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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Aggrenox Capsules safely and effectively. See full prescribing information for Aggrenox Capsules.

AGGRENOX® (aspirin/extended-release dipyridamole) Capsules
Initial U.S. Approval: 1999

----------INDICATIONS AND USAGE----------

- AGGRENOX is a 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 (1)

----------DOSAGE AND ADMINISTRATION----------

- One capsule twice daily (morning and evening) with or without food (2)
- In case of intolerable headaches during initial treatment, switch to one capsule at bedtime and low-dose aspirin in the morning; resume BID dosing within one week (2)
- Do not chew capsule (2)
- **Not interchangeable with the individual components of aspirin and dipyridamole tablets** (2)
- Dispense in this unit-of-use container (16)

----------DOSAGE FORMS AND STRENGTHS----------

- Capsule: 25 mg aspirin/200 mg extended-release dipyridamole (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to any product ingredients (4.1)
- Patients with known allergy to NSAIDs (4.2)
- Patients with the syndrome of asthma, rhinitis, and nasal polyps (4.2)

----------WARNINGS AND PRECAUTIONS----------

- The risk of GI bleeding is increased, especially in patients who are heavy alcohol users, have a history of peptic ulcer, or have coagulation abnormalities due to liver disease or vitamin K deficiency (5.1)
- As with other antiplatelets, there is a risk of intracranial hemorrhage (5.1).
- Avoid use in patients with severe hepatic or renal insufficiency (5.2, 5.3)
- Can cause fetal harm when administered to a pregnant woman, especially in the third trimester (5.4)

----------ADVERSE REACTIONS----------

- The most frequently reported adverse reactions (>10% and greater than placebo) were headache, dyspepsia, abdominal pain, nausea, and diarrhea (6)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Co-administration with anti-coagulants or NSAIDS can increase risk of bleeding (7.4, 7.10)
- Decreased renal function can occur with co-administration with NSAIDS (7.10)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy Category D (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2009

FULL PRESCRIBING INFORMATION

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AGGRENOX is indicated to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis.

2 DOSAGE AND ADMINISTRATION

AGGRENOX is not interchangeable with the individual components of aspirin and dipyridamole tablets.

The recommended dose of AGGRENOX is one capsule given orally twice daily, one in the morning and one in the evening. Swallow capsules whole without chewing. AGGRENOX can be administered with or without food.

2.1 Alternative Regimen in Case of Intolerable Headaches

In the event of intolerable headaches during initial treatment, switch to one capsule at bedtime and low-dose aspirin in the morning. Because there are no outcome data with this regimen and headaches become less of a problem as treatment continues, patients should return to the usual regimen as soon as possible, usually within one week.

3 DOSAGE FORMS AND STRENGTHS

25 mg/200 mg capsules with a red cap and an ivory-colored body, containing yellow extended-release pellets incorporating dipyridamole and a round white tablet incorporating immediate-release aspirin. The capsule body is imprinted in red with the Boehringer Ingelheim logo and with "01A".

4 CONTRAINDICATIONS

4.1 Hypersensitivity

AGGRENOX is contraindicated in patients with known hypersensitivity to any of the product components.

4.2 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.

4.3 Reye Syndrome

Do not use aspirin in children or teenagers with viral infections because of the risk of Reye syndrome.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Bleeding

Intracranial Hemorrhage

In ESPS2 the incidence of intracranial hemorrhage was 0.6% in the AGGRENOX group, 0.5% in the extended-release dipyridamole (ER-DP) group, 0.4% in the aspirin (ASA) group and 0.4% in the placebo groups *[see Warnings and Precautions (5.5)]*.

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 *[see Drug Interactions (7.4)]*.

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. Inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

In ESPS2 the incidence of gastrointestinal bleeding was 4.1% in the AGGRENOX group, 2.2% in the extended-release dipyridamole group, 3.2% in the aspirin group, and 2.1% in the placebo groups.

Peptic Ulcer Disease

Avoid using aspirin in patients with a history of active peptic ulcer disease, which can cause gastric mucosal irritation and bleeding.

Alcohol Warning

Because AGGRENOX contains aspirin, counsel patients who consume three or more alcoholic drinks every day about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

5.2 Renal Failure

Avoid aspirin in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute) *[see Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

5.3 Hepatic Insufficiency

Elevations of hepatic enzymes and hepatic failure have been reported in association with dipyridamole administration *[see Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

5.4 Pregnancy

Because AGGRENOX contains aspirin, 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), avoid AGGRENOX in the third trimester of pregnancy *[see Use in Specific Populations (8.1)]*.

