DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Daniel T. Coleman, Ph.D.
Associate Director, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

RE: NDA # 20-884
Aggrenox® (aspirin/extended-release dipyridamole) Capsules
MACMIS ID # 12917

Dear Dr. Coleman:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a journal ad (AG-8951R) for Aggrenox® (aspirin/extended-release dipyridamole) Capsules submitted by Boehringer Ingelheim Pharmaceuticals, Inc. (Boehringer Ingelheim) under cover of Form FDA 2253 on September 19, 2004. The journal ad is false or misleading because it contains unsubstantiated superiority claims and fails to include pertinent information about risks associated with Aggrenox, and, therefore, misbrands the drug in violation of section 502(n) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. § 352(n), and FDA's implementing regulations, 21 CFR 202.1(e)(3)(i); (e)(5)(ii); (e)(6)(ii).

Background

According to the FDA-approved product labeling (PI), Aggrenox is an oral combination antiplatelet agent indicated "to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis."

The PI for Aggrenox contains several Contraindications, Warnings, Precautions, and Adverse Reactions, including Warnings regarding the consumption of alcohol, coagulation abnormalities, gastrointestinal (GI) side effects (including ulceration and bleeding), peptic ulcer disease, and pregnancy, as well as a Precaution regarding the risk of gastrointestinal bleeding and intracranial hemorrhage.

Unsubstantiated Superiority Claim

The journal ad claims that "Based on indirect comparisons, [Aggrenox] may be more effective than clopidogrel, 75 mg…" This claim, in the context of the other claims in the ad, suggests that Aggrenox is more effective than Plavix (clopidogrel). As the journal ad states, this claim is based on "indirect comparisons" (a review of studies directly comparing ticlopidine, clopidogrel, and dipyridamole/aspirin with aspirin alone). Drug comparisons that represent or suggest that a

drug is safer or more effective than another drug are misleading if the representation or suggestion has not been demonstrated by substantial evidence obtained from adequate and well-controlled head-to-head clinical trial(s). See 21 CFR 202.1(e)(6)(ii). The paper referenced in the ad as support for this claim is, in effect, a historically controlled trial that is inadequate to support a superiority claim. We are not aware of substantial evidence or substantial clinical experience demonstrating that Aggrenox is superior to Plavix.

Omission of Risk Information

The main part of the ad contains various safety and effectiveness claims for Aggrenox. The headline, "People With Prior Stroke Or TIA Have The Greatest Need For BIG Protection Against Stroke Recurrence" is followed by: "Aggrenox Prevents Twice As Many Strokes As Aspirin" and other efficacy claims regarding Aggrenox's ability to prevent strokes. The main part of the ad also includes a reference to the brief summary of prescribing information for Aggrenox on the adjacent page, and the following statement of risk information:

> "The most common adverse event with Aggrenox was headache (39.2% vs 32.9% for placebo), which was more frequent at the onset of therapy, but diminished over time. GI bleeding with Aggrenox was comparable to aspirin (4.1% vs 3.2%)."

The main part of the ad fails to include information on the major risks associated with Aggrenox, including information about the Warnings concerning alcohol consumption, coagulation abnormalities, peptic ulcer disease, and pregnancy. Additionally, the ad fails to disclose the Precaution from the PI concerning the risks of intracranial hemorrhage. Although some of these risks relate to aspirin, this does not diminish the need to reflect them in promotion of Aggrenox, which contains aspirin as well as dipyridamole. See 21 CFR 202.1(e)(3)(i) and (e)(5)(ii).

Conclusion and Requested Action

The journal ad contains unsubstantiated superiority claims and omits information on the risks associated with Aggrenox, and, therefore, misbrands the drug in violation of section 502(n) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. § 352(n), and FDA's implementing regulations, 21 CFR 202.1(e)(3)(i); (e)(5)(ii); (e)(6)(ii).

DDMAC requests that Boehringer Ingelheim immediately cease the dissemination of promotional materials for Aggrenox the same as or similar to those described above. Please submit a written response to this letter on or before April 05, 2005, describing your intent to comply with this request, listing all promotional materials for Aggrenox the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at (301) 594-6771. In all future correspondence regarding this matter, please refer to MACMIS # 12917 in addition to the NDA numbers. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Aggrenox comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Lance McLeroy, Pharm.D., M.S.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lance McLeroy

3/22/05 02:52:27 PM

PEOPLE WITH PRIOR STROKE OR TIA HAVE THE GREATEST NEED FOR

BIG PROTECTION AGAINST STROKE RECURRENCE

AGGRENOX® PREVENTS TWICE AS MANY STROKES AS ASPIRIN

When both Aggrenox and aspirin were compared vs placebo, aspirin prevented 44 strokes and Aggrenox prevented 93 strokes.

