CENTENE Corporation

MEDICAL NECESSITY GUIDELINE

DEPARTMENT: Pharmacy	**DOCUMENT NAME:** aspirin dipyridamole (Aggrenox®)
PAGE: 1 of 6	**REFERENCE NUMBER:** NH.PMN.20
EFFECTIVE DATE: 09/06	**REPLACES DOCUMENT:**
RETIRED:	**REVIEWED:** 02/14, 01/15, 12/16, 10/17
PRODUCT TYPE: Medicaid	**REVISED:** 02/10, 02/11, 02/12, 02/13, 02/14, 4/16

IMPORTANT REMINDER

This Clinical Policy has been developed by appropriately experienced and licensed health care professionals based on a thorough review and consideration of generally accepted standards of medical practice, peer-reviewed medical literature, government agency/program approval status, and other indicia of medical necessity.

The purpose of this Clinical Policy is to provide a guide to medical necessity. Benefit determinations should be based in all cases on the applicable contract provisions governing plan benefits ("Benefit Plan Contract") and applicable state and federal requirements, as well as applicable plan-level administrative policies and procedures. To the extent there are any conflicts between this Clinical Policy and the Benefit Plan Contract provisions, the Benefit Plan Contract provisions will control.

Clinical policies are intended to be reflective of current scientific research and clinical thinking. This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

Description: Aggrenox® is a combination capsule of two antiplatelet agents: aspirin in a 25mg immediate-release and extended release dipyridamole 200mg. Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells, and erythrocytes in vitro and in vivo; the inhibition occurs in a dose-dependent manner at therapeutic concentrations (0.5 to 1.9 mcg/mL). This inhibition results in an increase in local concentrations of adenosine that acts on the platelet A2-receptor, thereby stimulating platelet adenylate cyclase and increasing platelet cyclic-3′,5′-adenosine monophosphate (cAMP) levels. Via this mechanism, platelet aggregation is inhibited in response to various stimuli, such as platelet activation factor, collagen, and adenosine diphosphate (ADP). Dipyridamole inhibits phosphodiesterase (PDE) in various tissues. Though the

inhibition of cAMP-PDE is weak, therapeutic levels of dipyridamole inhibit cyclic-3′,5′-guanosine monophosphate-PDE (cGMP-PDE), thereby augmenting the increase in cGMP produced by endothelium-derived relaxing factor (now identified as nitric oxide)

Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclooxygenase and thus inhibits the generation of thromboxane A2, a powerful inducer of platelet aggregation and vasoconstriction.

Dipyridamole: Peak plasma levels (Cmax) of dipyridamole are achieved approximately 2 hours (range, 1 to 6 hours) after administration of a daily dose of dipyridamole 400 mg ER/aspirin (given as dipyridamole 200 mg ER/aspirin twice daily). The Cmax at steady state is approximately 1.98 mcg/mL (1.01 to 3.99 mcg/mL) and the steady-state trough concentration is approximately 0.53 mcg/mL (0.18 to 1.01 mcg/mL).

Aspirin: Peak plasma levels of aspirin are achieved approximately 0.63 hours (0.5 to 1 hour) after administration of a daily dose of dipyridamole ER/aspirin 50 mg (given as dipyridamole ER/aspirin 25 mg twice daily). The Cmax at steady state is approximately 319 ng/mL (175 to 463 ng/mL). Aspirin undergoes moderate hydrolysis to salicylic acid in the liver and the GI wall, with 50% to 75% of an administered dose reaching the systemic circulation as intact aspirin.

Renal Function Impairment – No changes were observed in the pharmacokinetics of dipyridamole or its glucuronide metabolite with creatinine clearances ranging from approximately 15 mL/min to greater than 100 mL/min if data were corrected for differences in age.

Population Uniqueness

Renal Dysfunction/Failure – Avoid aspirin in patients with severe renal failure (GFR less than 10 mL/min). No study has been conducted with dipyridamole ER/aspirin in patients with renal dysfunction.

