ANTICOAGULATION PRESCRIBING TIPS

These prescribing tips are intended to assist prescribers, and advise on the appropriate dosing, when a new oral anticoagulant (NOAC) 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 considers **WARFARIN** to be the agent of choice and the first line anticoagulant for most patients with Atrial Fibrillation (1).
The following points should be noted prior to choosing oral anticoagulation:

1) Warfarin is the established anticoagulant of choice for many patients including those with (2):

✓ Mechanical heart valves	✓ Valvular atrial fibrillation (AF)	✓ Severe renal impairment	✓ Cancer related venous thromboembolism	✓ Complicated VTE such as patients with recurrent VTE	✓ Patients with antiphospholipid syndrome

2) Non Vitamin K Oral Anticoagulants (NOACs)*: important considerations based on clinical trial evidence

- The NOACs were not shown to be superior to optimal warfarin therapy in clinical trials for stroke prevention in Atrial Fibrillation i.e. where time in therapeutic range (TTR) for warfarin is over 70% (3,4) (ROCKET-AF: mean TTR = 55% (5), RE-LY: mean TTR = 64% (6), ENGAGE AF-TIMI 48: mean TTR = 68.4% (7), Aristotle: mean TTR = 62% (8))
- The pivotal clinical trial for rivaroxaban for stroke prevention in AF was a non-inferiority trial (ROCKET-AF) with a TTR of 55% (5)
- **Patients with severe renal dysfunction were excluded from the pivotal clinical trials in AF** i.e. exclusion criteria for rivaroxaban in ROCKET-AF: Creatinine Clearance (CrCl) <30ml/min (5), for dabigatran in RE-LY was < 30ml/min (6), for edoxaban in ENGAGE AF-TIMI 48 was < 30ml/min (7) and for apixaban in Aristotle was < 25ml/min (8).

Therefore the Medicines Management Programme advises extreme caution when using NOACs in patients with CrCl of 15-30ml/min. Apixaban, edoxaban and rivaroxaban are contraindicated with CrCl <15ml/min while **dabigatran** is **contraindicated** with CrCl <30ml/min.

*** Now also known as Direct Oral Anticoagulants (DOACs)**

Patients on NOAC therapy should have regular assessment of their renal function and have their dose adjusted or therapy reviewed as appropriate (at least 6 monthly review and more frequently if renal impairment or risk factors for impaired renal function)

- Similar exclusion criteria for renal dysfunction were used in VTE prophylaxis trials and treatment of DVT/PE trials (9,10,11,12,13,14,15,16,17)
- The trials for treatment of DVT/PE with dabigatran and rivaroxaban studied the standard treatment doses only (150mg BD and 20mg once daily respectively). The lower doses of 110mg BD dabigatran and 15mg once daily rivaroxaban to treat DVT/PE have not been studied in a clinical setting (13,15,18,19)
- Trials for the treatment of DVT and PE (for rivaroxaban and dabigatran) were also non-inferiority trials (13,14,15)

3) Significant drug interactions may also occur with NOAC therapy and the most common of these are highlighted in this prescribing aid (18,19,20,21)

4) Poor compliance with NOAC therapies carries a risk of thrombotic events due to the short half-life of these agents (18,19,20,21)

5) Reversal agents: an antidote (idarucizumab) is now available for the direct thrombin inhibitor, dabigatran. There is currently no antidote available for the haemorrhagic complications associated with the factor Xa inhibitors.

WARFARIN DOSING AND MONITORING

Please refer to ICGP guidance: "Anticoagulants in general practice/primary care Part 1: Warfarin (2014)" (available on www.ICGP.ie)

References:

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20. Eliquis® (apixaban) 2.5mg, 5mg film coated tablets SmPC. Last revised August 2013. Accessed at www.hpra.ie (www.ema.europa.eu) on 29/05/14 (now www.hpra.ie)
21. Lixiana® (edoxaban) 15mg, 30mg, 60mg SmPC. Date of first authorisation 19th June 2015. Last updated 01/09/2015. Accessed on www.medicines.ie on 04/09/2015

STROKE PREVENTION IN ADULTS WITH NON-VALVULAR ATRIAL FIBRILLATION (NVAF)

