Supplementary Tables

Non-vitamin K Antagonist Oral Anticoagulant Use in Patients with Renal Impairment

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**Supplemental Table S1: NOAC indications for major markets**

|        | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|--------|------------|----------|----------|-------------|
|        | AF | VTE | OS | ACS | AF | VTE | OS | ACS | AF | VTE | OS | ACS |
| Canada | ✓ | ✓ | ✓ | - | ✓ | ✓ | ✓ | - | ✓ | ✓ | ✓ | - |
| US     | ✓ | ✓ | ✓ | - | ✓ | ✓ | ✓ | - | ✓ | ✓ | ✓ | - |
| EU     | ✓ | ✓ | ✓ | - | ✓ | ✓ | ✓ | - | ✓ | ✓ | ✓ | - |
| Japan  | ✓ | - | - | - | ✓ | ✓ | - | - | ✓ | ✓ | - | - |

ACS: acute coronary syndrome; AF: atrial fibrillation; OS: orthopedic surgery; VTE: venous thromboembolism.
**Supplemental Table S2: NOAC Dose Recommendations for AF in Major Jurisdictions**

| Drug       | Canada                                      | United States                                  | Europe                                      |
|------------|---------------------------------------------|------------------------------------------------|---------------------------------------------|
| Dabigatran | • Recommended dose 150 mg BID              | • CrCl >30 mL/min: 150 mg BID                  | • Recommended dose 150 mg BID              |
|            | • Patients ≥80 years or those at higher risk of bleeding, including elderly ≥75 years with ≥1 bleeding risk factor; recommended dose 110 mg BID | • CrCl 15-30 mL/min: 75 mg BID | • Patients ≥80 years or who receive concomitant verapamil; recommended dose 110 mg BID |
|            | • Contraindicated if eCrCl <30 mL/min      | • Not recommended if CrCl <15 mL/min or on dialysis | • Contraindicated if CrCl <30 mL/min       |
| Apixaban   | • Recommended dose 5 mg BID                | • Recommended dose 5 mg BID                    | • Recommended dose 5 mg BID                |
|            | • Patients with at least 2 of the following: ≥80 years, body weight ≤60 kg, or sCr ≥133 μmol/L (1.5 mg/dL); recommended dose 2.5 mg BID | • Patients with at least 2 of the following: ≥80 years, body weight ≤60 kg, or sCr ≥133 μmol/L (1.5 mg/dL); recommended dose 2.5 mg BID | • Patients with at least 2 of the following: ≥80 years, body weight ≤60 kg, or sCr ≥133 μmol/L (1.5 mg/dL); recommended dose 2.5 mg BID |
|            | • No dosing recommendation for CrCl 15-24 mL/min | • Not recommended if CrCl <15 mL/min           | • Patients with CrCl 15-29 mL/min; recommended dose 2.5 mg BID |
|            | • Not recommended if CrCl <15 mL/min       |                                                 | • Not recommended if CrCl <15 mL/min, or in patients undergoing dialysis |
| Edoxaban   | • Recommended dose 60 mg OD                | • CrCl >50 to ≤ 95 mL/min: 60 mg OD           | • Recommended dose 60 mg OD                |
|            | • In patients with moderate renal impairment (CrCl 30-50 mL/min), weight ≤60 kg, or concomitant use of P-gp inhibitors (except amiodarone and verapamil) recommended dose is 30 mg OD | • CrCl 15-50 mL/min: 30 mg OD                  | • Patients with ≥1 of the following: CrCl 15-50 mL/min, body weight ≤60 kg, concomitant use of P-gp inhibitors (ciclosporin, dronedarone, erythromycin, or ketoconazole); recommended dose 30 mg OD |
|            | • Not recommended in patients with CrCl <30 mL/min | • Not recommended/avoid use if CrCl >95 mL/min | • Not recommended if CrCl <15 mL/min or on dialysis |
|            |                                             |                                                 |                                             |
| Rivaroxaban| • Recommended dose 20 mg OD                | • Recommended dose 20 mg OD                    | • Recommended dose 20 mg OD                |
|            | • CrCl 30-49 mL/min: 15 mg OD              | • CrCl 15-50 mL/min: 15 mg OD                  | • CrCl 15-49 mL/min: 15 mg OD              |
|            | • Not recommended if CrCl <30 mL/min       | • Avoid use if CrCl <15 mL/min                 | • Not recommended if CrCl <15 mL/min       |
### Supplemental Table S3: NOAC Dose Recommendations for VTE in Major Jurisdictions