Aspirin has been shown to be teratogenic in rats (spina bifida, exencephaly, microphthalmia and coelosomia) 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/m^2 basis, about 66 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/m^2 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

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the rat, the resorption rate approached 100%, indicating potentiation of aspirin-related fetal toxicity. There are no adequate and well-controlled studies of the use of AGGRENOX in pregnant women. If AGGRENOX is used during pregnancy, or if the patient becomes pregnant while taking AGGRENOX, inform the patient of the potential hazard to the fetus.

5.5 Coronary Artery Disease

Dipyridamole has a vasodilatory effect. Chest pain may be precipitated or 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.

5.6 Hypotension

Dipyridamole produces peripheral vasodilation, which can exacerbate pre-existing hypotension.

5.7 General

AGGRENOX capsules are not interchangeable with the individual components of aspirin and dipyridamole tablets.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labeling:

- Hypersensitivity *[see Contraindications (4.1)]*
- Allergy [*see Contraindications (4.2)]*
- Risk of Bleeding *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The efficacy and safety of AGGRENOX was established in the European Stroke Prevention Study-2 (ESPS2). ESPS2 was a double-blind, placebo controlled study that evaluated 6602 patients over the age of 18 years who had a previous ischemic stroke or transient ischemic attack within ninety days prior to entry. Patients were randomized to either AGGRENOX, aspirin, ER-DP, or placebo [*see Clinical Studies (14)*]; primary endpoints included stroke (fatal or nonfatal) and death from all causes.

This 24-month, multicenter, double-blind, randomized study (ESPS2) was conducted to compare the efficacy and safety of AGGRENOX 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 1 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							
	AGGRENOX		ER-DP Alone		ASA Alone		Placebo	
Body System/Preferred Term								
	1650		1654		1649		1649	
Total Number of Patients								
Total Number (%) of Patients With at Least One On-Treatment Adverse Event								
	1319	(80%)	1305	(79%)	1323	(80%)	1304	(79%)
Central and Peripheral Nervous System Disorders								
Headache	647	(39%)	634	(38%)	558	(34%)	543	(33%)
Convulsions	28	(2%)	15	(1%)	28	(2%)	26	(2%)
Gastrointestinal System Disorders								
Dyspepsia	303	(18%)	288	(17%)	299	(18%)	275	(17%)
Abdominal Pain	289	(18%)	255	(15%)	262	(16%)	239	(14%)
Nausea	264	(16%)	254	(15%)	210	(13%)	232	(14%)
Diarrhea	210	(13%)	257	(16%)	112	(7%)	161	(10%)
Vomiting	138	(8%)	129	(8%)	101	(6%)	118	(7%)
Hemorrhage Rectum	26	(2%)	22	(1%)	16	(1%)	13	(1%)
Melena	31	(2%)	10	(1%)	20	(1%)	13	(1%)
Hemorrhoids	16	(1%)	13	(1%)	10	(1%)	10	(1%)
GI Hemorrhage	20	(1%)	5	(0%)	15	(1%)	7	(0%)
Body as a Whole - General Disorders								

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Pain	105	(6%)	88	(5%)	103	(6%)	99	(6%)
Fatigue	95	(6%)	93	(6%)	97	(6%)	90	(5%)
Back Pain	76	(5%)	77	(5%)	74	(4%)	65	(4%)
Accidental Injury	42	(3%)	24	(1%)	51	(3%)	37	(2%)
Malaise	27	(2%)	23	(1%)	26	(2%)	22	(1%)
Asthenia	29	(2%)	19	(1%)	17	(1%)	18	(1%)
Syncope	17	(1%)	13	(1%)	16	(1%)	8	(0%)
Psychiatric Disorders								
Amnesia	39	(2%)	40	(2%)	57	(3%)	34	(2%)
Confusion	18	(1%)	9	(1%)	22	(1%)	15	(1%)
Anorexia	19	(1%)	17	(1%)	10	(1%)	15	(1%)
Somnolence	20	(1%)	13	(1%)	18	(1%)	9	(1%)
Musculoskeletal System Disorders								
Arthralgia	91	(6%)	75	(5%)	91	(6%)	76	(5%)
Arthritis	34	(2%)	25	(2%)	17	(1%)	19	(1%)
Arthrosis	18	(1%)	22	(1%)	13	(1%)	14	(1%)
Myalgia	20	(1%)	16	(1%)	11	(1%)	11	(1%)
Respiratory System Disorders								
Coughing	25	(2%)	18	(1%)	32	(2%)	21	(1%)
Upper Respiratory Tract Infection	16	(1%)	9	(1%)	16	(1%)	14	(1%)
Cardiovascular Disorders, General								
Cardiac Failure	26	(2%)	17	(1%)	30	(2%)	25	(2%)
Platelet, Bleeding and Clotting Disorders								
Hemorrhage NOS	52	(3%)	24	(1%)	46	(3%)	24	(1%)
Epistaxis	39	(2%)	16	(1%)	45	(3%)	25	(2%)
Purpura	23	(1%)	8	(0%)	9	(1%)	7	(0%)
Neoplasm								
Neoplasm NOS	28	(2%)	16	(1%)	23	(1%)	20	(1%)
Red Blood Cell Disorders								
Anemia	27	(2%)	16	(1%)	19	(1%)	9	(1%)