Individual Summary of Product Characteristics (SmPCs) are available on www.medicines.ie or www.hpra.ie

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

APIXABAN — Adjust dose for AGE, BODY WEIGHT, RENAL FUNCTION, and consider INTERACTIONS

DOSING	Stroke prevention in NVAF
Standard dose	5 mg twice daily (BD)
Serum creatinine > 133micromol/L (measured) ***AND*** ≥80yrs ***OR*** weight ≤60kg (Or any two of three above i.e. serum creatinine, age ≥80, weight ≤60kg)	2.5mg BD
CrCl 15-29ml/min [use Cockroft-Gault equation (SI units)] (regardless of age or weight)	2.5mg BD – **EXTREME CAUTION**, consider alternative (review HAS-BLED and other risk factors)
CONTRAINDICATED in CrCl < 15ml/min	

Interactions : this list is not exhaustive; See SmPC for full details

CONTRAINDICATED with other anticoagulants (unless switching, then refer to individual 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
CAUTION (risk of reduced efficacy): Strong **inducers** of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St Johns Wort)
CAUTION (increased bleeding risk): NSAIDS including aspirin
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.*

DABIGATRAN — Adjust dose for AGE, RENAL FUNCTION, GORD, and INTERACTIONS

DOSING	Stroke prevention in NVAF
Standard dose	150mg twice daily (BD)
75-80 years	150mg BD or if LOW thrombotic risk and HIGH bleeding risk give 110mg BD
Over 80 years	110mg BD
Renal Impairment (CrCl 30ml/min - 50ml/min)	150mg BD (110mg BD if high bleeding risk)
CONTRAINIDICATED in CrCl < 30ml/min	
GORD/Gastritis/Oesophagitis	110mg BD
Concomitant Verapamil (take verapamil at the same time as dabigatran)	110mg BD

Interactions : this list is not exhaustive; See SmPC for full details

CONTRAINDICATED with other anticoagulants (unless switching, then refer to individual SmPC)
CONTRAINDICATED: Ciclosporin, dronedarone, itraconazole, ketoconazole, tacrolimus
AVOID CONCURRENT USE (reduced efficacy): P-gp **inducers** (e.g. carbamazepine, phenytoin, rifampicin, St Johns Wort
CAUTION: P-gp inhibitors (e.g. amiodarone, clarithromycin, quinidine, ticagrelor)
Verapamil (P-gp inhibitor **– increased bleeding risk**) – **REDUCE DOSE** of dabigatran (take both drugs at the same time)
CAUTION (increased bleeding risk): NSAIDs, including aspirin
SSRI/SNRIs – increased risk of bleeding
Not recommended in hepatic impairment and contraindicated *in* ***hepatic impairment*** *or liver disease that is expected to have any impact on survival.*

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

EDOXABAN — Adjust dose for RENAL FUNCTION, BODY WEIGHT and consider INTERACTIONS

DOSING	Stroke prevention in NVAF
Standard dose	60mg once daily
Renal impairment (CrCl 15ml/min - 50 ml/min) **or** low body weight (≤60kg)	30mg once daily
Concomitant ciclosporin, dronedarone, erythromycin or ketoconazole (P-gp-inhibitors)	30mg once daily (based on clinical data)
According to clinical data no dose adjustment is needed if concomitant use with amiodarone, quinidine or verapamil (P-gp-inhibitors)	
CONTRAINDICATED in CrCl < 15ml/min	

Interactions: this list is not exhaustive; See SmPC for full details

CONTRAINDICATED with other anticoagulants (unless switching, then refer to SmPC)
CAUTION: co-administration of aspirin in elderly patients. The concomitant chronic use of high dose aspirin (>300mg) is not recommended, doses higher than 100mg should only be performed under medical supervision
CAUTION: P-gp inhibitors – (increased bleeding risk) see dosing guidance opposite for dose reduction recommendations
CAUTION: (increased bleeding risk) chronic use of NSAIDS with edoxaban is not recommended
CAUTION: P-gp inducers (reduced efficacy) e.g. Phenytoin, carbamazepine, phenobarbital, St. Johns Wort
Caution in mild to moderate hepatic impairment, not recommended in severe hepatic impairment and contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

