**Supplementary material: DDI potency of DOACs**

- *Apixaban*

The manufacturer reports that apixaban retains equal efficacy up to a 25% decrease of exposure [1]. Therefore, DDIs resulting in an expected decrease of exposure up to 25% are considered irrelevant. To reduce bleeding risk and retain efficacy, they recommend to adjust the apixaban dose with DDIs resulting in a greater than 50% increase in exposure [1]. Although the benefit-risk ratio for increases up to 50% is expected to be favourable, monitoring may be warranted (yellow).

Apixaban is a substrate for BCRP, P-gp and CYP3A4 and excreted renally as unchanged drug for 25% of the administered dose [1, 2]. Exposure may alter when apixaban is coadministered with inhibitors or inducers of BCRP, P-gp and CYP3A4 [3, 4, 1, 2]. If apixaban is coadministered with a strong CYP3A4 and P-gp inhibitor or inducer, exposure may increase or decrease two-fold, respectively. Therefore, a dose reduction of 50% is recommended when coadministered with a strong CYP3A4 and P-gp inhibitor and a dose doubling is recommended when coadministered with a strong CYP3A4 and P-gp inducer. The P-gp inhibitor naproxen increased $AUC_{0-\infty}$ of apixaban by 54% [5] and, consequently, a dose reduction of 25% is recommended when apixaban is coadministered with P-gp inhibitors to avoid apixaban toxicity (amber). Diltiazem, a moderate CYP3A4 inhibitor and P-gp inhibitor, increased exposure to apixaban by approximately 40% [2, 1]. As this increase seems smaller compared to the increase demonstrated with P-gp inhibitors (e.g. naproxen), no dose adjustments are required when apixaban is coadministered with solely moderate CYP3A4 inhibitors, but monitoring may be warranted (yellow).

The effect of moderate and weak CYP3A4 inducers on exposure of apixaban has not been investigated. Taking into account the modest contribution of CYP3A4 for apixaban's elimination [6] and the smaller effect of moderate and weak than with strong CYP3A4 inducers, we do not expect the decrease of exposure to exceed the previously stated limit of 25%. We therefore categorize DDIs with weak and moderate CYP3A4 inducers green and yellow, respectively. The effect of BCRP

inhibitors or inducers on exposure of apixaban has not been investigated *in vivo*, but this possible DDI is expected to be of weak magnitude (yellow) and does not require dose adjustments as an *in vitro* reduction in BCRP transport was only observed with ketoconazole, but not with other BCRP inhibitors [1].

- *Betrixaban*

Betrixaban is a substrate for P-gp and 19% is excreted in urine as unchanged drug [7]. Exposure will change when coadministered with P-gp inhibitors or inducers [8]. Dose reductions to overcome increased exposure to P-gp inhibitors did not result in the desired reduction of bleeding risk [9]. Therefore, the use of P-gp inhibitors is contraindicated with betrixaban. No data are available regarding the effect of P-gp inducers on betrixaban exposure or efficacy, but considering the magnitude of effect of P-gp inhibitors on betrixaban exposure, a relevant effect of P-gp inducers on betrixaban exposure can be expected and combined use is contraindicated.

- *Dabigatran*

When comparing efficacy of the 150 and 110 mg b.i.d. dabigatran etexilate (prodrug, further referred to as “dabigatran”) dosing regimens, the 110mg b.i.d. dosing regimen was found to be inferior in terms of prevention of stroke [10]. Hence, a small decrease in exposure may result in reduced effectiveness of dabigatran. The effect of an increase in exposure on bleeding risk is less profound: in patients with moderate renal impairment an increase by 130% of exposure did not increase bleeding risk [10, 11]. An increase of exposure to dabigatran by 150% is therefore considered to be not clinically relevant by the manufacturer and does not require dose adjustments [10].
Dabigatran is a P-gp substrate and excreted renally for 80% of the administered dose as unchanged drug. Exposure may be altered by inhibitors and inducers of P-gp. The magnitude of P-gp inhibition varies between drugs, e.g. from no effect on exposure to dabigatran (clarithromycin, naproxen) up to an approximately 140% increase of exposure to dabigatran [10]. Since dabigatran is a prodrug, the

effect of a P-gp inhibitor can be decreased by administering dabigatran 2 hours before the P-gp inhibitor in fasted state [12]. When verapamil, a P-gp inhibitor, was administrated as an immediate release formulation 1 h prior to dabigatran, exposure to dabigatran increased by approximately 140%. When dabigatran was given 2h prior to verapamil, exposure to dabigatran was not significantly increased [10, 13]. Thus, coadministration of P-gp inhibitors with dabigatran requires administrating dabigatran 2h before the P-gp inhibitor in fasted state (amber). P-gp inducers have shown to decrease exposure to dabigatran by approximately 70% [11, 10]. Therefore, we recommend an increase of the dabigatran dose by 200% when coadministered with P-gp inducers to retain efficacy. Laboratory monitoring of dabigatran plasma concentrations may assist dosage adjustments (see "the potential role of laboratory monitoring to individualize DOAC treatment").

