

Texas Vendor Drug Program

Drug Use Criteria: Platelet Aggregation Inhibitors

Publication History

1. Developed December 2016.
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Medications listed in the tables and non-FDA approved indications that may be included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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TEXAS
Health and Human
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*Medical and
Social Services*

1 Dosage

1.1 Adults

Platelet aggregation inhibitors (PAIs) are FDA-approved to reduce thrombotic cardiovascular events in patients with a history of ischemic stroke, or to prevent stroke in patients with predisposing factors for atherosclerosis or symptomatic cerebrovascular disease. PAIs work by interfering with pathways that promote normal platelet function: inhibiting cyclooxygenase-1 (e.g., aspirin); inhibiting adenosine uptake into platelets, resulting in increased cyclic-3',5'-adenosine monophosphate (cAMP) and adenosine levels (e.g., dipyridamole); inhibiting the adenosine diphosphate (ADP) P2Y₁₂ receptor on the platelet surface and blocking activation of the glycoprotein GP IIb/IIIa complex (e.g., clopidogrel, prasugrel, ticagrelor); antagonizing protease-activated receptor 1 (PAR-1), which inhibits thrombin and thrombin receptor agonist peptide activity (e.g., vorapaxar); or inhibiting phosphodiesterase III (e.g., cilostazol).¹⁻¹⁰

Aspirin is available in combination with omeprazole, a proton pump inhibitor, to reduce the risk of aspirin-associated gastric ulcers in those patients requiring aspirin for secondary prevention of cardiovascular and cerebrovascular events.^{1,2,9} Aspirin is also available as combination therapy with dipyridamole, pairing two antiplatelet agents with different mechanisms of action for secondary stroke prevention.^{1,2,10} Maximum recommended adult dosages for PAIs 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 PAIs – Monotherapy¹⁻⁸

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
cilostazol (generics)	50 mg, 100 mg tablets	intermittent claudication	100 mg twice daily
clopidogrel (Plavix®, generics)	75 mg, 300 mg tablets	ACS, including UA/NSTEMI and STEMI	Initial: 300 mg or 600 mg loading dose, followed by 75 mg once daily for up to 12 months in combination with aspirin, followed by aspirin indefinitely
		thromboembolism prophylaxis in patients with recent MI or stroke, or established peripheral vascular disease	75 mg/day
dipyridamole (generics)	25 mg, 50 mg, 75 mg tablets	prevention of postoperative thrombotic complications in patients with prosthetic heart valves	400 mg/day (divided doses, in combination with warfarin) or 400 mg/day (divided doses, in combination with aspirin)
prasugrel (Effient®, generics)	5 mg, 10 mg tablets	ACS in patients to be managed with PCI	following a 60 mg loading dose, 10 mg/day ⁺ in combination with aspirin

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
ticagrelor (Brilinta®)	60 mg, 90 mg tablets	reduce risk of death, MI, and stroke in patients with ACS, history of MI, or acute ischemic stroke/ high risk transient ischemic attack	following a 180 mg loading dose, 90 mg twice daily [^] in combination with aspirin
		reduce risk of first MI or stroke in patients with CAD at high risk of events	60 mg twice daily in combination with aspirin
vorapaxar (Zontivity®)	2.08 mg tablet	MI, stroke, thrombosis prophylaxis in patients with a history of MI or PAD	2.08 mg/day in combination with aspirin or clopidogrel

ACS = acute coronary syndrome; CAD = coronary artery disease; MI = myocardial infarction; NSTEMI = non-ST-elevation acute coronary syndrome; NSTEMI = non-ST-elevation myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction; TIA = transient ischemic attack; UA = unstable angina

⁺patients 75 years or older or weigh < 60 kg may use prasugrel 5 mg/day as maintenance therapy in combination with aspirin to reduce bleeding risk