NOTE: 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

RIVAROXABAN — Adjust dose for RENAL FUNCTION and consider INTERACTIONS

DOSING	Stroke prevention in NVAF
Standard Dose	20mg once daily
CrCl: 30-49ml/min	15mg once daily (caution with concomitant medications which increase rivaroxaban plasma concentration)
CrCl: 15-30 ml/min (**CAUTION**)	15mg once daily – **EXTREME CAUTION**, consider alternative
CONTRAINDICATED in CrCl < 15ml/min	

Interactions : this list is not exhaustive; See SmPC for full details

CONTRAINDICATED with other anticoagulants (unless switching, then refer to individual SmPC for guidance)
AVOID CONCURRENT USE (increased bleeding risk): Strong **inhibitor**s of CYP3A4 and P-gp (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors
AVOID: Dronedarone – (limited clinical data)
CAUTION: Strong **inhibitors** of CYP3A4 (e.g. clarithromycin) **AND** renal impairment
CAUTION (risk of reduced efficacy): Strong **inducers** of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St Johns Wort)
CAUTION (increased bleeding risk): NSAIDs, Platelet aggregation inhibitors including aspirin
Contraindicated *in* ***hepatic disease*** *associated with coagulopathy and clinically relevant bleeding risk*

- **Important information: 15mg and 20mg tablets should be taken WITH FOOD**

Reference: SmPC for Eliquis® (Apixaban), Pradaxa® (Dabigatran) Lixiana® (edoxaban) and Xarelto® (Rivaroxaban) Version 1.4 MMP Feb 2017

TREATMENT OF DEEP VEIN THROMBOSIS (DVT) AND PULMONARY EMBOLISM (PE)

Individual Summary of Product Characteristics (SmPCs) are available on www.medicines.ie or www.hpra.ie

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

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 10mg BD before reducing to 5mg BD

APIXABAN

Remain aware of possible risks with increased AGE, low BODY WEIGHT, RENAL FUNCTION, and consider INTERACTIONS

DOSING: Treatment of DVT/PE	
Standard Dose	10mg **twice daily** for **7** days **then reduce** to **5mg twice daily** for at least 3 months
CrCl 15-29ml/min	No dose adjustment recommended, use with CAUTION
CONTRAINDICATED in CrCl <15ml/min	
Prevention of recurrent DVT and PE	2.5mg twice daily. 2.5mg twice daily dose should be started following completion of 6 months treatment with apixaban 5mg 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.

Interactions : this list is not exhaustive; See SmPC for full details

CONTRAINDICATED 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
CAUTION (risk of reduced efficacy): Strong **inducers** of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St Johns Wort)
CAUTION (increased bleeding risk): NSAIDS including aspirin
Antiplatelet agents including **aspirin** will increase risk of bleeding
Not recommended in severe hepatic impairment and contraindicated *in patients with* ***hepatic disease*** *associated with coagulopathy and clinically relevant bleeding risk.*

DABIGATRAN

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

DOSING : Treatment of DVT/PE	
Standard Dose: Initial treatment with 5 days of **parenteral anticoagulant. Then 150mg dabigatran twice daily** (BD) for at least 3 months (longer durations determined according to risk factors)	
Less than 75 years (see also options below)	150mg BD
75-80 years	150mg BD or if LOW thrombotic risk and HIGH bleeding risk: 110mg BD*
Over 80 years OR GORD/Gastritis/ Oesophagitis OR concomitant Verapamil (take at the same time)	110mg BD **NOTE**: For DVT/PE the recommendation for the use of 110 mg twice daily is based on pharmacokinetic and pharmacodynamic analyses and **has not been studied in this clinical setting**.
CrCl 30ml/min-50ml/min	150mg BD (110mg BD if high bleeding risk)*
CONTRAINIDICATED in CrCl < 30ml/min	