- *Edoxaban*

In dose-escalation studies of edoxaban, it was found that a 50% lower dose of 30mg once daily was non-inferior for prevention of thromboembolisms compared to the currently used dose of 60mg once daily (incidence thromboembolisms 12.5% vs. 9.1% respectively; p=0.466) [14]. Decreases in edoxaban exposure up to 50% were therefore considered irrelevant. Because edoxaban is a substrate for P-gp, coadministration with a P-gp inhibitor or inducer may alter exposure to edoxaban and may, consequently, influence the therapeutic effect of edoxaban [15, 16]. Approximately half of the administered dose is excreted as unchanged drug in urine [17].

Coadministration of edoxaban with P-gp inhibitors increased $AUC_{0\text{-}24h/\infty}$ up to 87% [18-20]. Therefore, in clinical trials the edoxaban dose was pragmatically halved in patients concomitantly receiving a P-gp inhibitor which increases exposure by ≥50% to avoid increases of edoxaban exposure and consequent toxicities [21]. This resulted in lower trough edoxaban plasma concentrations (~16 ng/mL) compared to patients receiving a full edoxaban dose without concomitant P-gp inhibitors (~28 ng/mL). This decrease in trough plasma concentrations is 43% and thus, lower than the previously stated 50%, but inferior efficacy was shown compared to patients treated with warfarin

[22]. Therefore, no dose reductions are required when combining edoxaban with a P-gp inhibitor, but monitoring may be warranted (yellow).

Concomitant use of edoxaban with rifampicin, a P-gp inducer, resulted in a 34% decrease of edoxaban exposure [23, 16]. Taking into consideration all information above, no dose adjustment is recommended when edoxaban is coadministered with SMIs that are P-gp inducers as no relevant reduction of edoxaban efficacy is expected with these DDIs, but monitoring may be warranted (yellow). This conclusion is further supported by the finding that prothrombin time and activated partial thromboplastin time was not altered when edoxaban was coadministered with rifampicin [23]. The active metabolite of edoxaban "M4" (<10% total edoxaban exposure) may play a role in this process, to which exposure is significantly elevated when combined with OATP1B1 inhibitors e.g. rifampicin and ciclosporin [23, 19].

- *Rivaroxaban*

Based on exposure-response analyses for rivaroxaban, there appears to be a relationship between rivaroxaban peak concentrations and the occurrence of bleeding at doses routinely used [24]. The relationship between exposure and efficacy seems to plateau from a peak concentration higher than 40 µg/L, which corresponds to concentrations observed for the 2.5 mg b.i.d. dose [24]. Thus, an increase in exposure will result in a higher bleeding risk and coadministration with agents that significantly increase exposure to rivaroxaban, is contraindicated. Coadministration with agents that reduce exposure to rivaroxaban may require dose increases to avoid decreased efficacy. Rivaroxaban is a CYP3A4, P-gp and BCRP substrate and one-third of the administered dose is renally excreted as unchanged drug [17]. Exposure may alter when rivaroxaban is administered with agents that influence these pathways [25, 26]. Strong inhibitors of P-gp and CYP3A4 will increase exposure to rivaroxaban by 50 to 160% [25, 27]. As the magnitude and therefore the clinical effect of this increase is unpredictable, coadministration with strong inhibitors of P-gp and CYP3A4 is contraindicated. Moderate combined inhibitors of P-gp and CYP3A4 or moderate inhibitors of CYP3A4 solo will

increase exposure to rivaroxaban by 30-40% [27]. As 2.5mg tablets are the lowest available administration size, no tablets are available for dose reductions to avoid increased rivaroxaban exposure and bleeding risk with DDIs. Therefore, coadministration with moderate combined P-gp and CYP3A4 or moderate solo CYP3A4 inhibitors is contraindicated. Strong combined inducers of CYP3A4 and P-gp will halve the exposure to rivaroxaban [28, 29] and thus, a doubling of the rivaroxaban dose is needed to avoid a decrease in exposure and in efficacy. To monitor no increase of rivaroxaban exposure occurs compared to plasma concentrations before start of the CYP3A4 and P-gp inducer, laboratory monitoring of rivaroxaban plasma concentrations may be useful (see “the potential role of laboratory monitoring to individualize DOAC treatment”). The effect of solely P-gp inhibition on exposure of rivaroxaban has not been investigated. As any increase of exposure will lead to increased risk of side effects, coadministration with all P-gp inhibitors is contra-indicated. In patients with renal or hepatic impairment, concomitant use of inhibitors of P-gp, BCRP or CYP3A4 could result in an excessive increase in exposure of rivaroxaban and hence, bleeding risk [27]. Thus, extra caution is warranted in these patients and a stricter classification is applied.

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