**ANTICOAGULATION PRESCRIBING TIPS**

These prescribing tips are intended to assist prescribers, and advise on the appropriate dosing, when a direct oral anticoagulant (DOAC) is selected for treatment. Dosing recommendations are based on the Summary of Product Characteristics (SmPC) for each product (available on www.hpra.ie and www.medicines.ie).

The Medicines Management Programme consider WARFARIN or APIXABAN to be the agents of choice for most patients with Non-Valvular Atrial Fibrillation (NVAF)¹

**WARFARIN** is an appropriate first-line treatment option for stroke prevention in NVAF when time in therapeutic range (TTR) > 70%

**APIXABAN** is the preferred DOAC for stroke prevention in NVAF and may be considered 1st line treatment, particularly if there are tolerability issues and/or labile international normalised ratios (INRs) with warfarin.

### The following points should be considered when prescribing a DOAC:

1. **Initiation and follow-up:** Ensure correct dose (and frequency) of individual DOAC is chosen at initiation and reviewed at all subsequent appointments based on: Age, renal function, licensed indication, weight, concomitant medicines etc.²⁻⁵ Renal function should be assessed regularly and dose adjusted or therapy reviewed as appropriate (at least every six months and more frequently if renal impairment or risk factors for impaired renal function). Refer to SmPCs for further details.

2. **For initiation of treatment for DVT/PE:** ensure initiation dose and dose adjustment is prescribed clearly. Review for requirement to continue treatment after 3 and/or 6 months.

3. **For treatment of NVAF:** refer to ICGP reference guide "Practical use of Direct Oral Anti-Coagulants (DOACs) in Atrial Fibrillation in General Practice (2020)" (available on www.icgp.ie).⁶

4. **Significant drug interactions may occur with DOAC therapy** and the most common of these are highlighted in this prescribing aid.²⁻⁵

5. **Poor compliance with DOAC therapies carries a risk of thrombotic events due to the short half-life of these agents.²⁻⁵**

### Abbreviations:

- ATC: Anatomical therapeutic classification; DOAC: Direct oral anticoagulant; DVT: Deep vein thrombosis; GMS: General Medical Services; ICGP: Irish College of General Practitioners; INR: International normalised ratio; HPRA: Health Products Regulatory Authority; NVAF: non-valvular atrial fibrillation; PE: Pulmonary embolism; SmPC: Summary of Product Characteristics; TTR: time in therapeutic range

### References

7. PCRS database. January 2020. Number of patients aged ≥ 80 years on DOACs. 40% of patients over 80 years. On file to the HPRA.

### Notes:

**NOTE: AGE**

Less than 20% of patients in key licensing trials for NVAF were ≥ 80 years of age. Data (Jan-June 2019) shows that at least 40% of patients in receipt of DOACs under the GMS scheme are aged ≥ 80 years.⁷

### SAFETY ALERT

A review published by the State Claims Agency detailed medication incidents reported by Irish acute hospitals (2017-2018). Anti-thrombotic agents were responsible for the greatest number of incidents in medication group ATC level 3. There were four antithrombotic agents in the top ten drugs involved in medication incidents including apixaban and rivaroxaban. Among the top ten antithrombotic agents involved in medication incidents, apixaban and rivaroxaban appeared in second and fourth places, respectively.⁸

### REPORTING OF SUSPECTED ADVERSE REACTIONS

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Health Products Regulatory Authority (HPRA) (www.hpra.ie).

Version 2.0 MMP October 2020
Contact mmp@hse.ie for more details

Available on www.hse.ie/yourmedicines
### APIXABAN

**GENERAL INFORMATION**

Creatinine Clearance (CrCl) should be measured using Cockcroft-Gault equation (SI units): 

\[
\text{CrCl} = \left( \frac{140 - \text{Age (yrs)}}{\text{Weight (kg)}} \right) \times \text{constant} \times \left( \frac{1.23}{\text{male}} \right) \times \left( \frac{1.04}{\text{female}} \right) / \text{Serum Creatinine (\(\mu\text{mol/L}\))} 
\]

**DOSING**

<table>
<thead>
<tr>
<th>Standard dose</th>
<th>Stroke prevention in NVAF</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine &gt; 133 micromol/L (measured) AND &gt; 80 yrs OR weight &gt; 60 kg (Or any two of three above i.e. serum creatinine, age &gt; 80, weight &gt; 60 kg)</td>
<td>2.5 mg BD</td>
<td>CONTRAINDICATED with other anticoagulants (unless switching, then refer to individual SmPC)</td>
</tr>
</tbody>
</table>