* 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 BID
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

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	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%)	166	(10%)	57	(3%)	69	(4%)
Dizziness	85	(5%)	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%)	28	(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%)	48	(3%)
Angina Pectoris	23	(1%)	20	(1%)	16	(<1%)	26	(2%)

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

Headache was most notable in the first month of treatment.

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.

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 and 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 and Nutritional Disorders: Hyperglycemia, thirst

Platelet, Bleeding and Clotting Disorders: Hematoma, 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

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 $0.13 \times 10^6/mm^3$.

6.2 Post-Marketing Experience
The following is a list of additional adverse reactions that have been reported either in the literature or are from post-marketing spontaneous reports for either dipyridamole or aspirin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to AGGRENOX.

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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 syndrome, hematemesis

Hearing and Vestibular Disorders: Hearing loss

Immune System Disorders: Hypersensitivity, acute anaphylaxis, laryngeal edema

Liver and Biliary System Disorders: Hepatitis, hepatic failure

Musculoskeletal: Rhabdomyolysis

Metabolic and 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, skin hemorrhages such as bruising, ecchymosis, and hematoma

Urogenital: Interstitial nephritis, papillary necrosis, proteinuria

Vascular (Extracardiac Disorders): Allergic vasculitis

Other adverse events: anorexia, aplastic anemia, migraine, pancytopenia, thrombocytosis.

7 DRUG INTERACTIONS

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

7.1 Adenosine

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

7.2 Angiotensin Converting Enzyme (ACE) Inhibitors

Due to the indirect effect of aspirin on the renin-angiotensin conversion pathway, the hyponatremic and hypotensive effects of ACE inhibitors may be diminished by concomitant administration of aspirin.

7.3 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.

7.4 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.

7.5 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.

7.6 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.

7.7 Cholinesterase Inhibitors

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

7.8 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.

7.9 Methotrexate

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

7.10 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

The concurrent use of aspirin with other NSAIDs may increase bleeding or lead to decreased renal function.

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

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

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic Effects, Pregnancy Category D. [see Warnings and Precautions (5.4)].

8.2 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 and Precautions (5.4)]*, avoid AGGRENOX in the third trimester of pregnancy and during labor and delivery.

8.3 Nursing Mothers
Both dipyridamole and aspirin are excreted in human milk. Exercise caution when AGGRENOX capsules are administered to a nursing woman.

8.4 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 (4.3)]*.

8.5 Geriatric Use
Of the total number of subjects in ESPS2, 61 percent were 65 and over, while 27 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.3)]*.

8.6 Patients with Severe Hepatic or Severe Renal Dysfunction
AGGRENOX has not been studied in patients with hepatic or renal impairment. Avoid using aspirin containing products, such as AGGRENOX in patients with severe hepatic or severe renal (glomerular filtration rate < 10 mL/min) dysfunction *[see Warnings and Precautions (5.2, 5.3) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE
Because of the dose ratio of dipyridamole to aspirin, overdosage of AGGRENOX 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.

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.

Salicylate toxicity may result from acute ingestion (overdose) or chronic intoxication. Severity of aspirin intoxication is determined by measuring the blood salicylate level. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approaching 200 µg/mL. In severe cases, hyperthermia and hypovolemia are the major immediate threats to life. 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 30g.

