DRUG INTERACTIONS THAT MAY AFFECT DOAC LEVELS

DOAC	CONTRA-INDICATED	RECOMMENDED TO AVOID	DOSE/ADMINISTRATION TIME ADJUSTMENT REQUIRED	NO DOSE ADJUSTMENT REQUIRED BUT USE WITH CAUTION	NO DOSE ADJUSTMENT REQUIRED	DETAILED METABOLISM INFO
APIXABAN	– Ketoconazole – Itraconazole – Voriconazole – Posaconazole – Ritonavir and other HIV protease inhibitors	**Expected to decrease DOAC levels** – Rifampin – Phenytoin – Carbamazepine – Phenobarbital – St. John's Wort		**Expected to increase DOAC levels** – Amiodarone – Diltiazem – Dronedarone – Naproxen – Clarithromycin	– Atenolol – Famotidine – Digoxin	CYP-450 Isoenzymes: • Apixaban is mainly metabolized by CYP3A4/5 with minor contributions from CYP 1A2, 2C8, 2C9, 2C19 and 2J2. • Apixaban does NOT inhibit or induce major CYP isoenzymes at standard plasma concentrations P-glycoprotein and other transport proteins: • Apixaban is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) • Apixaban does NOT inhibit P-glycoprotein (based on in vitro data)
	Apixaban is contraindicated in patients receiving concomitant treatment with strong inhibitors of both CYP 3A4 and P-gp					
DABIGATRAN	– Ketoconazole – Glecaprevir/ Pibrentasivir	**Expected to decrease DOAC levels** – Carbamazepine – Phenytoin – Rifampin – St. John's Wort **Expected to increase DOAC levels** – Dronedarone – Ticagrelor	**Expected to decrease DOAC levels** Antacids – administer at least 2h after dabigatran – for VTE prevention, see product monograph **Expected to increase DOAC levels** Amiodarone – for VTE prevention, see product monograph Quinidine – administer at least 2h after dabigatran – for VTE prevention, see product monograph Verapamil – administer at least 2h after dabigatran – for VTE prevention, see product monograph	**Expected to increase DOAC levels** – Amiodarone – Clarithromycin – Clopidogrel – Cyclosporine – Itraconazole – Nelfinavir – Posaconazole – Ritonavir – Saquinavir – Tacrolimus – Tipranavir **Expected to decrease DOAC levels** – Proton Pump Inhibitors	– Atorvastatin – Digoxin	CYP-450 Isoenzymes: • Based on in vitro evaluations, neither dabigatran etexilate nor its active moiety, dabigatran, are metabolised by the human cytochrome P450 system, nor do they exhibit effects on human CYPP450 isozymes. P-glycoprotein and other transport proteins: • Dabigatran etexilate, but not dabigatran, is a substrate with moderate affinity for the efflux P-glycoprotein (P-gp) transporter. Therefore, potent P-gp inducers or inhibitors may be expected to impact exposure to dabigatran
	Dabigatran is contraindicated in patients receiving concomitant systemic treatment with strong inhibitors of P-gp.					
EDOXABAN		**Expected to decrease DOAC levels** – Rifampin – Phenytoin – Carbamazepine – Phenobarbital	**Expected to increase DOAC levels** – Cyclosporine[£] – Dronedarone[£] – Erythromycin[£] – Ketoconazole[£] – Quinidine[£] – Azithromycin[†] – Clarithromycin[†] – Itraconozole[†] [£] reduce dose of edoxoban to 30 mg daily [†] not specifically listed in monograph but HOKUSAI VTE trial utilized half dose	**Expected to increase DOAC levels** – Amiodarone – ASA (doses of 325mg) – Protease Inhibitors – Verapamil **Expected to decrease DOAC levels** – Atorvastatin	– Digoxin – Esomeprazole	CYP-450 Isoenzymes: • Edoxaban does NOT inhibit the major cytochrome P450 enzymes and does not induce CYP1A2 or CYP3A4. P-glycoprotein and other transport proteins: • Edoxaban is a substrate of p-glycoprotein (P-gp) transporter and does not induce the P-gp transporter (MDR1). Edoxaban does not inhibit at clinically relevant concentrations: P-gp, the organic anion transporters OAT1 or OAT3; the organic cation transporters OCT1 or OCT2; or the organic ion transporting polypeptides OATP1B1 or OATP1B3.
RIVAROXABAN	– Ketoconazole – Itraconazole – Voriconazole – Posaconazole – Ritonavir (and Lopinavir/ Ritonavir – KALETRA) – Cobicistat	**Expected to decrease DOAC levels** – Rifampin – Phenytoin – Carbamazepine – Phenobarbital – St. John's Wort **Expected to increase DOAC levels** – Dronedarone		**Expected to increase DOAC levels** – Amiodarone* – Clarithromycin – Erythromycin** – Fluconazole *(no signal of increased bleeding in ROCKET-AF)* **(in mild to mod renal impairment)*	– Digoxin – Midazolam – Atorvastatin – Ranitidine – AlOH/MgOH – Omeprazole	CYP-450 Isoenzymes: • Rivaroxaban is metabolized via CYP 3A4, CYP 2J2, and CYP-independent mechanisms • Rivaroxaban does NOT inhibit or induce major CYP isoenzymes at standard plasm concentrations P-glycoprotein and other transport proteins: • Rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and BCRP (breast cancer resistance protein).
	Rivaroxaban is contraindicated in patients receiving concomitant treatment with strong inhibitors of both CYP 3A4 and P-gp *NB: Doses of 15mg or 20mg daily must be taken with FOOD for maximal absorption*					

