing regimens

	Initial intravenous bolus	**Continuous Intravenous infusion**
Low dose	400 mg at a target rate of 30 mg/min	4 mg/min for 120 minutes (480 mg)
High dose	800 mg at a target rate of 30 mg/min	8 mg/min for 120 minutes (960 mg)

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 or 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).

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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 or unknown	High dose	

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	19 March 2020
Formal control completed	23 March 2020
List of Questions (LoQ)	20 May 2020
Answers to LoQ	29 July 2020
Predecision	16 September 2020
Answers to Predecision	12 November 2020
Final Decision	02 December 2020
Decision	approval

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3 Medical Context

Andexanet alfa is a recombinant inactivated human factor Xa indicated when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

4 Quality Aspects

4.1 Drug Substance

Andexanet alfa is a recombinant modified human FXa protein that lacks catalytic activity, but retains the ability to bind FXa inhibitors. Andexanet alfa is designed to neutralise the anticoagulant effects of both direct and indirect factor Xa (FXa) inhibitors by binding and sequestering the inhibitors, thus allowing for restoration of the normal haemostatic processes. Andexanet alfa lacks the membrane-binding domain (Gla) of plasma-derived factor X (FX), and the active site serine has been exchanged with an alanine, resulting in the loss of both procoagulant and anticoagulant activity on its own.

Andexanet alfa is a two-chain molecule comprising a light chain (LC) of approximately 12 kDa and a heavy chain (HC) of approximately 28 kDa, connected by a single inter-chain disulphide bond. Andexanet alfa consists of 359 amino acid residues. Post-translational modifications include hydroxylation and glycosylation, as also found for the human factor X.

Andexanet alfa is manufactured using a recombinant mammalian cell line derived from Chinese hamster ovary. Direct expression from the vector construct results in a single protein strand comprising heavy chain, light chain and a cleavable linker LC. Enhancement of the linker cleavage is achieved by co-expression of recombinant human furin in the production cell line. A two-tiered cell bank system was developed and qualified according to ICH Q5D. No other animal-derived materials are used in the manufacturing process.
Suspension cells and serum-free media are used in the upstream manufacturing process. Andexanet alfa is secreted into the culture medium and separated from cell debris by centrifugation and filtration steps. The purification process comprises several chromatographic and filtration steps, as well as virus inactivation and nanofiltration.

The presented established control strategy and validation data demonstrated that the manufacturing process is capable of producing drug substance lots that consistently meet the requirements. Manufacturing process changes during development are supported by process and analytical comparability studies. Batch analysis data for non-clinical batches, clinical batches, and commercial batches are provided.
The physicochemical, biological, and immunological properties of andexanet alfa were extensively characterised using state of the art techniques.

The active substance batch release procedures include a panel of tests to confirm the identity, potency, and purity of andexanet alfa and to check that impurities are within acceptable limits. The analytical methods are adequately described and have been validated in accordance with ICH guidelines.

Stability studies according to ICH Q1A and B and ICH Q5C were performed. Based on the submitted stability data, the proposed storage conditions and shelf life of the drug substance in its commercial container are considered to be satisfactory.

4.2 Drug Product

Ondexxya is supplied as a sterile, white to off-white lyophilised cake or powder filled into a 20 mL glass vial containing 200 mg andexanet alfa. The lyophilised drug product is reconstituted with 20 mL of sterile water for injection (not supplied) to give a final concentration of 10 mg/mL andexanet alfa. The solution is preservative-free and intended for single use. The drug product is formulated in a Tris-

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buffered solution containing L-arginine, sucrose, mannitol, and polysorbate 80, with a target pH of 7.8. The reconstituted drug product is administered intravenously to the patient.

The manufacturing process for the finished drug product consists of thawing, pooling, sterile filtration, aseptic filling, partial stoppering, lyophilisation, capping, inspection, labelling and packaging steps. The manufacturing process for Ondexxya has been validated using four consecutive full-scale production batches using the same process and the same equipment as intended for commercial supply.

During the process development of the drug product, several changes were implemented. Analytical comparability was demonstrated based on the comparison of release data, head-to-head analysis and stability data.

For drug product batch release, a panel of test procedures are performed to confirm the identity, potency, and purity of Ondexxya and to check that impurities are within acceptable limits. The test procedures are validated according to ICH and/or comply with Ph. Eur. procedures.