Treatment of overdose consists primarily of supporting vital functions, increasing drug elimination, and correcting acid-base disturbances. Consider gastric emptying and/or lavage 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 may be beneficial if less than 3 hours have passed since ingestion. Charcoal absorption should not be employed prior to emesis and lavage. Follow acid-base status closely with serial blood gas and serum pH measurements. Maintain fluid and electrolyte balance. Administer replacement fluid intravenously and augment with correction of acidosis. Treatment may require the use of a vasopressor. Infusion of glucose may be required to control hypoglycemia.

Administration of xanthine derivatives (e.g., aminophylline) may reverse the hemodynamic effects of dipyridamole overdose. Plasma electrolytes and pH should be monitored serially to promote alkaline diuresis of salicylate if renal function is normal. In patients with renal insufficiency or in cases of life-threatening intoxication, dialysis is usually required to treat salicylic overdose, however since dipyridamole is highly protein bound, dialysis is not likely to remove dipyridamole. Exchange transfusion may be indicated in infants and young children.

11 DESCRIPTION
AGGRENOX is a combination antiplatelet agent intended for oral administration. Each hard gelatin capsule contains 200 mg dipyridamole in an extended-release form and 25 mg aspirin, as an immediate-release sugar-coated tablet. In addition, each capsule contains the following inactive ingredients: acacia, aluminum stearate, colloidal silicon dioxide, corn starch, dimethicone, hypromellose, hypromellose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide and triacetin.

Each capsule shell contains gelatin, red iron oxide and yellow iron oxide, titanium dioxide and water.

Dipyridamole
Dipyridamole is an antiplatelet agent chemically described as 2,2',2",2"'-[(4,8-Dipiperidinopyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinitrilo]-tetraethanol. It has the following structural formula:

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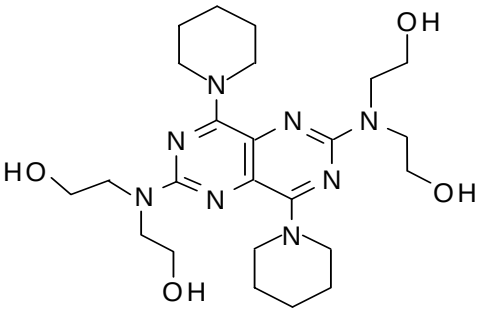
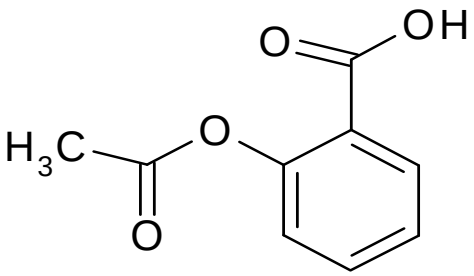


$C_{24}H_{40}N_8O_4$ Mol. Wt. 504.63

Dipyridamole is an odorless yellow crystalline substance, having a bitter taste. It is soluble in dilute acids, methanol and chloroform, and is practically insoluble in water.

Aspirin
The antiplatelet agent aspirin (acetylsalicylic acid) is chemically known as benzoic acid, 2- (acetyloxy)-, and has the following structural formula:



$C_9H_8O_4$ Mol. Wt. 180.16

Aspirin is an odorless white needle-like crystalline or powdery substance. When exposed to moisture, aspirin hydrolyzes into salicylic and acetic acids, and gives off a vinegary odor. It is highly lipid soluble and slightly soluble in water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The antithrombotic action of AGGRENOX is the result of the additive antiplatelet effects of dipyridamole and aspirin.

Dipyridamole
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 (0.5–1.9 µg/mL). This inhibition results in an increase in local concentrations of adenosine which acts on the platelet A_2-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 activating factor (PAF), collagen and adenosine diphosphate (ADP).

Dipyridamole inhibits phosphodiesterase (PDE) in various tissues. While 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 EDRF (endothelium-derived relaxing factor, now identified as nitric oxide).

Aspirin
Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclooxygenase and thus inhibits the generation of thromboxane A_2, a powerful inducer of platelet aggregation and vasoconstriction.

12.2 Pharmacodynamics

The effect of either agent on the other's inhibition of platelet reactivity has not been evaluated.

12.3 Pharmacokinetics

There are no significant interactions between aspirin and dipyridamole. The kinetics of the components are unchanged by their co-administration as AGGRENOX.