This tool lists drug interactions that are included as part of Health Canada's prescribing guidelines. The focus is on concomitant medications that may affect the pharmacokinetics of the DOAC – its absorption, distribution, metabolism or elimination – which may alter the expected concentration in the body. This list is not all-inclusive.Consider consultation with a pharmacist. Drug interactions may be more likely and more severe in patients with decreased renal function, particularly with dabigatran.

Other medications that can increase bleeding on their own may further increase bleeding when added to DOAC therapy without necessarily affecting DOAC concentration including: ASA, clopidogrel, ticagrelor, ticlopidine, NSAIDs, oral anticoagulants such as warfarin, injectable anticoagulants such as enoxaparin, and selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)

References: Eliquis® (apixaban) Product Monograph. Bristol-Myers Squibb Canada Co. 2019 Oct 20; Lixiana® (edoxaban) Product Monograph. Servier Canada Inc. 2020 Feb 12; Pradaxa®(dabigtran) Product Monograph. Boehringer Ingelheim Canada Ltd. 2020 Mar 23; Xarelto® (rivaroxaban) Product Monograph. Bayer Inc. 2020 Jan 21.

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DRUG INTERACTIONS THAT MAY AFFECT DOAC LEVELS

ALPHABETICAL

Generic DRUG NAME	APIXABAN	DABIGATRAN	EDOXABAN	RIVAROXABAN
Amiodarone	⚠	⚠	⚠	⚠
Antacids	–	RX Take at least 2h after Dabigatran	–	GO for AlOH/MgOH
Atenolol	GO	–	–	–
Atorvastatin	–	GO	⚠	GO
Azithromycin	–	–	RX Not listed however, HOKUSAI VTE trial indicates half dose	–
Carbamazepine	⊘	⊘	⊘	⊘
Clarithromycin	⚠	⚠	RX Not listed however, HOKUSAI VTE trial indicates half dose	⚠
Clopidogrel	–	⚠ (may increase levels)	–	–
Cobicistat	–	–	–	STOP
Cyclosporine	–	⚠	RX *	–
Digoxin	GO	GO	GO	GO
Diltiazem	⚠	–	–	–
Dronedarone	⚠	⊘	RX *	⊘
Erythromycin	–	–	RX *	⚠ (in mild-moderate renal impairment)
Famotidine	GO	–	–	–
Fluconazole	–	–	–	⚠
Glecaprevir/Pibrentasivir	STOP	STOP	⚠	–
Itraconazole	STOP	⚠	RX Not listed however, HOKUSAI VTE trial indicates half dose	STOP
Ketoconazole	STOP	STOP	RX *	STOP
Lopinavir-Ritonavir (Kaletra)	STOP	–	⚠	STOP
Midazolam	–	–	–	GO
Naproxen	⚠	–	–	–
Nelfinavir	–	⚠	⚠	–
Phenobarbital	⊘	–	⊘	⊘
Phenytoin	⊘	⊘	⊘	⊘
Posaconazole	STOP	⚠	–	STOP
Protease Inhibitors (see also individual agents)	STOP	–	⚠	–
Proton Pump Inhibitors	–	⚠	GO with Esomeprazole	GO with Omeprazole
Quinidine	–	RX See other side for details	RX *	–
Ranitidine	–	–	–	GO
Rifampin	⊘	⊘	⊘	⊘
Ritonavir	STOP	⚠	⚠	STOP
St. John's Wort	⊘	⊘	–	⊘
Saquinavir	STOP	⚠	⚠	–
Tacrolimus	–	⚠	–	–
Ticagrelor	–	⊘	–	–
Tipranivir	STOP	⚠	⚠	–
Verapamil	–	RX See other side for details	RX Not listed however, HOKUSAI VTE trial indicates half dose	–
Voriconazole	STOP	–	–	STOP

STOP CONTRAINDICATED	⊘ RECOMMENDED TO AVOID	RX DOSE/ADMINISTRATION TIME ADJUSTMENT REQUIRED	⚠ NO DOSE ADJUSTMENT REQUIRED BUT USE WITH CAUTION	GO NO DOSE ADJUSTMENT REQUIRED	NO INFORMATION AVAILABLE IN THE CURRENT PRODUCT MONOGRAPH

* Reduce dose of edoxaban to 30 mg daily.

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