The container closure systems in contact with the finished product consist of a type I colourless glass vial and a coated chlorobutyl elastomer stopper.
The claimed shelf life of 36 months when stored at 2 to 8°C is justified based on stability studies performed according to ICH guidelines.
Chemical and physical in-use stability has been demonstrated for up to 16 hours at 2 to 8°C in the primary container/closure, and for up to 8 hours at room temperature in the IV bag. From a microbiological point of view, once reconstituted, the product should be used immediately.

The manufacturing process for the drug substance and drug product includes adequate control measures to prevent contamination and maintain control with regard to adventitious agents safety.

4.3 Quality Conclusions

From a product quality perspective the data submitted in this application support the conclusion that the manufacture of Ondexxya is robust and sufficiently controlled to result in a consistent and safe product.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Ondexxya, Swissmedic conducted an abridged evaluation that was based on the assessment reports from the EMA (CHMP assessment report for Ondexxya dated 28.02.2019 and related documentation) and the FDA (Pharmacology/Toxicology Reviews for Andexxa), which were provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Ondexxya (active substance andexanet alfa) in the proposed indication. Pharmacology, pharmacokinetics, and the toxicological profile of andexanet alfa were sufficiently characterised. Studies on genotoxicity and carcinogenicity were not conducted and are not considered necessary in accordance with ICH guidelines S6 (R1) and S1A. Nor were any reproductive toxicity studies conducted. This is acceptable given the intended limited use (single-dose administration), the fact that crossing of the placental barrier is unlikely, and since there were no findings on reproductive organs in the toxicity studies. Moreover, neither apixaban nor rivaroxaban should be used during pregnancy and lactation, i.e. use of andexanet alfa in pregnant and breastfeeding women is expected to be very rare. The lack of studies/data on genotoxicity, carcinogenicity, and reproduction toxicity is addressed in the information for healthcare professionals. In the safety pharmacology and repeated-dose toxicity studies there were no particular safety issues identified that would be of concern for human use.

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6 Clinical and Clinical Pharmacology Aspects

The evaluation of the clinical and clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA and the FDA. The available assessment reports and corresponding product information texts from the EMA and the FDA were used as a basis for the clinical and clinical pharmacology evaluation.
For further details concerning clinical pharmacology, dosing recommendations, efficacy and safety, see section 8.1 of this report.

6.1 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Ondexxya was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.
Ondexxya 200 mg is temporarily authorised – see “Properties/Effects” section.

Ondexxya 200 mg powder for solution for infusion

Composition

Active substances

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

Excipients

Trometamol, trometamol hydrochloride, L-arginine hydrochloride, sucrose 200 mg, mannitol (E421), polysorbate 80 (E433)

Pharmaceutical form and active substance quantity per unit

Powder for solution for infusion

Each vial contains 200 mg of andexanet alfa.
After reconstitution, each mL of solution contains 10 mg of andexanet alfa.

Indications/Uses

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.

Dosage/Administration

Restricted to hospital use only.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

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 “Warnings and precautions”).

Special dosage instructions

Patients with impaired hepatic function

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

Patients with impaired renal function

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.

Elderly patients (aged 65 years and over)

No dose adjustment is required in elderly patients (see section “Pharmacokinetics”).

Children and adolescents

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

Mode 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 administered, via sterile large volume syringes in case a syringe pump is used for administration, or otherwise via a suitable empty intravenous bag comprised of polyolefin (PO) or polyvinyl chloride (PVC) material (see “Instructions for Handling” in section “Other information”). Intravenous administration should be carried out using a 0.2 or 0.22 micron in-line polyethersulfone (PES) or equivalent filter with appropriate low protein-binding.
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 “Instructions for Handling” in section “Other information”.

Contraindications

Hypersensitivity to the active substance or any of the excipients listed under Composition.
Known allergic reaction to hamster proteins.

Warnings and precautions

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 “Properties/Effects”).
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. 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 “Undesirable effects” and “Properties/Effects”). 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 “Properties/Effects”). 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.

Interaction with heparin

Use of andexanet alfa prior to heparinisation, e.g. before, during or after surgery, should be avoided as andexanet alfa neutralises the effect of heparin and the anticoagulant preventive effect is therefore lost. As a result of this interaction, neither the effect of heparin nor that of andexanet alfa can be monitored, as the clotting tests used in clinical practice give unreliable results and cannot be used for monitoring. The length of time after administration of andexanet alfa during which heparin neutralisation can be expected has not been evaluated.
Use of andexanet alfa as an antidote for heparin or low-molecular weight heparin has not been evaluated and is not recommended (refer to section “Interactions”).

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.

