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Re: ANDEXXA (andexanet alfa): Update on frequency of thrombotic events and patient subgroups at higher risk of thrombosis

Dear Healthcare Professional,

AstraZeneca in agreement with the national medicines authority, Saudi Food & Drug Authority (SFDA), would like to inform you of the following:

Summary

- The purpose of disseminating this Direct Healthcare Professional Communication (DHPC) is to inform about upcoming updates to Sections 4.4 and 4.8, Table 4 of the Saudi Arabia Summary of Product Characteristics (SmPC) for ANDEXXA (Andexanet alfa).

- Thrombotic events are recognised as Adverse Drug Reactions (ADRs) with the use of ANDEXXA. Based on cumulative clinical data from 2 completed clinical trials (ANNEXA-4 and ANNEXA-I) the frequency of several thrombotic events such as cerebral infarction, cerebrovascular accident, acute myocardial infarction, myocardial infarction, deep vein thrombosis and pulmonary embolism have been changed from 'uncommon' (≥ 1/1 000 to < 1/100) to 'common' (≥ 1/100 to < 1/10).

- Patients with a history of stroke, myocardial infarction or heart failure are known to have an inherently elevated risk of thrombotic events, independent of anticoagulant reversal therapy. Results from the

ANNEXA-I trial suggest that these patient subgroups may be at higher risk of thrombotic events following treatment with ANDEXXA.

- Healthcare professionals are strongly advised to closely monitor patients for signs and symptoms of thrombosis after initiating treatment with ANDEXXA, as per current recommendations in the Saudi Arabia SmPC.

- The overall benefit-risk for ANDEXXA remains positive, as the observed benefit in achieving hemostasis continues to outweigh the risks of thrombotic events.

Background on the safety concern

ANDEXXA (andexanet alfa) is indicated 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.

ANNEXA-4 was a phase 3b/4, open-label, single-arm, prospective, multicenter trial in patients presenting with acute major bleeding and receiving apixaban, rivaroxaban, edoxaban, or enoxaparin (Milling et al 2023). The current Saudi Arabia SmPC reflects adverse reaction frequencies derived from interim data of the ANNEXA-4 trial, which included 352 participants (Connolly et al 2019). The forthcoming update to the Saudi Arabia SmPC will incorporate data from the completed Annexa-4 trial expanding the number of participants to 477.

ANNEXA-I was the first randomized controlled clinical trial to compare ANDEXXA and usual care regarding efficacy and safety in patients with acute intracranial hemorrhage (ICH) after receiving a direct oral FXa inhibitor and was designed to test the hypothesis that ANDEXXA is superior to usual care in achieving effective hemostasis.

The trial was conducted in patients with acute ICH as this represents a condition of life-threatening and uncontrolled bleeding with an established method for objective measurement of hematoma size and expansion.

The overall safety profile of ANDEXXA in the ANNEXA-I population was consistent with the known safety profile of ANDEXXA and no new safety concerns were identified. The overall thrombotic event rate was 10.3% (n=262) and comparable to the previous single arm trial of ANNEXA-4 of 10.5% (n=477). The Thrombotic events rate derived from the Annexa-4 interim results was 9.7% (n=352). Review of data confirmed that observed benefit of

hemostatic efficacy outweighs the risk of thrombotic events and the overall benefit-risk profile of ANDEXXA remains positive (Connolly et al 2024)

The frequency of thrombotic events has been updated, based on cumulative clinical data from the ANNEXA-4 and ANNEXA-I trials, as follows:

List of Thrombotic Adverse Reactions in Bleeding Patients Receiving ANDEXXA

MedDRA System Organ Class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1 000 to < 1/100)**
Nervous system disorders	Ischemic stroke* Cerebral infarction Cerebrovascular accident	Transient ischemic attack*
Cardiac disorders	Myocardial infarction Acute myocardial infarction	Cardiac arrest*
Vascular disorders	Deep vein thrombosis	Iliac artery occlusion*
Respiratory, thoracic mediastinal disorders	Pulmonary embolism	

*The frequency has not changed since previous SmPC version

Patients being treated with FXa inhibitors have underlying disease states that predispose them to thrombotic events. Data from ANNEXA-I showed that patients with prior history of stroke, myocardial infarction, or heart failure may be at higher risk of thrombotic events. Patients treated with ANDEXXA should be monitored for signs and symptoms of arterial and venous thromboembolic events, ischemic events, and cardiac arrest as stated in the current Saudi Arabia SmPC.

Call for reporting

Report an adverse event and special situation, using one of the following methods:

- Directly to AstraZeneca Patient Safety:
  Email: ksa.ae@astrazeneca.com - Phone: +966 11 2249235
  Portal: https://contactazmedical.astrazeneca.com
- SFDA reporting information:
  Email: npc.drug@sfda.gov.sa -Toll-free phone: 19999
  Portal: https: //ade.sfda.gov.sa

As ANDEXXA is a biological medicinal product, also report the product name and batch details when reporting an adverse event.

Literature References

Connolly et al 2024
Connolly SJ, Sharma M, Cohen AT, Demchuk AM, Członkowska A, Lindgren AG, et al. Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage. N Engl J Med. 2024 May 15;390(19):1745-55.

Connolly et al 2019
Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, Yue P, et al. Full study report of Andexanet alfa for bleeding associated with Factor Xa inhibitors. N Engl J Med. 2019;380:1326-1335.

Milling et al 2023
Milling TJ Jr, Middeldorp S, Xu L, Koch B, Demchuk A, Eikelboom JW, Verhamme P, Cohen AT, Beyer- Westendorf J, Gibson CM, Lopez-Sendon J, Crowther M, Shoamanesh A, Coppens M, Schmidt J, Albaladejo P, Connolly SJ; ANNEXA-4 Investigators. Final Study Report of Andexanet Alfa for Major Bleeding With Factor Xa Inhibitors. Circulation. 2023 Mar 28;147(13):1026-38.

Best Regards,

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