ACCORDING TO THE ACCP:

"[Aggrenox] is more effective than aspirin alone for the prevention of stroke..."[1]

"Based on indirect comparisons, [Aggrenox] may be more effective than clopidogrel, 75 mg..."[1]

— Sixth Consensus Conference on Antithrombotic Therapy, American College of Chest Physicians, 2001.

The most common adverse event with Aggrenox was headache (39.2% vs 32.9% for placebo), which was more frequent at the onset of therapy, but diminished over time.[2] GI bleeding with Aggrenox was comparable to aspirin (4.1% vs 3.2%).

Please see the Brief Summary of Prescribing Information on the following page.

References: 1. Albers GW, Amarenco P, Easton JD, et al. Antithrombotic and thrombolytic therapy for ischemic stroke. Sixth ACCP Consensus Conference on Antithrombotic Therapy. Chest. 2001;119(suppl 1):300S-320S. 2. Data on file, Boehringer Ingelheim Pharmaceuticals, Inc.

www.aggrenox.com and www.Stroke-TIA.org

Aggrenox®

(aspirin/extended-release dipyridamole)
25 mg/200 mg capsules

Big protection against stroke

Aggrenox®

(aspirin/extended-release dipyridamole)
25 mg/200 mg capsules

Rx
AGGRENOX #60
Sig: 1 cap B/D

Brief Summary of Prescribing Information
CONTRAINDICATIONS
AGGRENOX (aspirin/extended-release dipyridamole) is contraindicated in patients with hypersensitivity to dipyridamole, aspirin or any of the other product components.

Allergy: Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema or bronchospasm (asthma).

Reye's Syndrome: Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.

WARNINGS
Alcohol Warning: Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

Coagulation Abnormalities: Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited or acquired (liver disease or vitamin K deficiency) bleeding disorders.

Gastrointestinal (GI) Side Effects: GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

Peptic Ulcer Disease: Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation, and bleeding.

Pregnancy: AGGRENOX can cause fetal harm when administered to a pregnant woman. Maternal aspirin use during later stages of pregnancy may cause low birth weight, increased incidence for intracranial hemorrhage in premature infants, stillbirths and neonatal death. Because of the above and because of the known effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the fetal cardiovascular system (closure of the ductus arteriosus), AGGRENOX should be avoided in the third trimester of pregnancy.

Aspirin has been shown to be teratogenic in rats (spina bifida, exencephaly, microphthalmia and cleft palate) and rabbits (congested fetuses, agenesis of skull and upper jaw, generalized edema with malformation of the head, and diaphanous skin) at oral doses of 330 mg/kg/day and 110 mg/kg/day, respectively. These doses, which also resulted in a high resorption rate in rats (63% of implantations versus 5% in controls), are, on a mg/m² basis, about 96 and 44 times, respectively, the dose of aspirin contained in the maximum recommended daily human dose of AGGRENOX. Reproduction studies with dipyridamole have been performed in mice, rabbits and rats at oral doses of up to 125 mg/kg, 40 mg/kg and 1000 mg/kg, respectively about 1½, 2 and 25 times the maximum recommended daily human oral dose, respectively, on a mg/m² basis) and have revealed no evidence of harm to the fetus due to dipyridamole. When 330 mg aspirin/kg/day was combined with 75 mg dipyridamole/kg/day in the rat, the resorption rate approached 100%, indicating potentiation of aspirin-related fetal toxicity. There are no adequate and well-controlled studies in pregnant women. If AGGRENOX is used during pregnancy, or if the patient becomes pregnant while taking AGGRENOX, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS
General
AGGRENOX® (aspirin/extended-release dipyridamole) is not interchangeable with the individual components of aspirin and Persantine® Tablets.

Coronary Artery Disease: Dipyridamole has a vasodilatory effect and should be used with caution in patients with severe coronary artery disease (e.g., unstable angina or recently sustained myocardial infarction). Chest pain may be aggravated in patients with underlying coronary artery disease who are receiving dipyridamole.

