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 <*national competent authority*> 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 after 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 to internal and external contract laboratories as well**.>* *(to be deleted if not applicable at national level)*

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

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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 state. 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.

The Summary of Product Characteristics of Ondexxya will be updated to reflect this information.

Call for reporting

Ondexxya is subject to additional monitoring. <A reminder of the need and how to report adverse reactions in accordance with the national spontaneous reporting system>. Healthcare professionals are asked to report any suspected adverse reactions directly to:

> <Details (name, postal address, fax number, website address) on how to access the national spontaneous reporting system >

Company contact point

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DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Ondexxya (andexanet alfa)
Marketing authorisation holder(s)	Portola Netherlands B.V.
Safety concern and purpose of the communication	Commercial anti-FXa activity assays are unsuitable for measuring anti-FXa activity following administration of andexanet alfa Purpose: To increase awareness that (1) treatment monitoring with andexanet alfa should continue to be based mainly on clinical parameters indicative of appropriate response and (2) commercially available anti-factor Xa activity assays shall not be used, as such assays are unsuitable for measuring anti-FXa-activity following administration of Ondexxya.
DHPC recipients	Hospital pharmacies Physicians working on intensive care units Physicians working on emergency care units Physicians working in cardiology departments <Hospital laboratories and contracted external laboratories in charge of coagulation testing>* *(to be deleted if not applicable at national level)* Target groups should be further defined on national level, depending on national health care systems.
Member States where the DHPC will be distributed	The DHPC will be distributed in those countries in which Ondexxya is marketed, currently Austria, Denmark, Finland, Germany, the Netherlands, Sweden, and the United Kingdom[1]. The DHPC will be distributed in other EU Member States at the time of product launch, in agreement with relevant NCAs. [1]As of 1.2.2020, the UK is no longer an EU Member State. However, EU law still applies to the UK during the transition period.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	14 May 2020
DHPC and communication plan (in English) agreed by CHMP	28 May 2020
Submission of translated DHPCs to the national competent authorities for review	4 June 2020
Agreement of translations by national competent authorities	10 June 2020
Dissemination of DHPC	17 June 2020

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