

## Indiana Medicaid Therapeutics Committee Therapeutic Class Review Summary

### **Therapeutic class:**

Platelet Aggregation Inhibitors

### **Overview:**

The five 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 secondary 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. A significant drug-drug interaction between clopidogrel and two widely used statins has been published (2003). Atorvastatin and simvastatin may decrease the antiplatelet activity of clopidogrel.

The CAPRIE study concluded that clopidogrel is more effective than aspirin in the prevention of secondary stroke, MI or other cardiovascular death in high-risk patients. In the CURE study, the combination of aspirin and clopidogrel produced a favorable effect in the prevention of vascular death compared to aspirin alone. ESPS compared aspirin, dipyridamole, the combination of both, and placebo; the combination of aspirin and dipyridamole significantly reduced the rate of stroke or death in high-risk patients with history of stroke or transient ischemic attack. 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.

For secondary prevention of cardiovascular events, ADP antagonists, ticlopidine and clopidogrel were shown to be beneficial in many clinical trials. The American College of Cardiology has recommended acute and long-term antiplatelet treatment with aspirin, clopidogrel or the combination of the two agents for patients with acute coronary syndromes or myocardial infarction. In stroke prevention, the combination of aspirin and dipyridamole (Agrenox®) as well as ADP antagonists demonstrated favorable outcomes in clinical trials. However, dipyridamole monotherapy has never been proven efficacious.

<b>Generic Name</b>	<b>Brand Name</b>	<b>Manufacturer</b>	<b>Generic Available</b>
Cilostazol	Pletal®	Various	Y
Clopidogrel	Plavix®	Bristol-Myers Squibb	Y
Dipyridamole	Persantine®	Boehringer Ingelheim	Y
Dipyridamole/aspirin	Aggrenox®	Boehringer Ingelheim	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.