For stroke or TIA patients for whom aspirin is indicated to prevent recurrent myocardial infarction (MI) or angina pectoris, the aspirin in this product may not provide adequate treatment for the cardiac indications.

Hepatic Insufficiency: Elevations of hepatic enzymes and hepatic failure have been reported in association with dipyridamole administration.

Hypotension: Dipyridamole should be used with caution in patients with hypotension since it can produce peripheral vasodilation.

Renal Failure: Avoid aspirin in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute).

Risk of Bleeding: In ESPS2 the incidence of gastrointestinal bleeding was 68 patients (4.1%) in the AGGRENOX group, 36 patients (2.2%) in the extended-release dipyridamole group, 52 patients (3.2%) in the aspirin group, and 34 patients (2.1%) in the placebo groups.

The incidence of intracranial hemorrhage was 9 patients (0.6%) in the AGGRENOX group, 6 patients (0.5%) in the extended release dipyridamole group, 6 patients (0.4%) in the aspirin group and 7 patients (0.4%) in the placebo groups.

Laboratory Tests
Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria and prolonged bleeding time.

Dipyridamole has been associated with elevated hepatic enzymes.

Drug Interactions
No pharmacokinetic drug-drug interaction studies were conducted with the AGGRENOX formulation. The following information was obtained from the literature.

Adenosine: Dipyridamole has been reported to increase the plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dosage may be necessary.

Angiotensin Converting Enzyme (ACE) Inhibitors: Due to the indirect effect of aspirin on the renin-angiotensin conversion pathway, the hypovolaemic and hypotensive effects of ACE inhibitors may be diminished by concomitant administration of aspirin.

Acetazolamide: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.

Anticoagulant Therapy (heparin and warfarin): Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and effects on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.

Anticonvulsants: Salicylic acid can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta Blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.

Cholinesterase Inhibitors: Dipyridamole may counteract the anticholinesterase effect of cholinesterase inhibitors, thereby potentially aggravating myasthenia gravis.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.

Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): The concurrent use of aspirin with other NSAIDs may increase bleeding or lead to decreased renal function.

Oral Hypoglycemics: Moderate doses of aspirin may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia.

Uricosuric Agents (probenecid and sulfinpyrazone): Salicylates antagonize the uricosuric action of uricosuric agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In studies in which dipyridamole was administered in the feed to mice (up to 111 weeks in males and females) and rats (up to 128 weeks in males and up to 142 weeks in females), there was no evidence of drug-related carcinogenesis. The highest dose administered in these studies (75 mg/kg/day) was, on a mg/m² basis, about equivalent to the maximum recommended daily human oral dose (MRHD) in mice and about twice the MRHD in rats.

Combinations of dipyridamole and aspirin (1:5 ratio) tested negative in the Ames test, *in vivo* chromosome aberration tests (in mice and hamsters), oral micronucleus tests (in mice and hamsters) and oral dominant lethal test (in mice). Aspirin, alone, induced chromosome aberrations in cultured human fibroblasts. Mutagenicity tests of dipyridamole alone with bacterial and mammalian cell systems were negative.

Combinations of dipyridamole and aspirin have not been evaluated for effects on fertility and reproductive performance. There was no evidence of impaired fertility when dipyridamole was administered to male and female rats at oral doses up to 500 mg/kg/day (about 12 times the MRHD on a mg/m² basis). A significant reduction in number of corpora lutea with consequent reduction in implantations and live fetuses was, however, observed at 1250 mg/kg (more than 30 times the MRHD on a mg/m² basis). Aspirin inhibits ovulation in rats.

Pregnancy
Teratogenic Effects: PREGNANCY CATEGORY D. See **WARNINGS**

Labor and Delivery
Aspirin can result in excessive blood loss at delivery as well as prolonged gestation and prolonged labor. Because of these effects on the mother and because of adverse fetal effects seen with aspirin during the later stages of pregnancy (see **WARNINGS, Pregnancy** subsection), AGGRENOX should be avoided in the third trimester of pregnancy and during labor and delivery.

Nursing Mothers
Both dipyridamole and aspirin are excreted in human milk. Caution should be exercised when AGGRENOX is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of AGGRENOX in pediatric patients have not been studied. Due to the aspirin component, use of this product in the pediatric population is not recommended (See **CONTRAINDICATIONS**).