Interactions : this list is not exhaustive; See SmPC for full details

CONTRAINDICATED with other anticoagulants (unless switching, then refer to individual SmPC)
CONTRAINDICATED: Ciclosporin, dronedarone, itraconazole, ketoconazole, tacrolimus
AVOID CONCURRENT USE (reduced efficacy): P-gp **inducers** (e.g. carbamazepine, phenytoin, rifampicin, St Johns Wort
CAUTION: P-gp **Inhibitors** (e.g. amiodarone, clarithromycin, quinidine, ticagrelor)
Verapamil (P-gp **inhibitor**) – **REDUCE DOSE** of dabigatran (take verapamil and dabigatran at the same time)
CAUTION (increased bleeding risk): NSAIDs, including aspirin
SSRI/SNRIs – increased risk of bleeding
Contraindicated *in* ***hepatic impairment*** *or liver disease expected to have any impact on survival. Not recommended in hepatic impairment.*
Important information: DO NOT OPEN OR CRUSH CAPSULE
Blister Pack : Store in the ORIGINAL PACKAGE in order to protect from moisture - not suitable for Monitored Dosage Systems (MDS)

EDOXABAN

Adjust dose for RENAL FUNCTION, BODY WEIGHT and consider INTERACTIONS

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

Interactions: this list is not exhaustive; See SmPC for full details

CONTRAINDICATED with other anticoagulants (unless switching, then refer to SmPC)
CAUTION: co-administration of aspirin in elderly patients. The concomitant chronic use of high dose aspirin (>300mg) is not recommended, doses higher than 100mg should only be performed under medical supervision
CAUTION (increased bleeding risk): chronic use of NSAIDS with edoxaban is not recommended
CAUTION: P-gp inducers **(reduced efficacy)** e.g. Phenytoin, carbamazepine, phenobarbital, St. JohnsWort
Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Not recommended in severe hepatic impairment, caution in mild to moderate hepatic impairment
NOTE: 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.

RIVAROXABAN

Adjust dose for RENAL FUNCTION and consider INTERACTIONS

DOSING : Treatment of DVT/PE	
Standard Dose: Initial dose of 15mg **twice daily** (BD) for first **21** days **then reduce** to 20mg **once daily** thereafter for at least 3 months (longer durations determined according to risk factors)	
CrCl: 30-49ml/min	15mg BD for first 21 days then reduce to 15mg or 20mg **once daily** thereafter depending on bleeding risk versus risk of recurrent DVT/PE Limited evidence for 15mg dose – based on pharmacokinetic modelling EXTREME CAUTION if CrCl < 30ml/min, consider alternative
CrCl: 15-30 ml/min **(EXTREME CAUTION)**	
CONTRAINDICATED in CrCl<15ml/min	

Interactions: this list is not exhaustive; See SmPC for full details

CONTRAINDICATED with other anticoagulants (unless switching, then refer to individual SmPC for guidance)
AVOID CONCURRENT USE (increased bleeding risk): Strong **inhibitor**s of CYP3A4 and P-gp (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors).
AVOID: Dronedarone – (limited clinical data)
CAUTION: Strong **inhibitors** of CYP3A4 (e.g. clarithromycin) ***AND*** renal impairment
CAUTION (risk of reduced efficacy): Strong **inducers** of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St Johns Wort)
CAUTION (increased bleeding risk): NSAIDs, platelet aggregation inhibitors including aspirin
Contraindicated *in* ***hepatic disease*** *associated with coagulopathy and clinically relevant bleeding risk*
- **15mg and 20mg tablets should be taken WITH FOOD**

Ref: SmPC for Eliquis® (apixaban) Pradaxa® (dabigatran) Lixiana® (edoxaban) and Xarelto® (rivaroxaban)
Version 1.4 MMP Feb 2017

PROPHYLAXIS OF THROMBOEMBOLISM IN ADULT PATIENTS AFTER ELECTIVE TOTAL KNEE REPLACEMENT (TKR) OR TOTAL HIP REPLACEMENT (THR) SURGERY

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

APIXABAN — Adjust dose for AGE, BODY WEIGHT, RENAL FUNCTION, and consider INTERACTIONS

DOSING	**Prevention of VTE in adult patients who have undergone elective TKR or THR surgery**	**Interactions** : this list is not exhaustive; See Summary of Product Characteristics (SmPC) for full details (www.medicines.ie or www.hpra.ie)
Standard dose	2.5mg twice daily for 10-14 days (TKR) or for 32-38 days (THR). Initial dose should be taken 12-24 hours after surgery	• **CONTRAINDICATED** with other anticoagulants (unless switching, then refer to individual SmPC for guidance) • **AVOID CONCURRENT USE** (increased bleeding risk): Strong **inhibitors** of CYP3A4 and P-gp (e.g. ketoconazole, itraconazole, posaconazole, voriconazole) –Anti-retrovirals – check SmPC for details • **USE WITH CAUTION (risk of reduced efficacy):** Strong **Inducers** of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St Johns Wort) • **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.*
CONTRAINDICATED in CrCl < 15ml/min		