**CONTRAINDICATED in CrCl < 15 ml/min or if patient is undergoing dialysis**

### DABIGATRAN

**GENERAL INFORMATION**

**DOSING**

<table>
<thead>
<tr>
<th>Standard dose</th>
<th>Stroke prevention in NVAF</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>75-80 years</td>
<td>150 mg BD or 110 mg BD should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding</td>
<td>CAUTION (increased bleeding risk): P-gp inducers</td>
</tr>
</tbody>
</table>

**CONTRAINDICATED in CrCl < 30 ml/min**

**CONTRAINDICATED in CrCl < 15 ml/min or if patient is undergoing dialysis**

### EDOXABAN

**GENERAL INFORMATION**

**DOSING**

<table>
<thead>
<tr>
<th>Standard dose</th>
<th>Stroke prevention in NVAF</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment (CrCl 15 ml/min - 50 ml/min) or low body weight (≤ 60 kg)</td>
<td>30 mg once daily</td>
<td>CAUTION: P-gp inhibitors – (increased bleeding risk) see dosing guidance opposite for dose reduction recommendations</td>
</tr>
</tbody>
</table>

**CONTRAINDICATED in CrCl < 15 ml/min or if the patient is undergoing dialysis**

### RIVAROXABAN

**GENERAL INFORMATION**

**DOSING**

<table>
<thead>
<tr>
<th>Standard Dose</th>
<th>Stroke prevention in NVAF</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl: 30-49 ml/min</td>
<td>15 mg once daily (caution with concomitant medications which increase rivaroxaban plasma concentration)</td>
<td>CAUTION: co-administration of aspirin in elderly patients. The concomitant chronic use of high dose aspirin (&gt;300 mg daily) is not recommended, doses higher than 100 mg daily should only be performed under medical supervision</td>
</tr>
</tbody>
</table>

**CONTRAINDICATED in CrCl < 15 ml/min**

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**NOTES:**

- Edoxaban is predominately absorbed in the upper gastrointestinal tract. Therefore medicines or disease conditions that increase gastric emptying and gut motility may reduce edoxaban dissolution and absorption. Can be taken with or without food.
- Important information: Clinical trials showed a trend towards decreasing efficacy with INCREASING creatinine clearance - careful evaluation of patients with NVAF and high creatinine clearance is recommended
**TREATMENT OF DEEP VEIN THROMBOSIS (DVT) AND PULMONARY EMBOLISM (PE)**

**GENERAL INFORMATION**
- Creatinine Clearance (CrCl) should be measured using Cockcroft-Gault equation (SI units): CrCl = (140 – Age (yrs)) x Weight(kg) x constant [1.23 for males & 1.04 for females] / Serum Creatinine (μmol/L).

**Discharge prescription** (after first diagnosis) should clearly state intended DURATION OF TREATMENT. If rivaroxaban, state how many further days of BD dosing (i.e. 21 days minus number of days doses have already given in hospital) before reducing to once daily and if apixaban, how many further days of 10 mg BD before reducing to 5 mg BD.

**APIXABAN**

**DOsing: Treatment of DVT/PE**

- Standard Dose: 10 mg twice daily for 7 days then reduce to 5 mg twice daily for at least 3 months.
- CrCl 15-29 ml/min: No dose adjustment recommended, use with CAUTION.
- CONTRAINDIICATED in CrCl <15 ml/min or if the patient is undergoing dialysis.

**Prevention of recurrent DVT and PE**

- 2.5 mg twice daily; this dose should be started following completion of 6 months treatment with apixaban 5 mg twice daily or another anticoagulant. The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk of bleeding.

**DABIGATRAN**

**DOsing: Treatment of DVT/PE**

- Standard Dose: Initial treatment with 5 days of parenteral anticoagulant. Then 150 mg dabigatran twice daily (BD) for at least 3 months (longer durations determined according to risk factors).
- Less than 75 years (see also options below): 150 mg BD.
- 75-80 years or GORD/gastritis/oesophagitis: 150 mg BD or 110 mg BD should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding.
- 80 years and over OR concomitant Verapamil (take at the same time): 110 mg BD.

**CONTRAINDIICATED in CrCl < 30 ml/min**

**EDOXABAN**

**DOsing: Treatment of DVT/PE**

- Standard dose: Initial treatment with at least 5 days of parenteral anticoagulant. Then 60 mg edoxaban once daily for at least 3 months with longer durations based on permanent random risk factors or idiopathic DVT/PE.
- Renal impairment (CrCl 15 ml/min - 50 ml/min) or low body weight (≤ 60 kg) or concomitant use with ciclosporin, dronedarone, erythromycin, ketoconazole (P-gp inhibitors) (based on clinical data):
  - 30 mg once daily.