Interactions

No interaction studies with andexanet alfa have been performed.
In vitro data suggest interaction of andexanet alfa with heparin-anti-thrombin III (ATIII) complex and neutralisiation of the anticoagulant effect of heparin. A loss in the effect of heparin during off-label use of andexanet alfa pre-surgery with intended heparin-anticoagulation has been observed (refer to section “Warnings and precautions”). Use of andexanet alfa as an antidote for heparin or low-molecular weight heparin has not been evaluated and is not recommended.

Pregnancy, 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 “Preclinical data”). Andexanet alfa is not recommended during pregnancy or in women of childbearing potential not using contraception.

Lactation

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.

Effects on ability to drive and use machines

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

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 >2x 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 (≥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 in healthy subjects and bleeding patients

System organ class/ Preferred term	**Frequency in healthy volunteers**	**Frequency in bleeding patients**
Immune system disorders		
Urticaria	common	

System organ class/ Preferred term	Frequency in healthy volunteers	Frequency in bleeding patients
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
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	

System organ class/ Preferred term	Frequency in healthy volunteers	Frequency in bleeding patients
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 undesirable effects

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 “Warnings and precautions” and “Properties/Effects”).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

Properties/Effects

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 characterised. Andexanet alfa binds direct FXa inhibitors with high affinity, making them unavailable to exert their anticoagulant effects.

Pharmacodynamics

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.

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 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

The efficacy and safety of andexanet alfa have been evaluated in the following:

1) randomised, 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)

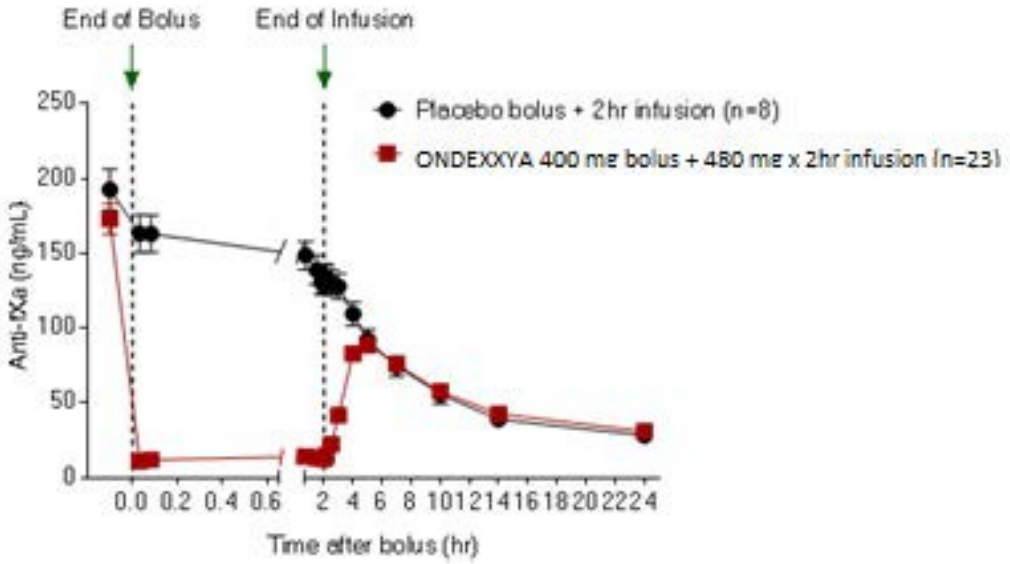
In a prospective, randomised, placebo-controlled study, healthy subjects with a median age of 56.5 years on apixaban 5 mg twice daily received andexanet alfa (n=24) administered as a 400 mg IV bolus immediately followed by a 4 mg per minute IV infusion for 120 minutes (480 mg) or placebo (n=8).
In a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

