



Indiana Medicaid Therapeutics Committee **Therapeutic Class Review Summary**

Therapeutic Class:

Platelet Aggregation Inhibitors

Overview:

The platelet aggregation inhibitors discussed in this review are distinctively different in their mechanisms of action. Aspirin is the oldest antiplatelet agent and works via inhibition of cyclooxygenase. Dipyridamole inhibits the uptake of adenosine and increases the levels of cyclic AMP. Aggrenox™, the combination of dipyridamole and aspirin, utilizes the different mechanisms of action of the two agents to inhibit platelet aggregation. Clopidogrel and ticlopidine inhibit the binding of adenosine diphosphate (ADP) to their platelet receptors and subsequently inhibit platelet aggregation. The indications for clopidogrel and ticlopidine include prevention of stroke, myocardial infarction, acute coronary syndrome or other vascular death. Cilostazol inhibits phosphodiesterase III and increases cyclic AMP in platelets, which leads to inhibition of platelet aggregation and vasodilation. Cilostazol is indicated only for intermittent claudication, although it has been studied for use after the placement of coronary artery stents. Serious side effects associated with this drug class include thrombocytopenia and agranulocytosis, which occur more frequently with ticlopidine. Additionally, proton pump inhibitors and statins may decrease the antiplatelet activity of clopidogrel; therefore potential drug-drug interactions should be considered when concurrently administering clopidogrel with proton pump inhibitors or statins. Prasugrel (Effient™) is a recently approved platelet aggregation inhibitor that is indicated to reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention (PCI). Prasugrel is associated with an increased risk of significant, sometimes fatal bleeding, especially in patients ≥ 75 years of age and those undergoing coronary bypass graft surgery (CABG). The prescribing information contains a black box warning regarding bleeding risks with the use of prasugrel.

For stroke prevention, the literature supports the use of clopidogrel or combination dipyridamole and aspirin therapy over aspirin alone in high-risk patients. Additionally, clopidogrel is recommended for patients allergic to aspirin;

and clopidogrel or combination dipyridamole and aspirin therapy is recommended in patients who have had a stroke while taking aspirin. In CLASSICS, which compared clopidogrel and ticlopidine, ticlopidine had a higher incidence of neutropenia, thrombocytopenia and major bleeding, although efficacy was equivalent. Cilostazol has shown to be more effective in treatment of intermittent claudication than pentoxifylline.

Ticlopidine and clopidogrel have been proven beneficial for prevention of cardiovascular events in clinical trials; however, the side effect profile of ticlopidine limits its use. Consequently, the American College of Cardiology recommends acute and long-term antiplatelet treatment with aspirin, clopidogrel or their combination for patients with acute coronary syndromes or myocardial infarction. Although combination therapy with aspirin/dipyridamole (Aggrenox[®]) as well as treatment with ADP antagonists have demonstrated favorable outcomes in stroke prevention, dipyridamole has never been proven efficacious as monotherapy.

Generic Name	Brand Name	Manufacturer	Generic Available
Cilostazol	Pletal [®]	Various	Y
Clopidogrel	Plavix [®]	Bristol-Myers Squibb	N
Dipyridamole	Persantine [®]	Boehringer Ingelheim	Y
Dipyridamole/aspirin	Aggrenox [®]	Boehringer Ingelheim	N
Prasugrel	Effient [™]	Eli Lilly	N
Ticlopidine	Ticlid [®]	Roche	Y

**Note: Other platelet aggregation inhibitors (glycoprotein IIb/IIIa inhibitors) and thrombolytic agents are used in inpatient acute care settings and are not discussed in this review.*

Summary:

The mechanisms of action and approved indications for the platelet aggregation inhibitors are varied. When considering agents for the preferred drug list (PDL), agents with a broad range of indications, fewer adverse events, and the potential for the most positive impact on health outcomes should be considered.