DABIGATRAN — Adjust dose for AGE, RENAL FUNCTION, GORD, and INTERACTIONS

DOSING	**Prophylaxis of DVT post TKR and THR surgery**	**Interactions** : this list is not exhaustive; See SmPC for full details (www.medicines.ie or www.hpra.ie)
Less than 75 years (see also options below)	110mg after surgery* then 220mg **once daily** (TKR: 10 days, THR, 28-35 days)	• **CONTRAINDICATED** with other anticoagulants (unless switching, refer to SmPCs for guidance) • **CONTRAINDICATED**: Ciclosporin, dronedarone, itraconazole, ketoconazole, tacrolimus • **AVOID CONCURRENT USE** (reduced efficacy): P-gp **inducers** (e.g. carbamazepine, phenytoin, rifampicin, St Johns Wort) • **CAUTION**: P-gp **inhibitors** (e.g. amiodarone, clarithromycin, quinidine, ticagrelor) • Verapamil (P-gp **inhibitor**) – REDUCE DOSE of dabigatran (take verapamil and dabigatran at the same time) • **CAUTION** (increased bleeding risk): NSAIDs, including aspirin • SSRI/SNRIs – increased risk of bleeding ***Contraindicated** in **hepatic impairment** or liver disease which is expected to have any impact on survival. Not recommended in hepatic impairment.*
> 75 years (treat with caution)	75mg after surgery* then 150mg **once daily** (TKR: 10 days, THR: 28-35 days)	
Renal Impairment (CrCl 30ml/min-50ml/min) [use Cockroft-Gault equation (SI units)]	75mg after surgery* then 150mg **once daily** (TKR: 10 days, THR: 28-35 days) – treat with caution	
CONTRAINIDICATED in CrCl < 30ml/min		
GORD/Gastritis/Oesophagitis	No adjustment – dose according to the above recommendations	**Important information: DO NOT OPEN OR CRUSH CAPSULE** **Blister : Store in the ORIGINAL PACKAGE in order to protect from moisture - not suitable for Monitored Dosage Systems (MDS)**
Concomitant P-gp inhibitors i.e. verapamil, amiodarone, quinidine (take these agents at same time as dabigatran)	75mg after surgery* then 150mg **once daily** (see also renal impairment)	
Moderate renal impairment (CrCl 30-50ml/min) AND on concomitant verapamil	75mg after surgery* then 75mg **once daily** should be considered	* 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

RIVAROXABAN — Adjust dose for RENAL FUNCTION and consider INTERACTIONS

DOSING	**Prophylaxis of DVT post TKR or THR surgery**	**Interactions** : this list is not exhaustive; See SmPC for full details (www.medicines.ie or www.hpra.ie)
Standard Dose	10mg once daily for 14 days (TKR) or for 35 days (THR)**	• **CONTRAINDICATED** with other anticoagulants (unless switching, then refer to individual SmPC for guidance) • **AVOID CONCURRENT USE** (increased bleeding risk): Strong **inhibitor**s of CYP3A4 and P-gp (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors) • **AVOID**: Dronedarone – (limited clinical data) • **CAUTION**: Strong **inhibitors** of CYP3A4 (e.g. clarithromycin) ***AND*** renal impairment – **CAUTION** • **CAUTION** (reduced efficacy)**: Inducers** of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St Johns Wort) • **CAUTION (increased bleeding risk):** NSAIDs, platelet aggregation inhibitors including aspirin ***Contraindicated** in **hepatic disease** associated with coagulopathy and clinically relevant bleeding risk* **Initial dose taken 6-10 hours after surgery provided haemostasis has been established
CrCl: 30-49ml/min	No dose adjustment required – 10mg once daily for 14 days (TKR) or 35 days (THR)**	
CrCl: 15-30 ml/min	**Extreme Caution required**	
CONTRAINDICATED in CrCl < 15ml/min		

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

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