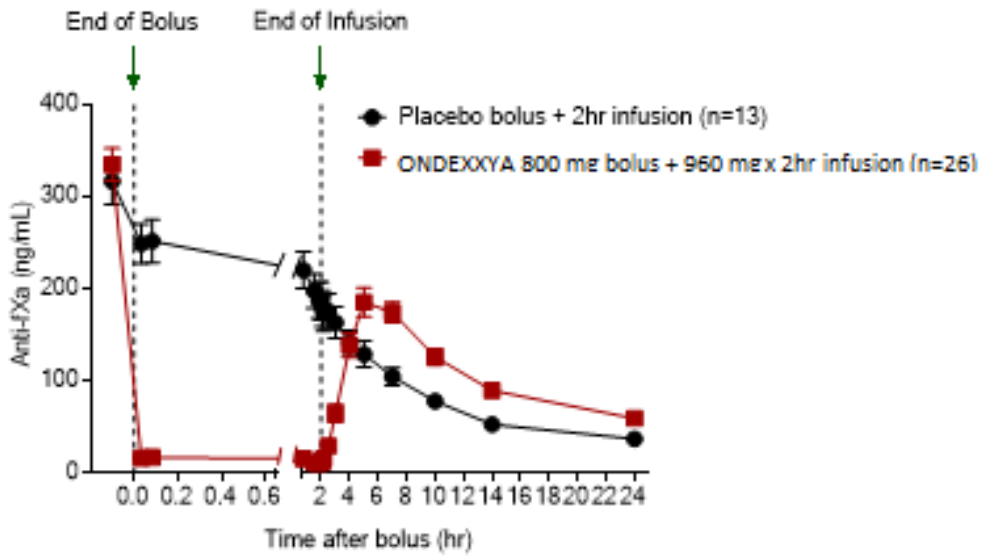
The primary endpoint for both Study 14-503 (apixaban) and Study 14-504 (rivaroxaban) was the percent change in anti-FXa activity from baseline to post-infusion nadir.
Among the apixaban-treated subjects in Study 14-503, the percent change in anti-FXa activity was -92.34% (±2.809%) for the andexanet alfa 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 in anti-FXa activity was -96.72% (±1.838%) for the andexanet alfa group and -44.75% (±11.749%) for the placebo group ($p < 0.0001$), the latter reflecting the intrinsic clearance of the anticoagulant.
The time courses of anti-FXa activity before and after andexanet alfa administration are shown in Figure 1. Reduction in anti-FXa activity correlates with restoration of thrombin generation. The anti-FXa activity thresholds for normalisation of thrombin generation (defined by mean ETP and standard

deviations) were estimated to be 44.2 ng/mL (within one standard deviation of normal ETP) based on pooled data from Studies 14-503 and 14-504, as indicated in the figure.

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



(A)



(B)

Restoration of thrombin generation

In both, Study 14-503 and Study 14-504, treatment with andexanet alfa also resulted in a statistically significant increase in thrombin generation in healthy subjects anticoagulated with apixaban or rivaroxaban versus placebo ($p < 0.0001$). Restoration of thrombin generation to within normal ranges (defined as one standard deviation from baseline levels) within two minutes and maintained for

20 hours was achieved with bolus only and bolus plus infusion for low-dose andexanet alfa in subjects on apixaban. For subjects on rivaroxaban, high-dose andexanet alfa (bolus plus infusion) resulted in increased thrombin generation above two standard deviations. No clinical evaluation for apixaban-treated subjects with high-dose andexanet alfa and no evaluation for rivaroxaban-treated subjects with low-dose andexanet alfa was performed in these studies.

Change from baseline in free FXa inhibitor concentration at nadir

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

Reversal of FXa inhibitor anticoagulation in patients with acute major bleeding

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 of 352 (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-neutralising 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-neutralising 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.

Safety and efficacy in paediatric patients

No data available (see section “Dosage/Administration”).

Temporary authorisation

The medicinal product Ondexxya has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary

authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

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 (Vd_{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.

Absorption

Not applicable.

Distribution

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

Metabolism

No data available.

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).

Kinetics in specific patient groups

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.

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.

Elderly patients

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.

Gender

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

Children and adolescents

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

Preclinical data

Safety pharmacology/Toxicity after repeat dose

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.

Genotoxicity/Carcinogenicity

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.

Reproductive toxicity

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

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

Reconstituted medicinal product

Chemical and physical in-use stability have been demonstrated for 16 hours at 2-8 °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, the diluted solution must be used immediately unless reconstitution/dilution has been carried out under controlled

and validated aseptic conditions. If the solution is not used immediately, the duration of storage and conditions are the responsibility of the user.

Special precautions for storage

Store in the refrigerator (2-8 °C).
Do not freeze.
Store in the original packaging.
Keep out of the reach and sight of children.
For storage conditions after reconstitution of the medicinal product, see section “Shelf life after opening”.

Instructions for handling

Reconstitution

The following are needed before starting reconstitution:

- Calculated number of vials (see section “Dosage/Administration”).
- Same number of 20 mL (or larger) solvent syringes equipped with a 20 gauge (or larger) 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 bags).
- 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 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 (50 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, 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 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 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.
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.

Authorisation number

67759 (Swissmedic)

Packs

Pack size of 4 vials.

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

Marketing authorisation holder

Alexion Pharma GmbH

Giesshübelstrasse 30

8045 Zürich

Schweiz

Date of revision of the text

September 2020