| Drug    | Canada                                                                 | United States                                                                 | Europe                                                                 |
|---------|------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Dabigatran | • Recommended dose 150 mg BID following 5-10 days with parenteral anticoagulant <br> • Patients ≥80 years or those at higher risk of bleeding, including elderly ≥75 years with ≥1 bleeding risk factor: recommended dose 110 mg BID <br> • Contraindicated if eCrCl <30 mL/min | • CrCl >30 mL/min: 150 mg BID, after 5-10 days of parenteral AC <br> • Not recommended if CrCl ≤30 mL/min or on dialysis <br> • Avoid co-administration of dabigatran and P-gp inhibitors in patients with CrCl <50 mL/min | • Recommended dose 150 mg BID following Tx with a parenteral AC for at least 5 days <br> • Patients ≥80 years or who receive concomitant verapamil, recommended dose 110 mg BID <br> • Contraindicated if CrCl <30 mL/min |
| Apixaban  | • 10 mg BID x 7 days, then 5 mg BID <br> • Continued prevention of recurrent DVT and PE following at least 6 months of Tx for DVT or PE: 2.5 mg BID <br> • Use with caution if eCrCl 15-29 mL/min <br> • Not recommended if CrCl <15 mL/min | • 10 mg BID x 7 days, then 5 mg BID <br> • Reduction in the risk of recurrence of DVT and PE following at least 6 months of treatment for DVT or PE: 2.5 mg BID <br> • Not Recommended if CrCl <15 mL/min | • Tx of DVT/PE: 10 mg BID x 7 days, then 5 mg BID <br> • Prevention of recurrent DVT and/or PE following completion of 6 months of Tx for DVT or PE: 2.5 mg BID <br> • To be used with caution if CrCl 15-29 mL/min <br> • Not recommended if CrCl <15 mL/min, or in patients undergoing dialysis |
| Edoxaban  | • Recommended dose 60 mg OD following initial use of a parenteral anticoagulant for 5-10 days <br> • Patients with moderate renal impairment (CrCl 30-50 mL/min), weight ≤60 kg, or concomitant use of P-gp inhibitors (except amiodarone and verapamil) recommended dose is 30 mg OD | • Recommended dose 60 mg OD following 5-10 days of initial therapy with a parenteral anticoagulant <br> • Patients ≤60 kg or CrCl 15-50 mL/min or using certain P-gp inhibitors: 30 mg OD <br> • Not recommended/avoid use if CrCl >95 mL/min | • Recommended dose 60 mg OD following at least 5 days of parenteral anticoagulant <br> • Patients with ≥1 of the following: CrCl 15-50 mL/min, ≤60 kg, concomitant use of P-gp inhibitors (ciclosporin, dronedarone, erythromycin, or ketoconazole): recommended dose 30 mg OD <br> • Not recommended if CrCL <15 mL/min or on dialysis |
| Rivaroxaban | • 15 mg BID x 21 days, then 20 mg OD <br> • Not recommended if CrCl <30 mL/min | • 15 mg BID x 21 days, then 20 mg OD <br> • Avoid use if CrCl <30 mL/min | • 15 mg BID x 21 days, then 20 mg OD <br> • CrCl 15-49 mL/min same as above. Consider dose reduction if risk of bleeding outweighs the risk of recurrent DVT and PE (then 15 mg BID x 21 days, then 15 mg OD) <br> • Not recommended if CrCl <15 mL/min |
**Supplemental Table S4: First ischemic stroke rates and outcomes in NOAC trials by renal function subgroup – FDA analysis**

| Drug, Trial | CrCl (mL/min) | First Stroke/SSE Rates (%/yr) | Hazard Ratio NOAC vs. Warfarin |
|-------------|---------------|--------------------------------|-----------------------------|
|             |               | NOAC                           | Warfarin                    |
| Dabigatran 150 mg, RE-LY | >50 to <80 | 0.94                           | 1.22                        | 0.77                        |
|             | ≥80           | 0.61                           | 0.72                        | 0.84                        |
| Apixaban, ARISTOTLE | >50 to <80 | 0.77                           | 0.89                        | 0.87                        |
|             | ≥80           | 0.69                           | 0.51                        | 1.35                        |
| Edoxaban 60/30 mg, ENGAGE AF | >50 to <80 | 1.21                           | 1.49                        | 0.81                        |
|             | ≥80           | 1.02                           | 0.73                        | 1.40                        |
| Rivaroxaban, ROCET-OF | >50 to <80 | 1.39                           | 1.70                        | 0.82                        |
|             | ≥80           | 0.94                           | 0.87                        | 1.07                        |

Adapted from: FDA. Cardiovascular and Renal Drugs Advisory Committee Edoxaban NDA 206316. Statistical Considerations, ENGAGE AF Trial. 2014. [http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM421612.pdf](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM421612.pdf).