Dipyridamole
Absorption
Peak plasma levels of dipyridamole are achieved 2 hours (range 1–6 hours) after administration of a daily dose of 400 mg AGGRENOX (given as 200 mg BID). The peak plasma concentration at steady-state is 1.98 µg/mL (1.01–3.99 µg/mL) and the steady-state trough concentration is 0.53 µg/mL (0.18–1.01 µg/mL).

Effect of Food
When AGGRENOX capsules were taken with a high fat meal, dipyridamole peak plasma levels (C_{max}) and total absorption (AUC) were decreased at steady-state by 20-30% compared to fasting. Due to the similar degree of inhibition of adenosine uptake at these plasma concentrations, this food effect is not considered clinically relevant.

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Distribution
Dipyridamole is highly lipophilic (log P=3.71, pH=7); however, it has been shown that the drug does not cross the blood-brain barrier to any significant extent in animals. The steady-state volume of distribution of dipyridamole is about 92 L. Approximately 99% of dipyridamole is bound to plasma proteins, predominantly to alpha 1-acid glycoprotein and albumin.

Metabolism and Elimination
Dipyridamole is metabolized in the liver, primarily by conjugation with glucuronic acid, of which monoglucuronide which has low pharmacodynamic activity is the primary metabolite. In plasma, about 80% of the total amount is present as parent compound and 20% as monoglucuronide. Most of the glucuronide metabolite (about 95%) is excreted via bile into the feces, with some evidence of enterohepatic circulation. Renal excretion of parent compound is negligible and urinary excretion of the glucuronide metabolite is low (about 5%). With intravenous (i.v.) treatment of dipyridamole, a triphasic profile is obtained: a rapid alpha phase, with a half-life of about 3.4 minutes, a beta phase, with a half-life of about 39 minutes, (which, together with the alpha phase accounts for about 70% of the total area under the curve, AUC) and a prolonged elimination phase λ_z with a half-life of about 15.5 hours. Due to the extended absorption phase of the dipyridamole component, only the terminal phase is apparent from oral treatment with AGGRENOX which, in Trial 9.123 was 13.6 hours.

Special Populations
Geriatric Patients: In ESPS2 *[see Clinical Studies (14)]*, plasma concentrations (determined as AUC) of dipyridamole in healthy elderly subjects (>65 years) were about 40% higher than in subjects younger than 55 years receiving treatment with AGGRENOX.

Hepatic Dysfunction: No study has been conducted with AGGRENOX in patients with hepatic dysfunction.

In a study conducted with an intravenous 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.

Renal Dysfunction: No study has been conducted with AGGRENOX in patients with renal dysfunction.

In ESPS2 patients *[see Clinical Studies (14)]*, with creatinine clearances ranging from about 15 mL/min to >100 mL/min, no changes were observed in the pharmacokinetics of dipyridamole or its glucuronide metabolite if data were corrected for differences in age.

Aspirin
Absorption
Peak plasma levels of aspirin are achieved 0.63 hours (0.5–1 hour) after administration of a 50 mg aspirin daily dose from AGGRENOX (given as 25 mg BID). The peak plasma concentration at steady-state is 319 ng/mL (175–463 ng/mL). Aspirin undergoes moderate hydrolysis to salicylic acid in the liver and the gastrointestinal wall, with 50%–75% of an administered dose reaching the systemic circulation as intact aspirin.

Effect of Food
When AGGRENOX capsules were taken with a high fat meal, there was no difference for aspirin in AUC at steady-state, and the approximately 50% decrease in C_{max} was not considered clinically relevant based on a similar degree of cyclooxygenase inhibition comparing the fed and fasted state.

Distribution
Aspirin is poorly bound to plasma proteins and its apparent volume of distribution is low (10 L). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration-dependent (nonlinear). At low concentrations (<100 µg/mL), approximately 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and fetal tissues. Early signs of salicylate overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approximating 200 µg/mL *[see Adverse Reactions (6) and Overdosage (10)]*.

Metabolism and Elimination
Aspirin is rapidly hydrolyzed in plasma to salicylic acid, with a half-life of 20 minutes. Plasma levels of aspirin are essentially undetectable 2–2.5 hours after dosing and peak salicylic acid concentrations occur 1 hour (range: 0.5–2 hours) after administration of aspirin. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10–20 g), the plasma half-life may be increased to over 20 hours.

