17th June 2020

Ondexxya (andexanet alfa):

Commercial anti-FXa activity assays are unsuitable for measuring anti-FXa activity following administration of andexanet alfa

Dear Healthcare professional,

Portola Netherlands, B.V., in agreement with the European Medicines Agency and the Medicines & Healthcare products Regulatory Agency, MHRA would like to inform you of the following information regarding Ondexxya (andexanet alfa):

Summary

- **Treatment monitoring after administration 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. In these assays, the FXa inhibitor dissociates from andexanet alfa. This results in the detection of erroneously elevated anti-FXa activity levels and consequently, a substantial underestimation of the reversal activity of andexanet alfa.**

- **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).**

- **Due to the nature of this safety concern, please provide this information also to internal and external contracted laboratories.**

Background on the safety concern

Andexanet alfa is indicated for adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

Current commercial clinical anti-FXa assay methodology yields falsely elevated anti-FXa activity results when andexanet alfa is present in the patient plasma samples because of a high dilution factor

in the assay. Similar to the reversible binding of FXa inhibitors with native FXa, andexanet alfa also binds reversibly to the FXa inhibitors. The reversible binding reaches an overall state of equilibrium, in accordance with the dissociation constant (Kd) of andexanet alfa for the FXa inhibitors. When the sample is undiluted (as in patient's plasma), the reaction equilibrium favors the "bound" state. However, when the sample is diluted significantly, the rate of binding decreases because the inhibitor and andexanet alfa tend to be physically farther apart.

Given the above, high sample dilution causes the andexanet-inhibitor binding/unbinding equilibrium to shift toward the unbound. This increases the amount of FXa inhibitor in the free or unbound state, thereby increasing the amount of inhibitor that is pharmacologically active in the anti-FXa assay. The result is an underestimation of the reversal activity of andexanet, and an erroneous elevation of the anti-FXa activity, which may impact treatment decision making.

It should be noted that in the absence of andexanet alfa, dilution of plasma samples does not affect the anti-FXa activity because the effect of dissociation of the andexanet-inhibitor complex is not an issue.

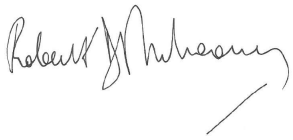
Call for reporting

Ondexxya is subject to additional monitoring. This will allow quick identification of new safety information. Reporting suspected adverse reactions after authorisation of the medicinal product is important.
It is easiest and quickest to report suspected adverse reactions online via the Yellow Card website - https://www.gov.uk/yellowcard/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Alternatively, prepaid Yellow Cards for reporting are available by writing to FREEPOST YELLOW CARD (no other address details necessary), by emailing yellowcard@mhra.gov.uk, at the back of the British National Formulary (BNF), by telephoning the Commission on Human Medicines (CHM) free phone line: 0800 731 6789, or by downloading and printing a form from the Yellow Card section of the MHRA website.
Suspected adverse reactions may also be reported to Portola. Tel: 0800 069 8041 or +31 20 225 4560. Email: info@portola.com.

Company contact point

If you have any questions about this letter or for more information about Ondexxya, please contact Portola Medical Information. Email: info@portolaEU.com or telephone, Phone: 0800 069 8041 or +31 20 225 4560.

Sincerely yours



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