Texas Vendor Drug Program

Drug Use Criteria: Direct Oral Anticoagulants

Publication History

1. Developed March 2017.
2. Revised **April 2022;** March 2020; May 2018; February 2018.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

1.1 Adults

Direct oral anticoagulants (DOACs) are FDA-approved to treat and prevent deep venous thrombosis (DVT) and pulmonary embolism (PE), reduce the risk of stroke and systemic embolism from non-valvular atrial fibrillation, and to be used as prophylaxis against DVT and PE after knee and hip surgery. DOACs work by interfering with pathways in the coagulation cascade: directly inhibiting thrombin (e.g., dabigatran); or selectively, reversibly inhibiting factor Xa (e.g., apixaban, edoxaban, rivaroxaban).[1-7] **In April 2020 Portola Pharmaceuticals removed Bevyxxa® (betrixaban) from the market for independent business reasons.[8]**

Maximum recommended adult dosages for DOACs are summarized in Tables 1 and 2. Medication profiles identifying patients prescribed dosages exceeding these recommendations will be reviewed.

Table 1. Maximum Daily Adult Dosages for DOACs: Direct Thrombin Inhibitors[1-4]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
dabigatran (Pradaxa®)	75 mg, 110 mg, 150 mg capsules	*Reduction in risk of stroke and systemic embolism in non-valvular AF*	**CrCl > 30 mL/min:** 150 mg twice daily **CrCl 15-30 mL/min: 75 mg twice daily** **CrCl < 15 mL/ min: dosing recommendations cannot be provided** **CrCl 30-50 mL/min with concomitant use of P-gp inhibitors: 75 mg twice daily** **CrCl < 30 mL/min with concomitant use of P-gp inhibitors: Avoid coadministration**
dabigatran		*Treatment of DVT and PE/reduction in the risk of recurrence of DVT and PE*	**CrCl > 30 mL/ min:** 150 mg twice daily* **CrCl ≤ 30 mL/ min: dosing recommendations cannot be provided** **CrCl < 50 mL/ min with concomitant use of P-gp inhibitors: Avoid coadministration**

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
dabigatran		*Prophylaxis of DVT and PE following hip replacement surgery*	**CrCl > 30 mL/min:** 110 mg for first day, then 220 mg once daily **CrCl ≤ 30 mL/ min: dosing recommendations cannot be provided** **CrCl < 50 mL/ min with concomitant use of P-gp inhibitors: avoid coadministration**

AF = atrial fibrillation; DVT = deep venous thrombosis; PE = pulmonary embolism
**Requires 5 to 10 days parenteral therapy before initiation of therapy*

Table 2. Maximum Daily Adult Dosages for DOACs: Factor Xa Inhibitors[1,2,5-7]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
apixaban (Eliquis®)	2.5 mg, 5 mg tablets	*Reduction of risk of stroke and systemic embolism in patients with non-valvular AF*	5 mg twice daily[#]
apixaban		*Prophylaxis of DVT following hip or knee replacement surgery*	2.5 mg twice daily
apixaban		*Treatment of DVT and PE*	10 mg twice daily for 7 days, then 5 mg twice daily
apixaban		*Reduction in risk of recurrence of DVT and PE*	2.5 mg twice daily^
edoxaban (Savaysa®)	15 mg, 30 mg, 60 mg tablets	*Non-valvular AF:* CrCl > 50 mL/min and ≤ 95 mL/min	60 mg once daily[+]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
edoxaban		*Non-valvular AF:* CrCl 15-50 mL/min	30 mg once daily
edoxaban		*Treatment of DVT and PE:* ≥ 60 kg:	60 mg once daily*
edoxaban		*Treatment of DVT and PE:* < 60 kg, CrCl 15-50 mL/min, adjunctive therapy with certain P-gp inhibitors	30 mg once daily*
rivaroxaban (Xarelto®)	2.5 mg, 10 mg, 15 mg, 20 mg tablets, **1 mg/ 1 mL granules for suspension**	*Reduction in the risk of stroke in non-valvular AF, CrCl > 50 mL/min*	20 mg once daily with evening meal
rivaroxaban		*Reduction in the risk of stroke in non-valvular AF, CrCl ≤ 50 mL/min*	15 mg once daily with evening meal
rivaroxaban		*Treatment of DVT and PE, CrCl ≥ 15 mL/min*	15 mg twice daily for 21 days, then 20 mg once daily
rivaroxaban		*Reduction in risk of recurrence of DVT and PE (following initial treatment), CrCl ≥ 15 mL/min*	10 mg once daily^
rivaroxaban		*Prophylaxis of DVT following hip or knee replacement surgery, CrCl ≥ 15 mL/min*	10 mg once daily
rivaroxaban		*VTE prophylaxis in hospitalized adults with acute illness and limited mobility and other risk factors for VTE, CrCl ≥ 15 mL/min*	10 mg once daily