The elimination of acetylsalicylic acid follows first-order kinetics with AGGRENOX and has a half-life of 0.33 hours. The half-life of salicylic acid is 1.71 hours. Both values correspond well with data from the literature at lower doses which state a resultant half-life of approximately 2–3 hours. At higher doses, the elimination of salicylic acid follows zero-order kinetics (i.e., the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher. Renal excretion of unchanged drug depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Alkalinization of the urine is a key concept in the management of salicylate overdose *[see Overdosage (10)]*. Following therapeutic doses, about 10% is excreted as salicylic acid and 75% as salicyluric acid, as the phenolic and acyl glucuronides, in urine.

Special Populations
Hepatic Dysfunction: Avoid aspirin in patients with severe hepatic insufficiency.

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

13 NONCLINICAL TOXICOLOGY

13.1 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/m^2 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/m^2 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/m^2 basis). Aspirin inhibits ovulation in rats.

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14 CLINICAL STUDIES

ESPS2 (European Stroke Prevention Study 2) was a double-blind, placebo-controlled, 24-month study in which 6602 patients over the age of 18 years had an ischemic stroke (76%) or transient ischemic attack (TIA, 24%) within three months prior to entry. Patients were enrolled in 13 European countries between February 1989 and May 1995 and were randomized to one of four treatment groups: AGGRENOX (aspirin/extended-release dipyridamole) 25 mg/200 mg; extended-release dipyridamole (ER-DP) 200 mg alone; aspirin (ASA) 25 mg alone; or placebo. The mean age in this population was 66.7 years with 58% of them being males. Patients received one capsule twice daily (morning and evening). Efficacy assessments included analyses of stroke (fatal or nonfatal) and death (from all causes) as confirmed by a blinded morbidity and mortality assessment group. There were no differences with regard to efficacy based on age or gender; patients who were older had a trend towards more events.

Stroke Endpoint

AGGRENOX reduced the risk of stroke by 22.1% compared to aspirin 50 mg/day alone (p = 0.008) and reduced the risk of stroke by 24.4% compared to extended-release dipyridamole 400 mg/day alone (p = 0.002) (Table 4). AGGRENOX reduced the risk of stroke by 36.8% compared to placebo (p <0.001).

Table 4 Summary of First Stroke (Fatal or Nonfatal): ESPS2: Intent-to-Treat Population

	Total Number of Patients n	Number of Patients With Stroke Within 2 Years n (%)	Kaplan-Meier Estimate of Survival at 2 Years (95% C.I.)	Gehan-Wilcoxon Test P-value	Risk Reduction at 2 Years	Odds Ratio (95% C.I.)
Individual Treatment Group						
AGGRENOX	1650	157 (9.5%)	89.9% (88.4%, 91.4%)	-	-	-
ER-DP	1654	211 (12.8%)	86.7% (85.0%, 88.4%)	-	-	-
ASA	1649	206 (12.5%)	87.1% (85.4%, 88.7%)	-	-	-
Placebo	1649	250 (15.2%)	84.1% (82.2%, 85.9%)	-	-	-
Pairwise Treatment Group Comparisons						
AGGRENOX vs. ER-DP	-	-	-	0.002**	24.4%	0.72 (0.58, 0.90)
AGGRENOX vs. ASA	-	-	-	0.008**	22.1%	0.74 (0.59, 0.92)
AGGRENOX vs. Placebo	-	-	-	<0.001**	36.8%	0.59 (0.48, 0.73)
ER-DP vs. Placebo	-	-	-	0.036*	16.5%	0.82 (0.67, 1.00)
ASA vs. Placebo	-	-	-	0.009**	18.9%	0.80 (0.66, 0.97)

*0.010 < p-value ≤0.050; **p-value ≤0.010.

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

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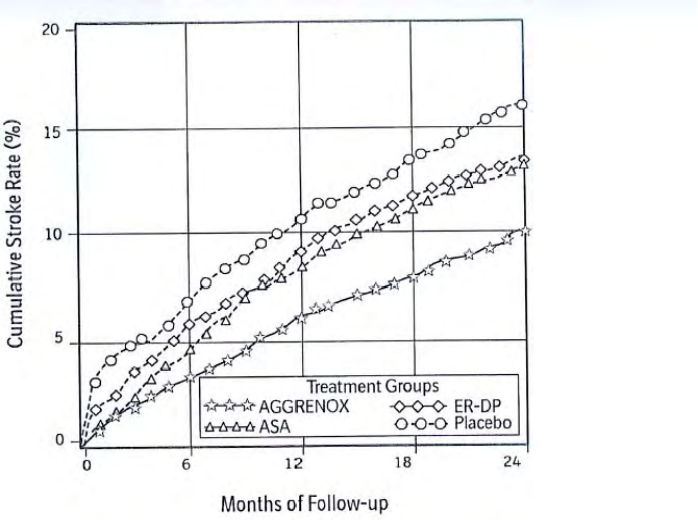
ESPS2: Cumulative Stroke Rate (Fatal or Nonfatal)
Over 24 months of Follow-UP