**CONTRAINDIICATED in CrCl < 15 ml/min or if on dialysis**

**RIVAROXABAN**

**DOsing: Treatment of DVT/PE**

- Standard Dose: Initial dose of 15 mg twice daily (BD) for first 21 days then reduce to 20 mg once daily thereafter for at least 3 months (longer durations determined according to risk factors). If extended prevention of recurrent DVT/PE is indicated (after at least 6 months therapy for DVT/PE), the recommended dose is 10mg once daily. Refer to SmPC for further details and dosing if risk of recurrence is high.
- CrCl: 30-49 ml/min:
  - 15 mg BD for first 21 days then reduce to 15 mg or 20 mg once daily thereafter depending on bleeding risk versus risk of recurrent DVT/PE. Limited evidence for 15 mg once daily dose – based on pharmacokinetic modelling.
- CrCl: 15-30 ml/min (EXTREME CAUTION)
  - EXTREME CAUTION if CrCl < 30 ml/min, consider alternative.

**CONTRAINDIICATED in CrCl < 15 ml/min**

**INTERACTIONS**

- For DVT/PE the recommendation for the use of 110 mg BD is based on pharmacokinetic and pharmacodynamic analyses and has not been studied in this clinical setting.

**NOTES**

- Reduced efficacy of dabigatran (take both drugs at the same time).
- NSAIDs including aspirin will increase the risk of bleeding.
- Not recommended in severe hepatic impairment and contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

**DURATION OF TREATMENT**

- Standard Dose for initial treatment of DVT/PE (e.g. amiodarone, clarithromycin, quinidine, tacrolimus, ticagrelor) can be reduced to once daily and if switching, then refer to SmPC.
- If used in association with other anticoagulants (unless switching, then refer to SmPC).
- Avoid Concurrent Use (increased bleeding risk): Strong inhibitors of CYP3A4 and P-gp, such as azole-antimycotics (e.g. ketoconazole, itraconazole, posaconazole, voriconazole) and HIV protease inhibitors (e.g. ritonavir) - check SmPC for more details.
- Reduced Dose: 50 mg once daily dose – based on pharmacokinetic and pharmacodynamic analyses.

**Interactions**

- For apixaban 5 mg twice daily or another anticoagulant.
- Reduced efficacy: Strong inhibitors of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin, St Johns Wort) - check SmPC for more details.
- Reduced efficacy: Strong inhibitors of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin, St Johns Wort) - check SmPC for more details.

**Not recommended in severe hepatic impairment and contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.**

**INTERACTIONS**

- For DVT/PE the recommendation for the use of 110 mg BD is based on pharmacokinetic and pharmacodynamic analyses and has not been studied in this clinical setting.

**NOTE**

- Reduced efficacy of dabigatran (take both drugs at the same time).
- NSAIDs including aspirin will increase the risk of bleeding.
- Not recommended in severe hepatic impairment and contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

**DURATION OF TREATMENT**

- Standard Dose for initial treatment of DVT/PE (e.g. amiodarone, clarithromycin, quinidine, tacrolimus, ticagrelor) can be reduced to once daily and if switching, then refer to SmPC.
- If used in association with other anticoagulants (unless switching, then refer to SmPC).
- Avoid Concurrent Use (increased bleeding risk): Strong inhibitors of CYP3A4 and P-gp, such as azole-antimycotics (e.g. ketoconazole, itraconazole, posaconazole, voriconazole) and HIV protease inhibitors (e.g. ritonavir) - check SmPC for more details.
- Reduced Dose: 50 mg once daily dose – based on pharmacokinetic and pharmacodynamic analyses.

**Interactions**

- For apixaban 5 mg twice daily or another anticoagulant.
- Reduced efficacy: Strong inhibitors of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin, St Johns Wort) - check SmPC for more details.
- Reduced efficacy: Strong inhibitors of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin, St Johns Wort) - check SmPC for more details.

**Not recommended in severe hepatic impairment and contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.**

**INTERACTIONS**

- For DVT/PE the recommendation for the use of 110 mg BD is based on pharmacokinetic and pharmacodynamic analyses and has not been studied in this clinical setting.

**NOTE**

- Reduced efficacy of dabigatran (take both drugs at the same time).
- NSAIDs including aspirin will increase the risk of bleeding.
- Not recommended in severe hepatic impairment and contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

**DURATION OF TREATMENT**

- Standard Dose for initial treatment of DVT/PE (e.g. amiodarone, clarithromycin, quinidine, tacrolimus, ticagrelor) can be reduced to once daily and if switching, then refer to SmPC.
- If used in association with other anticoagulants (unless switching, then refer to SmPC).
- Avoid Concurrent Use (increased bleeding risk): Strong inhibitors of CYP3A4 and P-gp, such as azole-antimycotics (e.g. ketoconazole, itraconazole, posaconazole, voriconazole) and HIV protease inhibitors (e.g. ritonavir) - check SmPC for more details.
- Reduced Dose: 50 mg once daily dose – based on pharmacokinetic and pharmacodynamic analyses.

