Alexion Pharma GmbH, Giesshübelstrasse 30, 8045 Zürich
Ondexxya 200 mg powder for solution for infusion
Swissmedic Authorisation Number: 67759

Swiss Summary of the Risk Management Plan for ONDEXXYA® (Andexanet Alfa)

Based on EU-RMP version number:	2.2
Data lock point for this RMP:	25 April 2020
Date of final sign off:	23 September 2020

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.
The RMP summary of ONDEXXYA is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of ONDEXXYA in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Alexion Pharma GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of ONDEXXYA.

PART VI: Summary of the Risk Management Plan

Summary of risk management plan for Ondexxya (andexanet alfa)

This is a summary of the risk management plan (RMP) for Ondexxya. The RMP details important risks of Ondexxya, how these risks can be minimised, and how more information will be obtained about Ondexxya's risks and uncertainties (missing information).

Ondexxya's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ondexxya should be used.

This summary of the RMP for Ondexxya should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ondexxya's RMP.

I. The medicine and what it is used for

Ondexxya is authorised 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 (see SmPC for the full indication). It contains andexanet alfa as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Ondexxya's benefits can be found in Ondexxya's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Ondexxya, together with measures to minimise such risks and the proposed studies for learning more about Ondexxya's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Ondexxya is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Ondexxya are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ondexxya. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Thrombotic events Antibody formation
Important potential risks	Off-label use in patients treated with anticoagulants other than as indicated Re-bleeding
Missing information	Use in patients who receive (pre-treatment) vitamin K antagonist, PCC products, recombinant FVIIa, whole blood or plasma fractions; or planned administration of these products within 12 hours of andexanet alfa treatment Use in pregnant or lactating patients Use in children

II.B Summary of important risks

Identified risk 1: Thrombotic events	
Evidence for linking the risk to the medicine	The evidence for the mechanism and frequency of thrombotic events (TEs) is drawn from clinical trials, published literature and the ANNEXA-4 study in bleeding patients. In Phase I-III healthy volunteer studies of andexanet alfa, elevations in F1+2 and D dimer and reductions in TFPI were observed both in the absence (Phase I) and presence (Phase II and III) of FXa inhibitors. However, the magnitude of elevations was attenuated in the presence of FXa inhibitors. In the nonclinical toxicology study NC-11-0395, similar elevations in F1+2 and D-dimer were evident. In the human Phase I-III studies, the elevations of F1+2 and D-dimer were coincident with a parallel decrease in levels of TFPI. As andexanet alfa is known to bind TFPI, this provides a plausible mechanism for these elevations and, by extension, a possible pro-coagulant effect.

Risk factors and risk groups	Patients taking FXa inhibitors who experience an episode of major bleeding are at increased risk of TEs if they survive the major bleed. Patients with acute major bleeding on anticoagulants are at high risk for TEs for three reasons. First, patients prescribed anticoagulants generally have an underlying condition that necessitates their use; these conditions (e.g. atrial fibrillation, venous thromboembolism) are pro-thrombotic in nature. Second, patients with acute major bleeding experience alterations in haemostatic parameters that results in a paradoxical pro-thrombotic state, especially when the bleeding is due to traumatic injury. Third, due to their bleeding event, patients are often not re-anticoagulated for days or even weeks. Available results from the ANNEXA-4 study showed that patients enrolled in this study had a high baseline thrombotic risk based on their age, comorbidities (indication for FXa inhibitor), acute major bleeding status, and level of disability.
Risk minimisation measures	Routine risk minimisation measures: – SmPC sections 4.2, 4.4, 4.8, and 5.1 – PL section 4 Re-introduction of anticoagulation treatment recommendation provided in SmPC section 4.4 Restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities – ANNEXA-4 (14-505) – ANNEXA-I (18-513) See section II.C of this summary for an overview of the post-authorisation development plan.

Identified risk 2: Antibody formation	
Evidence for linking the risk to the medicine	Subjects enrolled within the clinical development programme for andexanet alfa showed low titres of anti-andexanet alfa antibodies.
Risk factors and risk groups	There were no significant differences in antibody formation between men and women or across race/ethnicity.
Risk minimisation measures	Routine risk minimisation measures: – SmPC section 5.1 – PL section 4 Restricted medical prescription Additional risk minimisation measures: None

Additional pharmacovigilance activities	Additional pharmacovigilance activities: – ANNEXA-4 (14-505) – ANNEXA-I (18-513) See section II.C of this summary for an overview of the post-authorisation development plan.

Potential risk 1: Off-label use in patients treated with anticoagulants other than as indicated	
Evidence for linking the risk to the medicine	Andexanet alfa is expected to be approved only for use in patients taking apixaban or rivaroxaban which creates a potential for off-label use with other FXa inhibitors.
Risk factors and risk groups	The risk groups are those patients taking other FXa inhibitors such as edoxaban and enoxaparin, as all patients on anticoagulants have a risk of major bleeding.
Risk minimisation measures	Routine risk minimisation measures: – SmPC sections 4.1, 4.2, 4.4, and 5.1 – PL sections 1 and 2 Restricted medical prescription Additional risk minimisation measures: None

Potential risk 2: Re-bleeding	
Evidence for linking the risk to the medicine	ANNEXA-4 (14-505)
Risk factors and risk groups	Risk groups are patients taking FXa inhibitors who experience an episode of major bleeding. Risk factors for re-bleeding include: older age; hypertension; poor Hunt-Hess grades; intracerebral or intraventricular hematomas; aneurysms >10 mm in size; aneurysms in the posterior circulation; lobar ICH; concomitant use of ulcerogenic agents; renal impairment; Helicobacter pylori infection; a history of gastrointestinal bleeding; presence of an anticoagulant. These risk factors will be present in the patients irrespective of administration of andexanet alfa.
Risk minimisation measures	Routine risk minimisation measures: – SmPC section 4.2 – PL section 3 Restricted medical prescription Additional risk minimisation measures: None

Additional pharmacovigilance activities	Additional pharmacovigilance activities: – ANNEXA-4 (14-505) – ANNEXA-I (18-513) See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information 1: Use in patients who receive (pre-treatment) vitamin K antagonist, PCC products, recombinant FVIIa, whole blood or plasma fractions; or planned administration of these products within 12 hours of andexanet alfa treatment	
Risk minimisation measures	Routine risk minimisation measures: – SmPC section 4.4 Restricted medical prescription Additional risk minimisation measures: None

Missing information 2: Use in pregnant or lactating patients	
Risk minimisation measures	Routine risk minimisation measures: – SmPC sections 4.6 and 5.3 – PL section 2 Restricted medical prescription Additional risk minimisation measures: None

Missing information 3: Use in children	
Risk minimisation measures	Routine risk minimisation measures: – SmPC section 4.3 – PL section 2 Restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: – Paediatric Protocol See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

ANNEXA-4 (14-505)

Purpose of the study: To confirm correlation between FXa activity and haemostatic efficacy and clarify the risk of thromboses and thromboembolic events.

ANNEXA-I (18-513)

Purpose of the study: To substantiate correlation of the biomarker (anti-FXa-activity) with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events, the effect of andexanet versus standard of care will be studied in patients with intracranial haemorrhage (ICH) taking apixaban, rivaroxaban, or edoxaban.

II.C.2 Other studies in post-authorisation development plan

Paediatric Protocol

Purpose of the study: To evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of andexanet in paediatric patients taking enoxaparin.