

10/2025

Ondexxya

אונדקסיה

ANDEXANET ALFA 200 MG/VIAL

Powder for Solution for Infusion

רופא/ה, חוקח/ת נכבד/ה,

חברת אלקסיון פארמה ישראל בע"מ מבקשת להודיע על עדכוני בטיחות בעלון לרופא של התכשיר שבנדון. העלון עודכן בתאריך 10/2025.

ההתוויה הרשומה לתכשיר בישראל:

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.

בהודעה זו מצוינים השינויים המהותיים בלבד.

מקראה לעדכונים המסומנים:

מידע שהוסר - מסומן בקו אדום **XXX**; תוספת - כתב **כחול**; מידע בטיחותי מסומן עם רקע **צהוב**

עדכונים מהותיים שנעשו בעלון לרופא:

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Excipient with known effect

Each vial of Ondexxya contains 2 mg of polysorbate 80.

For the full list of excipients, see section 6.1.

4.2 Special warnings and precautions for use

Limitations of use

Clinical efficacy is based upon reversal of anti-FXa-activity in healthy volunteers and **achievement of haemostatic efficacy in** bleeding patients dosed with apixaban or rivaroxaban. **Clinical benefit in terms of reduced morbidity or mortality has not been demonstrated** (see section 5.1). Andexanet alfa is not suitable for pre-treatment of urgent surgery. Use for edoxaban or enoxaparin-reversal is not recommended due to lack of data. Andexanet alfa will not reverse the effects of non-FXa inhibitors (see section 5.1).

(...)

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

(...)

Thrombotic events

Serious arterial and venous thromboembolic Thrombotic events have been reported following treatment with andexanet alfa **including frequent reports of early manifestation (within 72 hours) after reversal. Patients with prior history of stroke, myocardial infarction or heart failure may be at higher risk of thrombotic events** (see sections 4.8 and 5.1).

(...)

Monitoring for signs and symptoms of thrombosis is, therefore, strongly recommended **and should be started early after treatment.**

(...)

Interaction with heparin

Use of andexanet alfa prior to heparinisation e.g. during **surgery surgeries or procedures** should be avoided as andexanet alfa causes unresponsiveness to heparin. Use of andexanet alfa as an antidote for heparin or low-molecular weight heparin has not been evaluated and is not recommended (**refer to see** section 4.5.).
(...)

Excipient with known effect

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with andexanet alfa have been performed.

In vitro data suggest interaction of andexanet alfa with the heparin- anti-thrombin III (ATIII) complex and neutralization of the anticoagulant effect of heparin. Off-label use of andexanet alfa pre-surgery **with intended heparin-anticoagulation intra-operatively, or during procedures requiring heparinisation** has been reported to cause unresponsiveness to heparin (**refer to see** section 4.4). Use of andexanet alfa as an antidote for heparin or low-molecular weight heparin has not been evaluated and is not recommended

4.8 Undesirable effects

Summary of the safety profile

The safety of andexanet alfa has been evaluated in clinical trials including 417 healthy subjects administered an FXa inhibitor, as well as in 419 patients in a Phase IIIb/IV trial (study 14-505), who had acute major bleeding and were under treatment with an FXa inhibitor (apixaban and rivaroxaban).

In clinical studies in healthy subjects who were administered a FXa inhibitor and then received andexanet alfa, the frequency of adverse reactions was similar in the andexanet alfa-treated group (16.8%) and in the placebo-treated group (12.2%). The most frequently observed adverse reactions **in healthy volunteers** were mild or moderate infusion-related reactions comprising symptoms such as flushing, feeling hot, cough, dysgeusia, and dyspnoea occurring within a few minutes to a few hours of the infusion. Among the healthy subjects studied, women experienced more adverse reactions (mainly infusion-related reactions) than men.

In clinical studies including patients with acute major bleeding and who were under treatment with a FXa inhibitor (apixaban or rivaroxaban), the most frequently observed adverse reactions were pyrexia (8.8%), ischaemic stroke (6.7%), and myocardial infarction (4.6%).

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.

In patients with major bleedings thrombosis-markers have not been investigated since bleeding can interfere with the thrombosis marker results. Thromboses and thromboembolic events have commonly been documented.

Table 4: List of adverse reactions in patients with major bleeds

System organ class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100
Nervous system disorders	Cerebrovascular accident	Cerebral infarction

	Ischaemic stroke ^b	Transient ischaemic attack
Cardiac disorders	Acute myocardial infarction Myocardial infarction ^c	Cardiac arrest
Vascular disorders	Deep vein thrombosis	Embolism arterial ^d Iliac artery occlusion
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	
General disorders and administrative site conditions	Pyrexia	
Injury, poisoning and procedural complications		Infusion related reaction ^a

^a reported signs/symptoms (rigors, chills, hypertension, oxygen desaturation, agitation and confusion) were transient and mild to moderate in severity.

