NOACs for thromboembolism – Drug comparisons

Licensed indications:
Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), prevention of recurrent DVT/PE and VTE prevention post-surgery in adults

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Usual dose for the treatment and prevention of acute DVT and PE Duration of therapy: the duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE Use in conjunction with anticoagulant guidelines	Usual dose: 150mg twice daily *following treatment with a parenteral anticoagulant for at least 5 days* Reduce to 110mg twice daily if > 80 years or concomitant verapamil Patients between 75 - 80 years, people with moderately reduced kidney function, people with gastritis, esophagitis or gastroesophageal reflux, and people at increased risk of bleeding, 150 mg or 110 mg twice daily can be given based on an individual assessment	15 mg twice daily for the first 3 weeks 20 mg daily from day 22	10 mg twice daily for the first 7 days followed by 5 mg taken orally twice daily. After 6 months of treatment, for continued therapy dose should be reduced to 2.5 mg twice daily	60 mg daily *following parenteral anticoagulant for at least 5 days* Reduce dose to 30 mg: moderate to severe renal impairment, ≤60kg, concomitant use of P-gp inhibitors
VTE prevention post-surgery	Stat dose of 110mg then 220mg once daily for: 10 days post knee surgery 4-5 weeks post hip surgery For patients with the following, reduce dose to 75mg initially, then 150mg daily: CrCl 30-50ml/min, Patients who receive concomitant verapamil, amiodarone, quinidine, Patients aged 75years and above. 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 initiated with 2 capsules once daily	10mg once daily for: 2weeks post knee surgery 5weeks post hip surgery	2.5 mg twice daily for 10 - 14 days post knee surgery 32 - 38 days post hip surgery	Not licensed
Converting from parenteral anticoagulant to NOAC	Discontinue the parenteral anticoagulant and start dabigatran 0 - 2 hours prior to the time that the next dose of the injectable therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)	Discontinue the parenteral anticoagulant and start rivaroxaban 0 - 2 hours prior to the time that the next dose of the injectable therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)	Discontinue the parenteral anticoagulant and start apixaban at the time of next scheduled dose	Discontinue the parenteral anticoagulant and start edoxaban at the time of next scheduled dose For UFH discontinue infusion and start 4 hours later
For procedures with no clinically important bleeding risk For dental procedures, consider prescribing tranexamic acid 5% mouthwash; instruct the person to use 10 mL as a mouthwash four times a day for 5 days https://cks.nice.org.uk/anticoagulation-oral#!management	Procedure can be performed: Just before the next dose of dabigatran is due, *or* Approximately 18 - 24 hours after the last dose of dabigatran was taken (dabigatran should be restarted 6 hours later). This means one dose of dabigatran may be missed	Procedure can be performed: Approximately at least 18–24 hours after the last dose of rivaroxaban was taken and rivaroxaban should be restarted 6 hours later	Procedure can be performed: Just before the next dose of apixaban is due *or* Approximately 18–24 hours after the last dose of apixaban was taken (apixaban should be restarted 6 hours later). This means one dose of apixaban may be missed.	Not stated
For procedures with a low bleeding risk https://cks.nice.org.uk/anticoagulation-oral#!management	Discontinue at least 24 hours prior to the intervention. CrCl ≥50-<80 ml/min , stop 36 hours before procedure CrCl ≥30-<50 ml/min, stop 2-3 days (>48 hours) before procedure	Stop 24 hours prior to the intervention. CrCl 15 – 30 ml/min rivaroxaban should be stopped 36 hours before the procedure	Stop at least 24 hours prior to the intervention. If CrCl 15 – 30 ml/min, apixaban should be stopped 36 hours before the procedure.	Discontinue at least 24 hours prior to the intervention (SPC Edoxaban)
Discontinuation prior to elective surgery with **high risk of bleeding or major surgery** https://cks.nice.org.ukanticoagulation-oral#!management	Discontinue 48 hours prior to the intervention CrCl 50 - <80 ml/min , stop 72 hours before procedure CrCl 30 - <50 ml/min, stop 96 hours before procedure	Stop 48 hours prior to the intervention	Discontinue at least 48 hours prior to surgery	