[^]ticagrelor dosages are decreased to 60 mg twice daily after 12 months

Table 2. Maximum Daily Adult Dosages for PAIs – Combination Therapy^{1,2,9,10}

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
aspirin/ omeprazole (Yosprala®)	81 mg/40 mg, 325 mg/40 mg delayed-release tablets	secondary prevention of cardiovascular and cerebrovascular events in patients predisposed to gastric ulcers	325 mg/40 mg once daily
dipyridamole/ aspirin (generics)	200 mg/25 mg extended-release capsule	secondary stroke prevention	200 mg/25 mg twice daily

1.2 Pediatrics

Dipyridamole is FDA-approved for use in pediatric patients 12 years of age and older as adjunctive therapy to prevent thromboembolism following cardiac valve replacement. The maximum recommended dose is 100 mg four times daily in combination with warfarin.^{1,2,5} Dosages exceeding these recommendations will be reviewed.

Cilostazol, prasugrel, ticagrelor, vorapaxar, aspirin/omeprazole, and dipyridamole/aspirin are not recommended for use in pediatric patients as safety and efficacy have not been established for these agents in this patient population.^{1-3,6-10} Although not FDA-approved, clopidogrel has effectively been used in pediatric patients to reduce thrombosis risk in infants and children with select types of heart disease, or as an alternative in patients with Kawasaki disease or ischemic stroke when aspirin is not tolerated.

2 Duration of Therapy

There is no basis for limiting PAI therapy duration when prescribed to prevent thromboembolic events associated with cardiovascular or cerebrovascular disease. However, PAI therapy duration varies based on medication utilized and indication for use. PAI treatment durations are summarized in Tables 3 and 4.

Table 3. PAI Recommended Treatment Duration (Adults) – Monotherapy^{1-4,6-8}

Drug Name	Treatment Indication	Maximum Treatment Duration
cilostazol	intermittent claudication	indefinite
clopidogrel	acute coronary syndrome (NSTEMI-ACS and STEMI)	up to 1 year, in combination with aspirin; aspirin then continued indefinitely ⁺
	thromboembolism prophylaxis	indefinite
prasugrel	ACS in patients to be managed with PCI	at least 12 months, in combination with aspirin, after stent placement
ticagrelor	ACS	90 mg twice daily x 1 year in combination with aspirin; then, 60 mg twice daily in combination with aspirin indefinitely

Drug Name	Treatment Indication	Maximum Treatment Duration
vorapaxar	MI, stroke, thrombosis prophylaxis in patients with a history of MI or PAD	indefinite, in combination with aspirin or clopidogrel

ACS = acute coronary syndrome; CAD = coronary artery disease; MI = myocardial infarction; NSTEMI = non-ST-elevation acute coronary syndrome; NSTEMI = non-ST-elevation myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction; TIA = transient ischemic attack

*in patients with aspirin allergy, clopidogrel monotherapy may be continued indefinitely

Table 4. Adult PAI Recommended Combination Therapy Treatment Duration^{1,2,9,10}

Drug Name	Treatment Indication	Maximum Treatment Duration
aspirin/omeprazole	secondary prevention of cardiovascular and cerebrovascular events in patients predisposed to gastric ulcers	indefinite
dipyridamole/aspirin	stroke prevention	indefinite

3 Duplicative Therapy

Adjunctive therapy with aspirin and clopidogrel, dipyridamole, prasugrel, ticagrelor, or vorapaxar has documented efficacy for acute coronary syndrome or thrombotic event prevention; concurrent therapy with clopidogrel and vorapaxar is also FDA-approved for thromboembolic event prophylaxis or acute coronary syndrome (see Tables 1-3).