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
rivaroxaban		*Reduction of major cardiovascular event risk in patients with chronic coronary heart disease, peripheral artery disease*	2.5 mg twice daily, plus aspirin 75-100 mg once daily

AF = atrial fibrillation; DVT = deep venous thrombosis; PE = pulmonary embolism; P-gp = P-glycoprotein; VTE = venous thromboembolism
[+]Avoid in patients with CrCl > 95 ml/min due to increased risk of ischemic stroke compared to warfarin
**Requires 5 to 10 days parenteral therapy before initiation of therapy*
[#]Dose should be decreased to 2.5 mg twice daily in patients receiving strong inhibitors of both CYP3A4 and P-glycoprotein concurrently, or those with at least two of the following: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL
[^]Following at least 6 months of DVT or PE treatment

1.2 Pediatrics

Apixaban and edoxaban are not recommended for use in pediatric patients, as the safety and efficacy have not been established for these agents in this patient population.[1,2,5,6]

In June 2021, the FDA approved Pradaxa® (dabigatran) oral pellets to treat venous thromboembolism after receiving at least five days of injectable or intravenous treatment for blood clots and to reduce the risk of recurrent thromboembolism in patients 3 months to less than twelve years of age who have completed treatment for a previous venous thromboembolism.[9]

Dabigatran oral capsules were approved to treat venous thromboembolism after receiving at least five days of injectable or intravenous treatment for blood clots and to reduce the risk of recurrent thromboembolism in patients 8 years of age and older who have completed treatment for a previous venous thromboembolism.[9]

In December 2021, the FDA approved Xarelto® (rivaroxaban) tablets and oral suspension to treat venous thromboembolism and to reduce the risk of recurrent venous thromboembolism in patients less than 18 years of age who received at least five days of injectable or intravenous treatment for blood clots. Rivaroxaban was also approved to reduce the risk of blood

clots in patients two years of age and older with congenital heart disease after the Fontan procedure.[10]

Maximum recommended pediatric dosages for DOACs are summarized in Table 3 through Table 6. Medication profiles identifying patients prescribed dosages exceeding these recommendations will be reviewed.

Table 3. Maximum Daily Pediatric Dosages for DOACs in Pediatric Patients Less than 2 Years of Age: Direct Thrombin Inhibitors[1,2,4]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
dabigatran (Pradaxa®) oral pellets[!]	**20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg oral pellets**	***Treatment of VTE and to reduce the risk of VTE recurrence: 3 months to <2 years of age***	***Actual Weight: 3kg to <4kg*^*** **3 to <6 months: 30 mg twice daily** ***Actual Weight: 4 kg to <5 kg*^*** **3 to <10 months: 40 mg twice daily** ***Actual Weight: 5 kg to <7 kg*^*** **3 to <5 months: 40 mg twice daily** **5 to <24 months: 50 mg twice daily** ***Actual Weight: 7 kg to <9 kg*^*** **3 to <4 months: 50 mg twice daily** **4 to <9 months: 60 mg twice daily** **9 to <24 months: 70 mg twice daily** ***Actual Weight: 9 kg to <11 kg*^*** **5 to <6 months: 60 mg twice daily** **6 to <11 months: 80 mg twice daily** **11 to <24 months: 90 mg twice daily** ***Actual Weight: 11 kg to <13 kg*^*** **8 to <18 months: 100 mg twice daily** **18 to <24 months: 110 mg twice daily** ***Actual Weight: 13 kg to <16 kg*^*** ***10* to <11 months: 100 mg twice daily** **11 to <24 months: 140 mg twice daily** Actual Weight: 16 kg to <21 kg*^ **12 to <24 months: 140 mg twice daily** ***Actual Weight: 21 kg to <26 kg*^*** **18 to <24 months: 180 mg twice daily**