**Interactions**

- For apixaban 5 mg twice daily or another anticoagulant.
- Reduced efficacy: Strong inhibitors of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin, St Johns Wort) - check SmPC for more details.
- Reduced efficacy: Strong inhibitors of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin, St Johns Wort) - check SmPC for more details.

**Not recommended in severe hepatic impairment and contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.**
**GENERAL INFORMATION**
Creatinine Clearance (CrCl) should be measured using Cockcroft-Gault equation (SI units): 

\[
\text{CrCl} = (140 - \text{Age (yrs)}) \times \text{Weight(kg)} \times \text{constant} \left[ 1.23 \text{ for males} & 1.04 \text{ for females} \right] / \text{Serum Creatinine (\(\mu\text{mol/L} \))}
\]

**AXIPABAN**
Remain aware of possible risks with older AGE, lower BODY WEIGHT, RENAL FUNCTION, and consider INTERACTIONS

**DOsing**
Prevention of VTE in adult patients who have undergone elective TKR or THR surgery

- Standard dose: 2.5 mg twice daily for 10-14 days (TKR) or for 32-38 days (THR). Initial dose should be taken 12-24 hours after surgery

**CONTRAINDICATED in CrCl < 15 ml/min or if patient is undergoing dialysis**

**Dabigatran**
Adjust dose for AGE, RENAL FUNCTION, GORD, and INTERACTIONS

**DOsing**
Prophylaxis of DVT post TKR and THR surgery

- Less than 75 years (see also options below)
  - 110 mg after surgery* then 220 mg once daily (TKR: 10 days, THR: 28-35 days)

- > 75 years (treat with caution)
  - 75 mg after surgery* then 150 mg once daily (TKR: 10 days, THR: 28-35 days)

- Renal Impairment (CrCl 30 ml/min – 50 ml/min)
  - 75 mg after surgery* then 150 mg once daily (TKR: 10 days, THR: 28-35 days) – treat with caution

**CONTRAINDICATED in CrCl < 30 ml/min**

GORD/Gastritis/Oesophagitis
No adjustment – dose according to the above recommendations

Concomitant P-gp inhibitors i.e. verapamil, amiodarone, quinidine (take these agents at same time as dabigatran)
75 mg after surgery* then 150 mg once daily (see also renal impairment)

Moderate renal impairment (CrCl 30-50 ml/min) AND on concomitant verapamil
75 mg after surgery* then 75 mg once daily should be considered

**Rivaroxaban**
Adjust dose for RENAL FUNCTION and consider INTERACTIONS

**DOsing**
Prophylaxis of DVT post TKR or THR surgery

- Standard Dose: 10 mg once daily for 14 days (TKR) or for 35 days (THR)**
- CrCl: 30 – 49 ml/min
  - No dose adjustment required – 10 mg once daily for 14 days (TKR) or 35 days (THR)**
- CrCl: 15 - 29 ml/min
  - Extreme Caution required

**CONTRAINDICATED in CrCl < 15 ml/min**

**Interactions**
: this list is not exhaustive; See Summary of Product Characteristics (SmPC) for full details (www.medicines.ie or www.hpra.ie)

- **CONTRAINDICATED with other anticoagulants (unless switching, then refer to individual SmPC for guidance)**
- **CONTRAINDICATED: Cyclesporin, dronedarone, itraconazole, ketoconazole.**
- **AVOID CONCURRENT USE (increased bleeding risk): P-gp inhibitors** of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin, St Johns Wort)
- **USE WITH CAUTION (risk of reduced efficacy): Strong Inducers** of CYP3A4 and P-gp (e.g. amiodarone, clarithromycin, quinidine, tacrolimus, ticagrelor)
- **CAUTION (increased bleeding risk): NSAIDs including aspirin**
- **CAUTION**: Antiplatelet agents including aspirin will increase risk of bleeding

**Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Not recommended in severe hepatic impairment.**

**Important information:** DO NOT OPEN OR CRUSH CAPSULE
Blister : Store in the ORIGINAL PACKAGE in order to protect from moisture - not suitable for Monitor Dosage Systems (MDS)

*After surgery: 1–4 hours post-surgery once haemostasis is achieved. If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be started with the higher dose once daily.

Reference: SmPC for Eliquis® (axipaban), Pradaxa® (dabigatran) and Xarelto® (rivaroxaban)