Ondexxya®

200 mg (Andexanet alfa),
Pulver zur Herstellung einer Infusionslösung

Summary of the Risk Management Plan (RMP) for Ondexxya ® (Andexanet alfa)

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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. “Name of the marketing authorisation holder” is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ondexxya.

VI: PART VI: SUMMARY OF THE 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.

VI: 1 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 (andexanet) 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.

VI: 2 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.

VI: 2.1 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).

Table 0–1 List of important risks and missing information

Important identified risks	Thrombotic events
Important potential risks	Antibody formation Medication error 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

VI: 2.2 Summary of important risks

Table 0-2 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 1-3 healthy volunteer studies of andexanet, elevations in F1+2 and D-dimer were observed both in the absence (Phase 1) and presence (Phase 2 and 3) of FXa inhibitors. However, the magnitude of elevations was attenuated in the presence of FXa inhibitors. In the nonclinical toxicology study NC-11-0394, similar elevations in F1+2 and D-dimer were evident. In the human Phase 1-3 studies, the elevations of F1+2 and D-dimer were coincident with a parallel decrease in levels of tissue factor pathway inhibitor (TFPI). As andexanet is known to bind TFPI, this provides a plausible mechanism for these elevations.
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 on FXa inhibitors 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 after the FXa inhibitor is discontinued. 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), severity of illness, and increased level of disability.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC sections “Dosage/Administration”, “Warnings and Precautions”, “Undesirable effects”, and “Properties/Effects” Re-introduction of anticoagulation treatment recommendation provided in SmPC sections “Dosage/Administration” and “Warnings and Precautions” Restricted medical prescription <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities</u> • ANNEXA-I (18-513) See section VI: 2.3 of this summary for an overview of the post-authorisation development plan.

Table 0-3 Potential risk 1: Antibody formation

Evidence for linking the risk to the medicine	This potential risk is based on the known potential of all therapeutic proteins to induce development of anti-drug antibodies. Subjects enrolled within the clinical development programme for andexanet showed low titres of antiandexanet antibodies without any meaningful undesirable clinical outcomes.
Risk factors and risk groups	Not yet established for andexanet.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section "Properties/Effects" Restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities • ANNEXA-I (18-513) See section VI: 2.3 of this summary for an overview of the post-authorisation development plan.

Table 0-4 Potential risk 2: Medication error

Evidence for linking the risk to the medicine	Ondexxya is a complex product with a dosing scheme depending on the FXa inhibitor used and other parameters. Administration of andexanet is associated with a potential for medication errors and as such, this potential risk was assessed as important for the risk management.
Risk factors and risk groups	No risk groups or risk factors have been identified.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections "Dosage/Administration", "Overdose", and "Other information" Restricted medical prescription Additional risk minimisation measures: None

Table 0-5 Potential risk 3: Off-label use in patients treated with anticoagulants other than as indicated

Evidence for linking the risk to the medicine	Because the mechanism of action of andexanet encompasses all FXa inhibitors, and andexanet has been studied with FXa inhibitors other than apixaban and rivaroxaban, it is anticipated that physicians will use andexanet in patients taking other FXa inhibitors.

Table 0-5 Potential risk 3: Off-label use in patients treated with anticoagulants other than as indicated

Risk factors and risk groups	No specific risk groups or risk factors have been identified.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections "Indications/Uses", "Dosage/Administration", "Warnings and Precautions", and "Properties/Effects" Restricted medical prescription Additional risk minimisation measures: None

Table 0-6 Potential risk 4: 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 haematomas; aneurysms > 10 mm in size; aneurysms in the posterior circulation; lobar intracranial haemorrhage; 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.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections "Dosage/Administration" and "Warnings and Precautions" Restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities • ANNEXA-I (18-513) See section VI: 2.3 of this summary for an overview of the post-authorisation development plan.

Table 0-7 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 "Warnings and Precautions" Restricted medical prescription Additional risk minimisation measures: None.

Table 0-8 Missing information 2: Use in pregnant or lactating patients

Risk minimisation measures	Routine risk minimisation measures: • SmPC sections "Pregnancy, lactation" and "Preclinical data" Restricted medical prescription Additional risk minimisation measures: None

Table 0-9 Missing information 3: Use in children

Risk minimisation measures	Routine risk minimisation measures: • SmPC sections "Dosage/Administration", "Properties/Effects", and "Pharmacokinetics" Restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Paediatric Protocol See section VI: 2.3 of this summary for an overview of the post-authorisation development plan.

VI: 2.3 Post-authorisation development plan

VI: 2.3.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

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 usual of care will be studied in patients with intracranial haemorrhage taking apixaban, rivaroxaban, or edoxaban.

Other purposes for this study include studying of re-introduction of anticoagulation and justification of posology in combination with PK/PD modelling study as specified in the SOB 3 and 4.

PK/PD modelling

Purpose of the study: This activity involves a submission of 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).

Other purposes for this study include studying of re-introduction of anticoagulation and justification of posology in combination with Study 18-513 as specified in the SOB 3 and 4.

VI: 2.3.2 Other studies in post-authorisation development plan

Paediatric Protocol

Purpose of the study: Changes in study scope (FXa inhibitors used), protocol, and timelines was were proposed by the MAH but any changes need to be first agreed by the Paediatric Committee (PCDO) within a paediatric investigation plan (PIP) modification procedure. The RMP will be updated once the PIP modification is approved by the PDCO.