ADVERSE REACTIONS
A 24-month, multicenter, double-blind, randomized study (ESPS2) was conducted to compare the efficacy and safety of AGGRENOX (aspirin/extended-release dipyridamole) with placebo, extended-release dipyridamole alone and aspirin alone. The study was conducted in a total of 6602 male and female patients who had experienced a previous ischemic stroke or transient ischemia of the brain within three months prior to randomization.

Table 2 presents the incidence of adverse events that occurred in 1% or more of patients treated with AGGRENOX where the incidence was also greater than in those patients treated with placebo. There is no clear benefit of the dipyridamole/aspirin combination over aspirin with respect to safety.

Table 1: Incidence of Adverse Events in ESPS2*

	Individual Treatment Group			
Body System/Preferred Term	**AGGRENOX**	**ER-DP Alone**	**ASA Alone**	**Placebo**
Total Number of Patients	1650	1654	1649	1649
Total Number (%) of Patients With at Least One On-Treatment Adverse Event	1319 (79.9%)	1305 (78.9%)	1323 (80.2%)	1304 (79.1%)
Central & Peripheral Nervous System Disorders				
Headache	647 (39.2%)	634 (38.3%)	556 (33.8%)	543 (32.9%)
Convulsions	28 (1.7%)	15 (0.9%)	28 (1.7%)	26 (1.6%)

Table 1: Incidence of Adverse Events in ESPS2*

	Individual Treatment Group			
Body System/Preferred Term	**AGGRENOX**	**ER-DP Alone**	**ASA Alone**	**Placebo**
Gastro-Intestinal System Disorders				
Dyspepsia	303 (18.4%)	288 (17.4%)	299 (18.1%)	275 (16.7%)
Abdominal Pain	289 (17.5%)	255 (15.4%)	252 (15.3%)	239 (14.5%)
Nausea	254 (15.0%)	254 (15.4%)	210 (12.7%)	232 (14.1%)
Diarrhea	210 (12.7%)	207 (15.5%)	112 (6.8%)	161 (9.8%)
Vomiting	136 (8.4%)	129 (7.8%)	101 (6.1%)	118 (7.2%)
Hemorrhage Rectum	26 (1.6%)	22 (1.3%)	18 (1.6%)	13 (0.8%)
Melena	31 (1.9%)	18 (0.6%)	20 (1.2%)	13 (0.8%)
Hemorrhoids	16 (1.0%)	13 (0.8%)	10 (0.6%)	10 (0.6%)
GI Hemorrhage	20 (1.2%)	5 (0.3%)	15 (0.9%)	7 (0.4%)
Body as a Whole - General Disorders				
Pain	105 (6.4%)	88 (5.3%)	103 (6.2%)	99 (6.0%)
Fatigue	95 (5.8%)	93 (5.6%)	97 (5.9%)	90 (5.5%)
Back Pain	76 (4.6%)	77 (4.7%)	74 (4.5%)	65 (3.9%)
Accidental Injury	42 (2.5%)	24 (1.5%)	51 (3.1%)	37 (2.2%)
Malaise	27 (1.6%)	23 (1.4%)	26 (1.6%)	22 (1.3%)
Asthenia	29 (1.8%)	19 (1.1%)	17 (1.0%)	18 (1.1%)
Syncope	17 (1.0%)	13 (0.8%)	16 (1.0%)	8 (0.5%)
Psychiatric Disorders				
Amnesia	39 (2.4%)	40 (2.4%)	57 (3.5%)	34 (2.1%)
Confusion	18 (1.1%)	9 (0.5%)	22 (1.3%)	15 (0.9%)
Anxiety	19 (1.2%)	17 (1.0%)	10 (0.6%)	15 (0.9%)
Somnolence	20 (1.2%)	13 (0.8%)	16 (1.1%)	9 (0.5%)
Musculoskeletal System Disorders				
Arthralgia	91 (5.5%)	75 (4.5%)	91 (5.5%)	76 (4.6%)
Arthritis	34 (2.1%)	25 (1.5%)	17 (1.0%)	19 (1.2%)
Arthrosis	18 (1.1%)	22 (1.3%)	13 (0.8%)	14 (0.8%)
Myalgia	20 (1.2%)	16 (1.0%)	11 (0.7%)	11 (0.7%)
Respiratory System Disorders				
Coughing	25 (1.5%)	18 (1.1%)	32 (1.9%)	21 (1.3%)
Upper Respiratory Tract Infection	16 (1.0%)	9 (0.5%)	19 (1.0%)	14 (0.8%)
Cardiovascular Disorders, General				
Cardiac Failure	26 (1.6%)	17 (1.0%)	30 (1.8%)	25 (1.5%)
Platelet, Bleeding & Clotting Disorders				
Hemorrhage NOS	52 (3.2%)	24 (1.5%)	46 (2.8%)	24 (1.5%)
Epistaxis	39 (2.4%)	16 (1.0%)	45 (2.7%)	25 (1.5%)
Purpura	23 (1.4%)	8 (0.5%)	9 (0.5%)	7 (0.4%)
Neoplasm				
Neoplasm NOS	28 (1.7%)	16 (1.0%)	23 (1.4%)	20 (1.2%)
Red Blood Cell Disorders				
Anemia	27 (1.6%)	16 (1.0%)	19 (1.2%)	9 (0.5%)