VTE = venous thromboembolism

[!]Avoid dabigatran in patients with a CrCl < 50 mL/min

****Requires at least 5 days parenteral therapy before initiation of therapy for treatment of VTE***

^Following appropriate treatment duration of DVT or PE treatment if used to reduce the risk of VTE recurrence

Table 4. Maximum Daily Pediatric Dosages for DOACs in Pediatric Patients 2 to Less than 12 Years of Age: Direct Thrombin Inhibitors[1,2,4]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
dabigatran (Pradaxa®) oral pellets[l]	**20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg oral pellets**	***Treatment of VTE and to reduce the risk of VTE recurrence: 2 to less than 12 years of age***	***Actual Weight: 7 kg to <9 kg*^*** **70 mg twice daily** ***Actual Weight: 9 kg to <11 kg*^*** **90 mg twice daily** ***Actual Weight: 11 kg to <13 kg*^*** **110 mg twice daily** ***Actual Weight: 13 kg to <16 kg*^*** **140 mg twice daily** ***Actual Weight: 16 kg to <21 kg*^*** **170 mg twice daily** ***Actual Weight: 21 kg to <41 kg*^*** **220 mg twice daily** ***Actual Weight: 41 kg or greater*^*** **260 mg twice daily**

VTE = venous thromboembolism

[l]Avoid dabigatran in patients with a CrCl < 50 mL/min

****Requires at least 5 days parenteral therapy before initiation of therapy for treatment of VTE***

^Following appropriate treatment duration of DVT or PE treatment if used to reduce the risk of VTE recurrence

Table 5. Maximum Daily Pediatric Dosages for DOACs in Pediatric Patients 8 to Less than 18 Years of Age: Direct Thrombin Inhibitors[1-3]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
dabigatran (Pradaxa®) capsules[!]	**75 mg, 110 mg, 150 mg oral capsules**	***Treatment of VTE and to reduce the risk of VTE recurrence: 8 to less than 18 years of age***	***11 kg to less than 16 kg*^*** **75 mg twice daily** ***16 kg to less than 26 kg*^*** **110 mg twice daily** ***26 kg to less than 41 kg*^*** **150 mg twice daily** ***41 kg to less than 61 kg*^*** **185 mg twice daily** ***61 kg to less than 81 kg*^*** **220 mg twice daily** ***81 kg or greater*^*** **260 mg twice daily**

VTE = venous thromboembolism

[!]Avoid dabigatran in patients with a CrCl < 50 mL/min

****Requires at least 5 days parenteral therapy before initiation of therapy for treatment of VTE***

^Following appropriate treatment duration of DVT or PE treatment if used to reduce the risk of VTE recurrence

Table 6. Maximum Daily Pediatric Dosages for DOACs in Patients Less than 18 Years of Age: Factor Xa Inhibitors[1,2,7]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage±
rivaroxaban (Xarelto®)	**10 mg, 15 mg, 20 mg tablets, 1 mg/ 1 mL granules for suspension**	***Treatment of VTE and to reduce the risk of VTE recurrence: less than 18 years of age***	***2.6 kg to 2.9 kg*^#*** **0.8 mg three times daily** ***3 kg to 3.9 kg*^#*** **0.9 mg three times daily** ***4 kg to 4.9 kg*^#*** **1.4 mg three times daily** ***5 kg to 6.9 kg*^#*** **1.6 mg three times daily** ***7 kg to 7.9 kg*^#*** **1.8 mg three times daily** ***8 kg to 8.9 kg*^#*** **2.4 mg three times daily** ***9 kg to 9.9 kg*^#*** **2.8 mg three times daily** ***10 kg to 11.9 kg*^#*** **3 mg three times daily** ***12 kg to 29.9 kg*^#*** **5 mg twice daily** ***30 kg to 49.9 kg*^!*** **15 mg once daily** ***≥50 kg*^!*** **20 mg once daily**

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage±
		Thromboprophylaxis in patients 2 years of age and older with congenital heart disease who have undergone Fontan procedure	***7 kg to 7.9 kg#*** **1.1 mg twice daily** ***8 kg to 9.9 kg#*** **1.6 mg twice daily** ***10 kg to 11.9 kg#*** **1.7 mg twice daily** ***12 kg to 19.9 kg#*** **2 mg twice daily** ***20 kg to 29.9 kg#*** **2.5 mg twice daily** **30 kg to 49.9 kg#** **7.5 mg once daily** ***≥50 kg!*** **10 mg once daily**