Hepatic Function Impairment – In a study conducted with an IV formulation of dipyridamole, patients with mild to severe hepatic insufficiency showed no change in plasma concentrations of dipyridamole but showed an increase in the pharmacologically inactive monoglucuronide metabolite. Dipyridamole can be dosed without restriction as long as there is no evidence of hepatic failure. Avoid aspirin in patients with severe hepatic impairment

Elderly – Plasma concentrations (determined as AUC) of dipyridamole in healthy elderly subjects older than 65 years were approximately 40% higher than in subjects younger than 55 years receiving treatment with dipyridamole ER/aspirin.

Brand: Aspirin/Dipyridamole (Aggrenox®): 25mg of ASA and 200mg of extended release dipyridamole per capsule

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FDA Labeled Indications: To reduce the risk of stroke in patients who have had transient ischemia of the brain or complete ischemic stroke due to thrombosis.

Criteria for Approval:

A. Age ≥ 18 years
B. Diagnosed with recent stroke or TIA by neurology specialist or in consult with a neurologist or vascular specialist.
C. Patient is not a candidate for Plavix® therapy (e.g. side effects, intolerance, drug interactions etc.).
D. Request does not exceed 2 tablets per day

Approval:

Initial Approval: 12 months.
Continued Approval: 12 months.

Special Instructions

- Aggrenox® is not interchangeable with individual components of ASA and immediate-release dipyridamole.
- Aggrenox® has been shown to be more effective in reducing the risk of stroke over aspirin or extended-release dipyridamole alone, suggesting that the effects of dipyridamole and ASA are additive. However, according to the American Heart Association, ASA is still the first line therapy. Aggrenox® is contraindicated in patients allergic to ASA, NSAIDS, dipyridamole, or any of its components. ASA is contraindicated in patients with nasal polyps, bleeding disorders, and severe renal and hepatic insufficiency, and used with caution in patients with asthma.
- Aggrenox® should not be given to children or teenagers with viral infections due to the risk of Reye's syndrome.
- Dipyridamole: Pregnancy category B/Aspirin: Pregnancy category D. There are no well controlled studies of Aggrenox® in pregnant women.

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This drug should only be used if the potential benefit justifies the potential risk.

- Aggrenox® should be used with caution in patients with severe coronary artery disease or hypotension.
- Use caution in patient with a history of GI bleeds. Providers should watch for signs of ulceration and bleeding.

References:

1. American Heart Association. "Guidelines for the Primary Prevention of Stroke" Goldstein et al. *Stroke* 2011; 42: 517-584. http://stroke.ahajournals.org/content/42/2/517
2. Aggrenox [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; September 2012. Accessed January 2015

Revision Log	
Revision	**Date**
Added the following two criteria points under the "Criteria for Approval" section: * Patient is not a candidate for Plavix® therapy (e.g. patients requiring PPI therapy) *Aggrenox® will be used a monotherapy.	02/10
Updated reference section to reflect current literature search.	02/10
References updated.	02/11
References updated.	02/12
Deleted "or intolerance to" under criteria for approval (patients intolerant to aspirin cannot use Aggrenox because it is composed of aspirin)	02/13
References updated.	02/13
Indications updated based on current package insert.	02/14
Add section for "Unique Population use of Aggrenox".	02/14
References updated.	02/14

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Updated References. No other changes.	02/14
Updated References. No other changes	01/15
Removed failure of aspirin therapy (e.g. patients who have experienced TIAs or stroke on ASA therapy).	06/15
Added age and quantity limit per labeling; Removed criteria for mono-therapy use as this not specific and cannot be truly enforced; Added Request does not exceed 2 tablets per day.	4/16
Annual Review, No Changes	12/16
Annual Review, No Changes	10/17

POLICY AND PROCEDURE APPROVAL

Pharmacy & Therapeutics Committee: Approval on file

V.P., Pharmacy Operations: Approval on file

Sr. V.P., Chief Medical Officer: Approval on file

NOTE: The electronic approval is retained in Compliance 360.