*Reported by ≥1% of patients during AGGRENOX treatment where the incidence was greater than in those treated with placebo.
Note: ER-DP = extended-release dipyridamole 200 mg; ASA = aspirin 25 mg. The dosage regimen for all treatment groups is b.i.d.
NOS = not otherwise specified.

Discontinuation due to adverse events in ESPS2 was 25% for AGGRENOX, 25% for extended-release dipyridamole, 19% for aspirin, and 21% for placebo (refer to Table 2).

Table 2: Incidence of Adverse Events That Led to the Discontinuation of Treatment: Adverse Events With an Incidence of ≥1% in the AGGRENOX Group

	Treatment Groups			
	AGGRENOX	**ER-DP**	**ASA**	**Placebo**
Total Number of Patients	1650	1654	1649	1649
Patients With at Least One Adverse Event That Led to Treatment Discontinuation	417 (25%)	419 (25%)	318 (19%)	352 (21%)
Headache	165 (10%)	168 (10%)	57 (3%)	69 (4%)
Dizziness	65 (3%)	97 (6%)	69 (4%)	68 (4%)
Nausea	91 (6%)	95 (6%)	51 (3%)	53 (3%)
Abdominal Pain	74 (4%)	64 (4%)	56 (3%)	52 (3%)
Dyspepsia	59 (4%)	61 (4%)	49 (3%)	46 (3%)
Vomiting	53 (3%)	52 (3%)	38 (2%)	24 (1%)
Diarrhea	35 (2%)	41 (2%)	9 (<1%)	16 (<1%)
Stroke	39 (2%)	48 (3%)	57 (3%)	73 (4%)
Transient Ischemic Attack	35 (2%)	40 (2%)	26 (2%)	46 (3%)
Angina Pectoris	23 (1%)	20 (1%)	16 (<1%)	29 (2%)

Note: ER-DP = extended-release dipyridamole 200 mg; ASA = aspirin 25 mg. The dosage regimen for all treatment groups is b.i.d.

Other adverse events:
Adverse reactions that occurred in less than 1% of patients treated with AGGRENOX in the ESPS2 study and that were medically judged to be possibly related to either dipyridamole or aspirin are listed below (See **WARNINGS**). *Body as a Whole:* Allergic reaction, fever. *Cardiovascular:* Hypotension. *Central Nervous System:* Coma, dizziness, paresthesia, cerebral hemorrhage, intracranial hemorrhage, subarachnoid hemorrhage. *Gastrointestinal:* Gastritis, ulceration and perforation. *Hearing & Vestibular Disorders:* Tinnitus, and deafness. Patients with high frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism. *Heart Rate and Rhythm Disorders:* Tachycardia, palpitation, arrhythmia, supraventricular tachycardia. *Liver and Biliary System Disorders:* Cholelithiasis, jaundice, hepatic function abnormal. *Metabolic & Nutritional Disorders:* Hyperglycemia, thirst. *Platelet, Bleeding and Clotting Disorders:* Hematuria, gingival bleeding. *Psychiatric Disorders:* Agitation. *Reproductive:* Uterine hemorrhage. *Respiratory:* Hyperpnea, asthma, bronchospasm, hemoptysis, pulmonary edema. *Special Senses Other Disorders:* Taste loss. *Skin and Appendages Disorders:* Pruritus, urticaria. *Urogenital:* Renal insufficiency and failure, hematuria. *Vascular (Extracardiac) Disorders:* Flushing.