VTE = venous thromboembolism
±Patients <6 months of age should meet the following criteria: at birth at least 37 weeks gestation, have at least 10 days of oral feeding, and weigh ≥2.6 kg at the time of dosing
****Requires at least 5 days parenteral therapy before initiation of therapy for treatment of VTE***
^Following appropriate treatment duration of DVT or PE treatment if used to reduce the risk of VTE recurrence
#May only use granules for suspension
!May use granules for suspension or oral tablets

2 Duration of Therapy

There is no basis for limiting DOAC therapy when prescribed to prevent thromboembolic events associated with cardiovascular or cerebrovascular disease in those with a high risk of recurrence and low risk of bleeding (e.g., unprovoked proximal DVT, recurrent DVT). However, DOAC treatment duration varies, based on medication utilized, indication for use, **underlying disease states**, and patient factors.[11] **The 2021 "Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guidelines and Expert Review Panel Report" indicates that extended-phase anticoagulation with DOACs does not have a defined**

stop date, and patients have been monitored for up to four years while on extended-phase anticoagulation. DOAC treatment durations are summarized in **Table 7 through Table 10**.

Table 7. DOAC Recommended Treatment Duration (Adults): Direct Thrombin Inhibitors[1-3,11]

Drug Name	Indication	Maximum Treatment Duration
dabigatran (Pradaxa®)	*Reduction of risk of stroke and systemic embolism in non-valvular AF*	indefinite
	DVT and PE treatment	3-12 months
	DVT and PE prevention	indefinite
	Prophylaxis of DVT and PE following hip replacement surgery	28-35 days

AF = atrial fibrillation; DVT = deep venous thrombosis; PE = pulmonary embolism

Table 8. DOAC Recommended Treatment Duration (Adults): Factor Xa Inhibitors[1,2,5-7,11]

Drug Name	Indication	Maximum Treatment Duration
apixaban (Eliquis®)	*Reduction of risk of stroke and systemic embolism in patients with non-valvular AF*	indefinite
	Prophylaxis of DVT following hip or knee replacement surgery	35 days (hip); 12 days (knee)
	Treatment of DVT and PE	3-12 months
	Reduction in risk of recurrence of DVT and PE	indefinite after at least 6 months of treatment
edoxaban (Savaysa®)	*Reduction of risk of stroke and systemic embolism in patients with non-valvular AF*	indefinite
	Treatment of DVT and PE	maximum of 12 months after 5-10 days of initial therapy with a parenteral anticoagulant
rivaroxaban (Xarelto®)	*Reduction in the risk of stroke in non-valvular AF*	indefinite
	Treatment of DVT and PE	3-12 months

Drug Name	Indication	Maximum Treatment Duration
	Reduction in risk of recurrence of DVT and PE	up to 12 months after an initial 6 months of treatment
	Prophylaxis of DVT following hip or knee replacement surgery	35 days (hip); 12 days (knee)
	VTE prophylaxis in hospitalized adults with acute illness and limited mobility and other risk factors for VTE	31 to 39 days
	Reduction of major cardiovascular event risk in patients with chronic coronary heart disease, peripheral artery disease	indefinite

AF = atrial fibrillation; DVT = deep venous thrombosis; PE = pulmonary embolism

The DIVERSITY trial was conducted in pediatric populations to determine the safety and efficacy of dabigatran compared to the standard of care for the treatment of VTE. The median duration of dabigatran for VTE was 84.5 days.[12] An additional trial evaluated the safety and effectiveness of dabigatran in patients requiring secondary VTE prophylaxis who completed the DIVERSITY trial. Pediatric patients were treated with dabigatran for up to 12 months after the initial treatment for VTE.[13]

Table 9. DOAC Recommended Treatment Duration (Pediatrics): Direct Thrombin Inhibitors[1-4,12-14]

Drug Name	Indication	Maximum Treatment Duration
dabigatran (Pradaxa®)	***VTE treatment***	**3-12 months**
	Reduction in risk of recurrence of DVT and PE	**up to 12 months after initial treatment for VTE**

The EINSTEIN Junior trial studied the safety and efficacy of rivaroxaban compared to standard of care in pediatric patients with VTE. When appropriate, treatment for VTE and VTE risk reduction was extended to up to 12 months in duration.[15] The UNIVERSE trial assessed the safety and efficacy of rivaroxaban for thromboprophylaxis in pediatric patients with congenital heart disease who have undergone the Fontan procedure.