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

Combined Stroke or Death Endpoint
In ESPS2, AGGRENOX reduced the risk of stroke or death by 12.1% compared to aspirin alone and by 10.3% compared to extended-release dipyridamole alone. These results were not statistically significant. AGGRENOX reduced the risk of stroke or death by 24.2% compared to placebo.

Death Endpoint
The incidence rate of all cause mortality was 11.3% for AGGRENOX, 11.0% for aspirin alone, 11.4% for extended-release dipyridamole alone and 12.3% for placebo alone. The differences between the AGGRENOX, aspirin alone and extended-release dipyridamole alone treatment groups were not statistically significant. These incidence rates for AGGRENOX and aspirin alone are consistent with previous aspirin studies in stroke and TIA patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

AGGRENOX capsules are available as a hard gelatin capsule, with a red cap and an ivory-colored body, 24.0 mm in length, containing yellow extended-release pellets incorporating dipyridamole and a round white tablet incorporating immediate-release aspirin. The capsule body is imprinted in red with the Boehringer Ingelheim logo and with “01A”.

AGGRENOX capsules are supplied in unit-of-use bottles of 60 capsules (NDC 0597-0001-60).

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from excessive moisture.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling

17.1 Risk of Bleeding

Inform patients that as with other antiplatelet agents, there is a general risk of bleeding including intracranial and gastrointestinal bleeding. Inform patients about the signs and symptoms of bleeding, including occult bleeding. Tell patients to notify their physician if they are prescribed any drug which may increase risk of bleeding.

Counsel patients who consume three or more alcoholic drinks daily about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

17.2 Pregnancy

Inform patients that aspirin is known to be harmful to fetuses and ask the patient to notify them if they are or become pregnant.

17.3 Headaches

Some patients may experience headaches upon treatment initiation; these are usually transient. In case of intolerable headaches, tell the patient to contact their physician.

17.4 Dosage and Administration

Tell patients that AGGRENOX capsules should be swallowed whole, and not chewed or crushed. If you miss a dose, continue with your next dose on your regular schedule. Do not take a double dose.

17.5 Storage

Inform patients to protect AGGRENOX from moisture.

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Patient Information

Aggrenox® (AG-reh-nox)
(aspirin/extended-release dipyridamole)
Capsules

Read this Patient Information before you start taking AGGRENOX and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is AGGRENOX?

AGGRENOX is a prescription medicine that contains aspirin and a medicine that is slowly released in your body, called dipyridamole. AGGRENOX is used to lower the risk of stroke in people who have had a "mini-stroke" (transient ischemia attack or TIA) or stroke due to a blood clot.

It is not known if AGGRENOX is safe and effective in children. See "Who should not take AGGRENOX?"

Who should not take AGGRENOX?

Do not take AGGRENOX if you:

- are allergic to any of the ingredients in AGGRENOX. See the end of this leaflet for a list of ingredients in AGGRENOX.
- are allergic to non-steroidal anti-inflammatory drugs (NSAIDS)
- have asthma in combination with runny nose and nasal polyps

Do not give AGGRENOX to a child or teenager with a viral illness. Reye's syndrome, a life-threatening condition, can happen when aspirin (an ingredient in AGGRENOX) is used in children and teenagers who have certain viral illnesses.

What should I tell my doctor before using AGGRENOX?

Before taking AGGRENOX, tell your healthcare provider if you:

- have stomach ulcers
- have a history of bleeding problems
- have heart problems
- have kidney or liver problems
- have low blood pressure
- have myasthenia gravis
- have any other medical conditions
- are pregnant or plan to become pregnant. AGGRENOX can harm your unborn baby, especially if you take it in the last (third) trimester of pregnancy. You should not take AGGRENOX during pregnancy without first talking to your healthcare provider. Tell your healthcare provider right away if you become pregnant while taking AGGRENOX.
- are breast-feeding or plan to breast-feed. AGGRENOX can pass into your milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take AGGRENOX.