^b Ischaemic stroke includes, e.g. the preferred terms: cerebrovascular accident, cerebellar stroke and cerebral infarction.

^c Myocardial infarction includes, e.g. the preferred term: acute myocardial infarction.

^d Embolism arterial includes, e.g. the preferred terms: iliac artery occlusion, renal infarct and femoral artery embolism

Description of selected adverse reactions

Thrombotic events

Arterial and venous thrombotic events including ischaemic stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, arterial systemic embolism and transient ischaemic attack have been observed in clinical trials, with frequent reports of early manifestation (within 72 hours) following treatment with andexanet alfa (see section 4.4 and 5.1).

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

Based on data from 419 patients from the Phase IIIb/IV study 14-505 treated with apixaban and rivaroxaban and experiencing an acute major bleeding episode, two patients (0.5%) experienced an infusion-related reaction, neither of which was assessed as severe (1 moderate; 1 mild).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

(...)

Immunogenicity

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

(...)

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.**

(...)

Deaths

In the safety population (n=419), 75 patients (18%) died. ~~Of the 75 subjects who died, the bleeding type was intracranial bleeding in 55 (73%), gastrointestinal bleeding in 14 (19%), and other bleeding types in 6 (8%) subjects.~~ The mortality rates were 19.0% (55/289) in patients presenting with ICH, 14.7% (14/95) with GI bleeding, and 17.1% (6/35) with other types of bleeding. ~~The mortality rates were 23.0% (64/278) in patients aged > 75 years old and 7.8% (11/141) in patients aged ≤ 75 years. According to region, death rates were 24.9% (53/213) in patients recruited in the European Union and 11.3% (22/194) in patients recruited in North America. The higher mortality rate in Europe is only present in older patients or patients with heart failure. Compared with patients recruited in North America, EU patients were significantly older (81.0 years vs. 79.0 years), more frequently had ICH as index event (75.1% vs. 60.3%) and more ICHs were intraparenchymal (69.3% vs. 42.7%).~~ Cardiovascular causes of death (n=36) included: haemorrhagic stroke (n=6), ischaemic stroke (n=10), sudden cardiac death (including unwitnessed) (n=6), cardiomechanical/pump failure (n=4), myocardial infarction (n=2), bleeding other than haemorrhagic stroke (n=2), and other cardiovascular causes (n=6). Non-cardiovascular deaths (n=39) included: infection/sepsis (n=11), respiratory failure (n=6), accident/trauma (n=2), cancer (n=2), and other/non-vascular cause (n=18). The average time to death was 15 days after treatment. All deaths occurred before Day 44.

Thromboembolic events

In study 14-505, 45/419 (11%) patients experienced one or more of the following thromboembolic events: cerebrovascular accident (CVA) (19/45; 42%), deep venous thrombosis (11/45; 24%), myocardial infarction (MI) including acute myocardial infarction and myocardial ischaemia (9/45; 20%), pulmonary embolism (PE) (5/45; 11%), and transient ischaemic attack (TIA) (1/45; 2%). The median time to first thromboembolic event was 10 days. A total of 38% of patients with thromboembolic events (17/45) experienced the thromboembolic event during the first three days. Of the 419 subjects who received andexanet alfa, 266 received at least one anticoagulation dose within 30 days after treatment as a prophylactic measure **based on clinical judgment**. ~~Of these 266, 14 subjects (5%) had a thrombotic event after resumption of anticoagulation; while of the 153 subjects who did not receive anticoagulation as a prophylactic, 31 (20.3%) had a thrombotic event (see section 4.4).~~
(...)

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. The occurrence of positive, non-neutralizing antibodies to andexanet alfa following treatment in patients in the study 14-505 (8% or 22/276 patients) has been similar to that observed in healthy subjects.~~

6.6 Special precautions for disposal and other handling

(...)

syringes equipped with a 20 gauge (or **larger smaller in diameter, e.g. 21 gauge**) needle.

בעלון קיימים עדכונים נוספים.

למידע נוסף יש לעיין בעלון לרופא המעודכן אשר נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות. כמו כן, ניתן לקבלו מודפס על ידי פניה לבעל הרישום: אלקסיון פארמה ישראל בע"מ, ת.ד. 7063, פתח תקווה 4917001. טלפון: 03-9373753, פקס: 03-9373774

בברכה, עוז וולך, רוקח/ת ממונה של בעל הרישום