Participants took rivaroxaban for up to 12 months in the study.[16] However, thromboembolic risk may persist for several years after the procedure, and further therapy with antiplatelet or anticoagulant drugs may be appropriate.[16]

Table 10. DOAC Recommended Treatment Duration (Pediatrics): Factor Xa Inhibitors[1,2,7,14-16]

Drug Name	Indication	Maximum Treatment Duration
rivaroxaban (Xarelto®)	***VTE treatment***	**3-12 months**
	Reduction in risk of recurrence of VTE	**up to 12 months**
	Thromboprophylaxis in patients at least 2 years of age with congenital heart disease who have undergone Fontan procedure	**up to 12 months[a]**

[a]Specific patient factors may require a longer duration of antiplatelet or anticoagulant therapy

3 Duplicative Therapy

Combined administration of multiple DOACs should be avoided. Concomitant DOAC use results in additive factor Xa inhibition and prolonged prothrombin time (PT), which increases bleeding risk.[1-7] No evidence demonstrating increased efficacy or augmentation of therapy from use of multiple DOACs currently exists.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens, which may result in clinically significant drug-drug interactions. Major drug-drug interactions considered clinically significant for DOACs are summarized in **Table 11**. Only those drug-drug interactions classified as clinical significance level 1/contraindicated or those considered life threatening which have not yet been classified will be reviewed.

Table 11. DOAC Drug-Drug Interactions[1-7]

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
dabigatran	P-gp inhibitors (e.g., amiodarone, clarithromycin)	increases dabigatran exposure and bleeding risk	*Non-valvular AF*: avoid use with CrCl < 30 mL/min; reduce dose to 75 mg twice daily with CrCl 30-50 mL/min (dronedarone, systemic ketoconazole only) *Treatment and prevention of DVT and PE:* avoid use with CrCl < 50 mL/min *Prevention of DVT and PE after hip replacement surgery:* avoid use with CrCl < 50 mL/min; separate by several hours with CrCl >50 mL/min	dabigatran, major; itraconazole, contraindicated (DrugReax) 2 – major (CP)
dabigatran, edoxaban	P-gp inducers (e.g., rifampin)	reduces serum dabigatran, edoxaban serum levels and increases thrombosis risk	avoid concurrent use	major (DrugReax) 2 – major (CP)
DOACs	anticoagulants, NSAIDs, aspirin, antiplatelet agents, fibrinolytics	increases bleeding risk	avoid concurrent use; if adjunctive administration necessary, use cautiously and monitor closely for signs/ symptoms of bleeding	major (DrugReax) anticoagulants, 2 – major; fibrinolytics, 1 – severe (CP)
DOACs	defibrotide	enhances DOAC pharmacologic effects, increasing bleeding risk	avoid concurrent use	contraindicated (DrugReax) 1 – severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
DOACs	selective serotonin reuptake inhibitors (SSRIs)/ serotonin norepinephrine reuptake inhibitors (SNRIs)	may increase bleeding risk	avoid concurrent use; if adjunctive administration necessary, use cautiously and monitor closely for signs/ symptoms of bleeding	major (DrugReax) 2 – major (CP)
DOACs	orlistat	may increase INR due to decreased vitamin K absorption	if adjunctive administration necessary, use cautiously and monitor closely for changes in coagulation factors	major (DrugReax) 3 – moderate (CP)
rivaroxaban, apixaban	dual P-gp and CYP3A4 inhibitors (e. g., ritonavir, ketoconazole)	increases serum rivaroxaban, apixaban levels, which increases bleeding risk	avoid concurrent use; reduce dose of apixaban by 50%; avoid use in patients receiving apixaban 2.5 mg twice daily	major (DrugReax) 2 – major (CP)
rivaroxaban, apixaban	dual P-gp and CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine)	decreases rivaroxaban exposure by 50%; rifampin decreases apixaban exposure by 50%; increases thrombosis risk	avoid concurrent use	major (DrugReax) 2 – major (CP)

5 References

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