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Tell your doctor about all the medicines you take including, prescription and non-prescription medicines, vitamins and herbal supplements. AGGRENOX and other medicines may affect each other causing side effects. AGGRENOX may affect the way other medicines work, and other medicines may affect how AGGRENOX works.

Especially tell your healthcare provider if you take:

- **a medicine for high blood pressure, irregular heart beat, or heart failure**
- **acetazolamide [Diamox®]**
- **the blood thinner medicine warfarin sodium [Coumadin®, Jantoven®] or a heparin medicine**
- **a seizure medicine**
- **a medicine for Alzheimer's disease**
- **a water pill**
- **methotrexate sodium [Trexall®]**
- **aspirin or a non-steroidal anti-inflammatory drug (NSAIDS). You should not take NSAIDS during treatment with AGGRENOX.** Using these medicines with AGGRENOX can increase your risk of bleeding.
- **a medicine for diabetes**
- **probenecid [Probalan®, Col-Probenecid®]**

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take AGGRENOX?

- Take AGGRENOX exactly as prescribed. Your healthcare provider will tell you how many AGGRENOX to take and when to take them.
- Headaches are not uncommon when you first start taking AGGRENOX, but often lessen as treatment continues. Tell your healthcare provider if you have a severe headache. Your healthcare provider may change the instructions for taking AGGRENOX.
- Swallow AGGRENOX whole. Do not crush or chew the capsules.
- You can take AGGRENOX with or without food.
- ***If you miss a dose, take your next dose at the usual time. Do not take two doses at one time.***
- If you take more AGGRENOX (overdose) than prescribed, call your healthcare provider or Poison Control Center, or get emergency help right away.

Symptoms of an overdose of AGGRENOX include:

- a warm feeling or flushing
- sweating
- restlessness
- weakness or dizziness
- a fast heart rate
- ringing in the ears

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What should I avoid while using AGGRENOX?

- **heavy alcohol use.** People who drink three or more alcoholic drinks every day have a higher risk of bleeding during treatment with AGGRENOX, because it contains aspirin.

What are the possible side effects of AGGRENOX?

AGGRENOX may cause serious side effects, including:

- **increased risk of bleeding**. You may bleed more easily during AGGRENOX treatment, and it may take longer than usual for bleeding to stop. This can include:
    - **bleeding into your brain (intracranial hemorrhage).** This can be a medical emergency. Get medical help right away if you have any of these symptoms while taking AGGRENOX:
        - severe headache with drowsiness
        - confusion or memory change
        - pass out (become unconscious)
    - **bleeding in your stomach or intestine.**
        - stomach pain
        - heartburn or nausea
        - vomiting blood or vomit looks like “coffee grounds”
        - red or bloody stools
        - black stools that look like tar

- **new or worsening chest pain in some people with heart disease.** Tell your healthcare provider if you have new chest pain or have any change in your chest pain during treatment with AGGRENOX.
- **liver problems,** including increased liver function tests and liver failure. Tell your healthcare provider if you have any of these symptoms of a liver problem while taking AGGRENOX:
    - loss of appetite
    - pale colored stool
    - stomach area (abdomen) pain
    - yellowing of your skin or whites of your eyes
    - dark urine
    - itching

Call your healthcare provider right away if you have any of the symptoms listed above.

The most common side effects of AGGRENOX include:

- headache
- upset stomach
- diarrhea

These are not all the possible side effects of AGGRENOX. Tell your healthcare provider or pharmacist if you have any side effect that bothers you or that does not go away.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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How should I store AGGRENOX?

- Store AGGRENOX at 59°F to 86°F (15°C to 30°C).
- Keep AGGRENOX capsules dry.
- Safely throw away medicine that is out of date or no longer needed.

Keep AGGRENOX and all medicines out of the reach of children.

General information about AGGRENOX

Medicines are sometimes prescribed for purposes other than those listed in a Patient Package Insert. Do not use AGGRENOX for a condition for which it was not prescribed. Do not give AGGRENOX to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information summarizes the most important information about AGGRENOX. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about AGGRENOX that is written for health professionals. For more information, call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906.

What are the ingredients in AGGRENOX?

Active Ingredients: dipyridamole in an extended-release form and aspirin
Inactive Ingredients: acacia, aluminum stearate, colloidal silicon dioxide, corn starch, dimethicone, hypromellose, hypromellose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide and triacetin. Each capsule shell contains gelatin, red iron oxide and yellow iron oxide, titanium dioxide, and water.

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