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens that may result in clinically significant drug-drug interactions. Major drug-drug interactions considered clinically significant for platelet aggregation inhibitors 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: Major Platelet Aggregation Inhibitor Drug-Drug Interactions¹⁻¹⁰

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
aspirin	methotrexate (MTX)	potential for increased MTX serum levels, risk of enhanced pharmacologic/toxic effects as NSAIDs can reduce MTX clearance	avoid concurrent aspirin use within 10 days of high-dose MTX; otherwise, use cautiously together; monitor for increased myelosuppressive, GI adverse effects; may consider using longer leucovorin rescue	major (DrugReax) 1-severe (CP)
cilostazol, dipyridamole	riociguat (Adempas®)	concurrent administration may result in increased hypotension risk	avoid concurrent use	contraindicated (DrugReax) dipyridamole: 1-severe; cilostazol: 3-moderate (CP)
cilostazol, ticagrelor, vorapaxar	itraconazole, strong CYP3A4 inhibitors	co-administration may result in elevated serum concentrations of select platelet aggregation inhibitors (PAIs) and potential bleeding complications as cilostazol, ticagrelor, and vorapaxar metabolized by CYP3A4	avoid use; ticagrelor therapy should not be initiated for at least 2 weeks after itraconazole discontinuation; if adjunctive administration necessary, use cautiously and monitor patient closely for enhanced pharmacologic/adverse effects, especially bleeding	ticagrelor: contraindicated; cilostazol, vorapaxar: major (DrugReax) ticagrelor: 1-severe; cilostazol, vorapaxar: 2-major (CP)
clopidogrel	dasabuvir/ ombitasvir/ paritaprevir/ ritonavir (Viekira®)	adjunctive administration with clopidogrel (strong CYP2C8 inhibitor) contraindicated by manufacturer, as dasabuvir metabolized by CYP2C8, which increases risk for dasabuvir-induced QT interval prolongation; ritonavir, a CYP3A4 inhibitor, may limit clopidogrel	avoid concurrent use	1-severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
		conversion to active metabolite		
clopidogrel	omeprazole	strong CYP2C19 inhibitor (e.g. omeprazole) may result in reduced plasma concentrations of clopidogrel active metabolite and diminish antiplatelet activity	avoid concurrent use; consider alternative proton pump inhibitor (e.g. pantoprazole)	major (DrugReax) 2-major (CP)
PAIs	defibrotide	increased risk of hemorrhage when used adjunctively with antithrombotic/fibrinolytic drugs like PAIs	avoid concurrent use	contraindicated (DrugReax) 1-severe (CP)
PAIs, including aspirin	low molecular weight heparins	potential for additive bleeding adverse effects; PAIs inhibit platelet aggregation and have increased bleeding risk, prolonged bleeding time	avoid concurrent therapy, if possible; if drug combination necessary, use cautiously, monitor for signs/symptoms of bleeding	major, moderate (DrugReax) 2-major, 3-moderate (CP)
PAIs, including aspirin	selective serotonin reuptake inhibitors (SSRIs)/, serotonin norepinephrine reuptake inhibitors (SNRIs)	increased bleeding risk with combined therapy; SSRIs/SNRIs deplete platelet serotonin, which may impair platelet aggregation	monitor for signs/symptoms of bleeding; may consider substituting tricyclic antidepressant for SSRI/SNRI	SSRIs –major; SNRIs-major (DrugReax) 3-moderate (CP)
PAIs, including aspirin	anticoagulants	combined administration may increase bleeding risk, due to additive effects	if combined therapy necessary, monitor patients closely for bleeding signs/symptoms	major (DrugReax) 2-major, 3-moderate (CP)
PAIs	nonsteroidal anti-inflammatory drugs (NSAIDs)	concurrent use may increase risk for bleeding especially with	monitor for signs of bleeding with concurrent use	major (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
		chronic NSAID use		
ticagrelor, vorapaxar	strong CYP3A inducers (e.g., rifampin)	strong inducers substantially reduce ticagrelor, vorapaxar exposure and efficacy as both are CYP3A4 substrates	avoid use	major (DrugReax) 2–major (CP)
ticagrelor	simvastatin, lovastatin	adjunctive use may increase lovastatin, simvastatin serum levels as ticagrelor is CYP3A4 inhibitor and lovastatin and simvastatin are metabolized by CYP3A4	avoid lovastatin, simvastatin doses higher than 40 mg; observe for adverse effects if combined use necessary	moderate (DrugReax) 2–major (CP)

5 References

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