TEXAS Health and Human Services

Medicaid Drug Use Criteria

Direct Oral Anticoagulants

- Developed March 2017.
- Revised May 2020; March 2020; May 2018; February 2018.

Notes: Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

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. Rivaroxaban has also recently gained approval for use in acutely ill hospitalized and post hospital discharge medical patients with limited mobility requiring venous thromboembolism

prophylaxis as well as risk reduction of cardiovascular events in those patients with chronic coronary artery disease or peripheral artery disease. 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, betrixaban, edoxaban, rivaroxaban).[1-9] 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[1-5]

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	150 mg twice daily
dabigatran		Treatment of DVT and PE/reduction in the risk of recurrence of DVT and PE	150 mg twice daily*
dabigatran		Prophylaxis of DVT and PE following hip replacement surgery	110 mg for first day, then 220 mg once daily

- 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[1-4, 6-9]

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

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
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^
betrixaban (Bevyxxa®)	40 mg, 80 mg capsules	VTE prophylaxis in hospitalized adults with acute illness and limited mobility and other risk factors for VTE, CrCl greater than 30 mL/min	80 mg once daily (after initial single dose of 160 mg)
betrixaban		VTE prophylaxis in hospitalized adults with acute illness and limited mobility and other risk factors for VTE: CrCl greater than or equal to 15 mL/min and less than 30 mL/min	40 mg once daily (after initial single dose of 80 mg)
edoxaban (Savaysa®)	15 mg, 30 mg, 60 mg tablets	Non-valvular AF: CrCl greater than 50 mL/min and less than or equal to 95 mL/min	60 mg once daily+
edoxaban		Non-valvular AF: CrCl 15-50 mL/min	30 mg once daily
edoxaban		Treatment of DVT and PE: Greater than 60 kg:	60 mg once daily*
edoxaban		Treatment of DVT and PE: Less than 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	Reduction in the risk of stroke in non-valvular AF, CrCl greater than 50 mL/min	20 mg once daily with evening meal

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
rivaroxaban		Reduction in the risk of stroke in non-valvular AF, CrCl less than or equal to 50 mL/min	15 mg once daily with evening meal
rivaroxaban		Treatment of DVT and PE, CrCl greater than 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 greater than or equal to 15 mL/min	10 mg once daily^
rivaroxaban		Prophylaxis of DVT following hip or knee replacement surgery, CrCl greater than or equal to 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 greater than or equal to 15 mL/min	10 mg once daily
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
- +Avoid in patients with CrCl greater than 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 greater than or equal to 80 years, body

weight less than or equal to 60 kg, or serum creatinine greater than or equal to 1.5 mg/dL

- ^following at least 6 months of DVT or PE treatment

1.2 Pediatrics

Dabigatran, apixaban, betrixaban, edoxaban, and rivaroxaban are not recommended for use in pediatric patients as safety and efficacy have not been established for these agents in this patient population.

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., unproved proximal DVT, recurrent DVT). However, DOAC treatment duration varies, based on medication utilized, indication for use, and patient factors.[1-15] DOAC treatment durations are summarized in Tables 3 and 4.[1-25]

Table 3. DOAC Recommended Treatment Duration (Adults): Direct Thrombin Inhibitors[1-5, 10-15]

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

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

Table 4. DOAC Recommended Treatment Duration (Adults): Factor Xa Inhibitors[1-4, 6-15]

Drug Name	Indication	Maximum Treatment Duration
apixaban (Eliquis®)	Reduction of risk of stroke and systemic embolism in patients with non-valvular AF	indefinite
apixaban	Prophylaxis of DVT following hip or knee replacement surgery	35 days (hip); 12 days (knee)
apixaban	Treatment of DVT and PE	3-12 months
apixaban	Reduction in risk of recurrence of DVT and PE	indefinite after at least 6 months of treatment
betrixaban	VTE prophylaxis in hospitalized adults with acute illness and limited mobility and other risk factors for VTE	42 days
edoxaban (Savaysa®)	Reduction of risk of stroke and systemic embolism in patients with non-valvular AF	indefinite
edoxaban	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
rivaroxaban	Treatment of DVT and PE	3-12 months
rivaroxaban	Reduction in risk of recurrence of DVT and PE	up to 12 months after an initial 6 months of treatment
rivaroxaban	Prophylaxis of DVT following hip or knee replacement surgery	35 days (hip); 12 days (knee)
rivaroxaban	VTE prophylaxis in hospitalized adults with acute illness and limited mobility and other risk factors for VTE	31 to 39 days
rivaroxaban	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

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.[1-9, 16] 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 5. 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 5. DOAC Drug-Drug Interactions[1-9]

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
betrixaban	P-gp inhibitors (e.g., amiodarone, clarithromycin)	may elevate serum betrixaban levels and increase bleeding risk as betrixaban is P-gp substrate	reduce doses by 50% (initial single dose: 80 mg, followed by daily dose of 40 mg); monitor for bleeding	major (DrugReax) 2-major (CP)

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 less than 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 less than 50 mL/min Prevention of DVT and PE after hip replacement surgery: avoid use with CrCl less than 50 mL/min; separate by several hours with CrCl greater than 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

1. DRUGDEX® System (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at micromedexsolutions.com.libproxy.uthscsa.edu/. Accessed March 16, 2020.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at clinicalpharmacology-ip.com.ezproxy.lib.utexas.edu/. Accessed March 16, 2020.

3. Facts and Comparisons eAnswers [database online]. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020. Available at fco-factsandcomparisons-com.ezproxy.lib.utexas.edu. Accessed March 16, 2020.
4. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020. Available at online-lexi-com.ezproxy.lib.utexas.edu/lco/action/home. Accessed March 16, 2020.
5. Dabigatran etixilate mesylate capsules (Pradaxa®) package insert. Boehringer Ingelheim Pharmaceuticals, Inc., November 2019.
6. Apixaban tablets (Eliquis®) package insert. Bristol-Myers Squibb Company, November 2019.
7. Edoxaban tablets (Savaysa®) package insert. Daiichi Sankyo, Inc., August 2019.
8. Rivaroxaban tablets (Xarelto®) package insert. Janssen Pharmaceuticals, Inc., March 2020.
9. Betrixaban (Bevyxxa®) package insert. Portola Pharmaceuticals, Inc., June 2017.
10. Lip GYH, Hull RD. Overview of the treatment of lower extremity deep vein thrombosis. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. uptodate.com (Accessed on March 16, 2020.)
11. Hull RD, Lip GYH. Venous thromboembolism: anticoagulation after initial management. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. uptodate.com (Accessed on March 16, 2020.)
12. Lip GYH, Hull RD. Rationale and indications for indefinite anticoagulation in patients with venous thromboembolism. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. uptodate.com (Accessed on March 16, 2020.)
13. Manning WJ, Singer DE, Lip GYH. Atrial fibrillation: anticoagulant therapy to prevent embolization. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. uptodate.com (Accessed on March 16, 2020.)
14. The Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013; 369:1406-15.
15. Streiff MB, Agnelli G, Connors JM, et al. Guidance for the treatment of deep vein thrombosis and pulmonary embolism. J Thromb Thrombolyis. 2016; 41:32-67.