Restarting NOACs after surgery		Treatment should be restarted after the invasive procedure or surgical intervention as soon as possible **provided the clinical situation allows and adequate haemostasis has been established**.			
Renal Impairment	CrCl– 15ml/min	Contra-indicated	Not recommended	Not recommended	Not recommended
	CrCl 15 – 29ml/min	Contra-indicated	15 mg daily and caution	2.5 mg twice daily	30 mg daily
	CrCl 30 – 49ml/min	No dosage adjustment unless bleeding risk	15 mg daily	No dosage adjustment	30 mg daily
Hepatic Impairment	(Hepatic disease-coagulopathy, bleeding risk inc. cirrhotic patients with child pugh B and C)	Contra-indicated where expected to have impact on survival	Contra-indicated in hepatic disease	Severe – not recommended Mild to moderate - caution	Measure LFTs prior to initiating Contra-indicated in hepatic disease and severe hepatic impairment. Caution with mild to moderate hepatic impairment
	Patients with elevated liver enzymes >2 ULN	Not recommended	Not stated	Caution (including total bilirubin ≥1.5 x ULN)	Caution (including total bilirubin ≥1.5 x ULN)
Drug Interactions	Strong CYP 3A4 and P-gp inhibitors[a]	Contra-indicated	Not recommended	Not recommended	Reduce to 30 mg
	Mild to moderate P-gp inhibitors	Caution	Not stated	No dosage adjustment	No dosage adjustment
	Co-administration with P-gp inducers[c]	Avoid	Avoid	Not recommended	Caution
Reversibility		Idarucizumab (Praxbind®)	No licensed antidote Phase 3 trials ongoing Activated charcoal may be considered	No licensed antidote. Phase 3 trials ongoing Prothrombin complex concentrates or recombinant factor VIIa may be considered for life threatening conditions	No licensed antidote. Phase 3 trials ongoing 4-factor prothrombin complex concentrate or recombinant factor VIIa can also be considered for life threatening conditions
Half- life (t ½)		Healthy elderly - 11 hours; multiple doses - 12 - 14 hours If renal impairment: GFR (ml/min) / Half-life (range, hours) ≥80 / 13.4 (11.0 – 21.6) ≥50 - <80 / 15.3 (11.7 - 34.1) ≥30 - <50 / 18.4 (13.3 - 23) ≥30 - <50 / 27.2 (21.6 - 35)	Young individuals: t ½ 5 - 9 hours, t ½ 11 - 13 hours in the elderly	Approximately 12 hours	10 -14 hours
Switching from NOAC to warfarin		Adjust the starting time of the Warfarin based on CrCL as follows: ▪ CrCL ≥50 mL/min, start warfarin 3 days before discontinuing dabigatran ▪ CrCL ≥30 - <50 mL/min, start warfarin 2 days before discontinuing dabigatran Because dabigatran can increase INR, the INR will better reflect warfarin's effect only after dabigatran has been stopped for at least 2 days. Until then, INR values should be interpreted with caution	Warfarin should be given concurrently until the INR is ≥2.0. For the first two days of the conversion period, standard initial dosing of warfarin should be used followed by warfarin dosing, as guided by INR testing. While patients are on both rivaroxaban and warfarin the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban. Once rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose	Continue administration of apixaban for at least 2 days after beginning warfarin therapy. After 2 days of co-administration of apixaban with warfarin therapy, obtain an INR prior to the next scheduled dose of apixaban. Continue co-administration of apixaban and warfarin therapy until the INR is ≥2.0	**60 mg dose:** administer 30 mg + warfarin **30 mg dose**: administer 15 mg + warfarin Do not give a loading dose of warfarin in order to promptly achieve INR 2 - 3. It is recommended to take account of maintenance dose of warfarin and if patient was previously taking warfarin or to use validated INR driven warfarin treatment algorithm. INR ≥2, discontinue edoxaban. Most patients should be able to achieve INR ≥2 within 14 days of edoxaban + warfarin. After 14 days discontinue edoxaban and titrate warfarin to achieve INR 2 - 3
NICE guidance: DVT and PE		TA 327	TA 287 and TA261	TA 341	TA354
NICE guidance: Prevention of VTE after elective hip or knee replacement		TA 157	TA 170	TA 245	Not licensed
Bleeding risk (see NICE TAGs, available at www.nice.org.uk)		RE-COVER, RE-MEDY vs Warfarin (NICE TA 327) (p value not reported) Major, clinically relevant bleeding or any bleeding : lower events compared to warfarin GI bleeding: higher rate compared to warfarin Intracranial haemorrhage: fewer cases than warfarin	EINSTEIN-DVT -comparable number of clinically relevant bleeding episodes vs. enoxaparin and a vitamin K antagonist EINSTEIN-Ext higher rate of clinically relevant non-major bleeding vs. placebo and not active control. The Committee concluded that treatment with rivaroxaban had an acceptable adverse event profile compared with the combination of LMWH and warfarin. EINSTEIN-PE : no statistically significant difference in major bleeding and clinically relevant non-major bleeding between rivaroxaban and LMWH with a vitamin K antagonist, incidence of major bleeds statistically significantly lower with rivaroxaban.	Lower rates of bleeding (the composite outcome of major or clinically relevant non major bleeding, major bleeding assessed separately and clinically relevant non−major bleeding) with apixaban compared with LMWH/vitamin K agonist, LMWH/dabigatran and rivaroxaban	Bleeding (major or clinically relevant non−major bleeding, primary safety outcome): edoxaban was associated with fewer bleeding events (p=0.004). Major bleeding in critical sites included 5 intracranial haemorrhage events (none of which were fatal) in the edoxaban group, and 18 (6 fatal) in the warfarin group. Major bleeding in non-critical sites included 27 gastrointestinal tract bleed events (1 fatal) in the edoxaban group and 18 (2 fatal) in the warfarin group.
Compliance Aids		Unsuitable as it needs to be kept in original pack to protect from moisture	No special precautions for storage	No special precautions for storage	No special precautions for storage
Cost/28 days at usual dose (Drug Tariff, MIMS December 2016)		£57.00	£50.40	£53.20	£51.80 (less rebate)

This information is a summary guide – for further information please consult individual SPCs at www.medicines.org.uk