The following is a list of additional adverse reactions that have been reported either in the literature or are from postmarketing spontaneous reports for either dipyridamole or aspirin. *Body as a Whole:* Hypothermia, chest pain. *Cardiovascular:* Angina pectoris. *Central Nervous System:* Cerebral edema. *Fluid and Electrolyte:* Hyperkalemia, metabolic acidosis, respiratory alkalosis, hypokalemia. *Gastrointestinal:* Pancreatitis, Reye's syndrome, hemalemesis. *Hearing and Vestibular Disorders:* Hearing loss. *Hypersensitivity:* Acute anaphylaxis, laryngeal edema. *Liver and Biliary System Disorders:* Hepatitis, hepatic failure. *Musculoskeletal:* Rhabdomyolysis. *Metabolic & Nutritional Disorders:* Hypoglycemia, dehydration. *Platelet, Bleeding and Clotting Disorders:* Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia. *Reproductive:* Prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding. *Respiratory:* tachypnea, dyspnea. *Skin and Appendages Disorders:* Rash, alopecia, angioedema, Stevens-Johnson syndrome. *Urogenital:* Interstitial nephritis, papillary necrosis, proteinuria. *Vascular (Extracardiac Disorders)* Allergic vasculitis.

The following is a list of additional adverse events that have been reported either in the literature or are from postmarketing spontaneous reports for either dipyridamole or aspirin. The causal relationship of these adverse events has not been established: anorexia, aplastic anemia, pancytopenia, thrombocytosis.

Laboratory Changes
Over the course of the 24-month study (ESPS2), patients treated with AGGRENOX showed a decline (mean change from baseline) in hemoglobin of 0.25 g/dL, hematocrit of 0.75%, and erythrocyte count of 0.13x10⁶/mm³.

OVERDOSAGE
Because of the dose ratio of dipyridamole to aspirin, overdosage of AGGRENOX (aspirin/extended-release dipyridamole) is likely to be dominated by signs and symptoms of dipyridamole overdose. In case of real or suspected overdose, seek medical attention or contact a Poison Control Center immediately. Careful medical management is essential.

Dipyridamole
Based upon the known hemodynamic effects of dipyridamole, symptoms such as warm feeling, flushes, sweating, restlessness, feeling of weakness and dizziness may occur. A drop in blood pressure and tachycardia might also be observed.

Symptomatic treatment is recommended, possibly including a vasopressor drug. Gastric lavage should be considered. Administration of xanthine derivatives (e.g. aminophylline) may reverse the hemodynamic effects of dipyridamole overdose. Since dipyridamole is highly protein bound, dialysis is not likely to be of benefit.

Aspirin
Salicylate toxicity may result from acute ingestion (overdose) or chronic intoxication. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approaching 200 µg/mL. Plasma concentrations of aspirin above 300 µg/mL are clearly toxic. Severe toxic effects are associated with levels above 400 µg/mL. A single lethal dose of aspirin in adults is not known with certainty but death may be expected at 30 g.

Treatment consists primarily of supporting vital functions, increasing salicylate elimination, and correcting the acid-base disturbance. Gastric emptying and/or lavage are recommended as soon as possible after ingestion, even if the patient has vomited spontaneously. After lavage and/or emesis, administration of activated charcoal, as a slurry, is beneficial, if less than 3 hours have passed since ingestion. Charcoal absorption should not be employed prior to emesis and lavage.

Severity of aspirin intoxication is determined by measuring the blood salicylate level. Acid-base status should be closely followed with serial blood gas and serum pH measurements. Fluid and electrolyte balance should also be maintained.

In severe cases, hyperthermia and hypovolemia are the major immediate threats to life. Children should be sponged with tepid water. Replacement fluid should be administered intravenously and augmented with correction of acidosis. Plasma electrolytes and pH should be monitored to promote alkaline diuresis of salicylate if renal function is normal. Infusion of glucose may be required to control hypoglycemia.

Hemodialysis and peritoneal dialysis can be performed to reduce the body drug content. In patients with renal insufficiency or in cases of life-threatening intoxication, dialysis is usually required. Exchange transfusion may be indicated in infants and young children.

AGGRENOX is not interchangeable with the individual components of aspirin and Persantine® Tablets.

Rx only
42633/USI/4

Marketed by: Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT 06877 USA
Manufactured by: Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany
(Licensed from: Boehringer Ingelheim International GmbH Patent No. 6,015,577 Revised: (7/02/03) AG-BS (07/03)

Boehringer Ingelheim

AG-8951R