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(we will no longer accept paper/disc submissions)

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For detailed instructions regarding style and layout refer to "Uniform requirements for manuscripts submitted to biomedical journals". Copies of this document may be obtained on the website http://www.icmje.org. Articles should be submitted under conventional headings of introduction, methods and materials, results, discussion, but other headings will be considered if more suitable. For Uniform Requirements for Sample References go to http://www.nlm.nih.gov/bsd/uniform_requirements.html.

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A cover letter is required and must state that the manuscript: has not been published elsewhere, except in abstract form is not under simultaneous consideration by another journal. Once a decision is made by the Editor on your manuscript, the CJNS office will send you an Author Release form and a Conflict of Interest form if your manuscript has been accepted for revision.

Abstracts

Original Articles and Case Reports should be accompanied by an abstract of 250 words or less on a separate page, in either English or French. The Journal will provide translation to the other language if required. Abstracts should consist of four paragraphs headed: Background (or Objective), Methods, Results and Conclusions.

Acknowledgements

Acknowledgements, including recognition of financial support, should be typed on a separate page at the end of the text. The SI system (système international d'unités) should be used in reporting all laboratory data, even if originally reported in another system. Temperatures are reported in degrees celsius. English language text may use either British or American spelling, but should be consistent throughout.

References

References should be numbered in the order of their citation in the text. Those cited only in tables and legends for illustrations are numbered according to the sequence established by the first identification in the text of a particular table or illustration.

Titles of journals should be abbreviated according to the style used in Index Medicus. References should list the names of up to six authors; if there are more, cite the first SIX, then et al.

Provide the full title, year of publication, volume number and inclusive pagination for journal articles. Do not reference unpublished or "submitted" papers; these can be mentioned in the body of the text and authors must provide five copies of "submitted" manuscripts.

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For Reference Guidelines
www.nlm.nih.gov/bsd/uniform_requirements.html

Examples of correct forms of reference:

Journals

Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

Tables

Type tables double-spaced on pages separate from the text. Provide a table number and title for each. Particular care should be taken in the preparation of tables to ensure that the data are presented clearly and concisely. Each column should have a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Do not submit tables as photographs.

Review Articles

Review articles on selected topics are also published. They are usually invited, but unsolicited reviews will be considered. Review articles should be accompanied by an abstract of 150 words or less.

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Peer Reviewed Letters to the Editor are published on various topics. The Letters should be limited to approximately six double-spaced manuscript pages (2-3 Journal pages) and may include illustrations and tables.

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Correspondence to the Editor concerning matters arising in recent articles are welcome. Correspondence should be limited to two double-spaced pages and may include one illustration and a maximum of four references.

Neuroimaging Highlights

Neuroimaging highlights are selected by the editor-in-chief and neuroimaging highlight editors on the basis of two factors. The first is high quality "state of the art" imaging of a novel and uncommon (or common with an uncommon twist) neurological or neurosurgical disorder. The second factor is the clinical novelty of the case.

Neuroimaging highlights require a figure of several panels that clearly outlines all features of the relevant imaging. For example, for MR images this may require different cuts and sequences, etc. Combining more than one imaging modality strengthens the report. The report may also benefit from a single additional panel in a figure if it is directly relevant, e.g. a pathological image or patient image. The text should include a very brief discussion of the case history confined to the relevant history, pertinent abnormal findings, and clinical course with outcome. An additional one to two paragraphs should briefly describe the neuroimaging panels present, and very briefly review relevant aspects of the literature. Overall, the neuroimaging highlights should be 500 words or less, with no more than 10 references.

Images should be of the highest quality, submitted either as glossy prints or electronically as a tiff file at a minimum of 300 dpi and at a size large enough for the printed journal (i.e. not less than 2" wide).

Suitability for publication is judged by the neuroimaging highlight editors, the editor-in-chief and up to one additional external referee.

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PrAGGRENOX®

Dipyridamole/Acetylsalicylic Acid Capsules
200 mg Extended Release Dipyridamole/25 mg Immediate Release Acetylsalicylic Acid (ASA)
Therapeutic Classification: Antiplatelet Agent

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	capsules, 200mg/25 mg	Non-medicinal ingredients (in alphabetical order): acacia, aluminium stearate, colloidal silicon dioxide, corn starch, dimethicone, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide, and triacetin. The capsule shell contains gelatine, red iron oxide and yellow iron oxide, titanium dioxide and water.

INDICATIONS AND CLINICAL USE

AGGRENOX is indicated for:

- the prevention of stroke in patients who have had a previous stroke or a transient ischemic attack (TIA).

Pediatrics (< 18 years of age): Safety and effectiveness of AGGRENOX in pediatric patients has not been studied. Therefore, AGGRENOX should not be used in pediatric patients.
ASA 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 ASA in certain viral illnesses.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Due to the ASA component, AGGRENOX is also contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis and nasal polyps.
- Patients with rare hereditary problems of fructose intolerance and/or galactose intolerance (e.g. galactosaemia) should not take this medicine. AGGRENOX contains approximately 23 mg sucrose and 106 mg of lactose per maximum recommended daily dose.

WARNINGS AND PRECAUTIONS

General

ALCOHOL WARNING
Patients who consume three or more alcoholic drinks every day should be counselled about the bleeding risks involved with chronic, heavy alcohol use while taking AGGRENOX, due to the ASA component.
If a patient is to undergo elective surgery, consideration should be given to discontinue AGGRENOX 10 days prior to surgery to allow for the reversal of the effect.
BLEEDING
As any antiplatelet agents, which cause bleeding, the use of AGGRENOX may increase the risk of bleeding such as skin haemorrhage, gastrointestinal bleeding and intracerebral haemorrhage. The addition of other antiplatelet agents (e.g. Clopidogrel, Ticlopidine) to AGGRENOX may further increase the risk of serious bleeding. Even though no study has been conducted, such combination is not recommended.
Due to the ASA component, the concomitant use of AGGRENOX with either selective serotonin reuptake inhibitors (SSRIs) or corticosteroids can increase the gastrointestinal bleeding.
This product contains 106 mg of lactose and 22.5 mg sucrose per maximum recommended daily dose. Patients with rare hereditary problems of fructose intolerance and/ or galactose intolerance e.g. galactosaemia should not take this medicine.

Carcinogenesis and Mutagenesis

CARCINOGENESIS
In carcinogenicity studies in rats and mice with the combination of dipyridamole and ASA at the ratio of 1:6 over a period of 125 and 105 weeks respectively, no significant tumorigenic effect was observed at maximum doses of 450 mg/kg (corresponding to a share of 75 mg/kg of dipyridamole, 9 times the maximum recommended daily human dose for a 50 kg person on a mg/kg basis [or 1.5-2.1 times on a mg/m2 basis]), and 375 mg/kg ASA, 375 times the maximum recommended daily human dose for a 50 kg person on a mg/kg basis (or 58-83 times on a mg/m^2 basis).

Cardiovascular

AGGRENOX should be used with caution in patients with severe coronary artery disease (e.g. unstable angina or recently sustained myocardial infarction), due to the vasodilatory effect of the dipyridamole component. Chest pain may be aggravated in patients with underlying coronary artery disease who are receiving dipyridamole. Patients being treated with AGGRENOX should not receive additional intravenous dipyridamole. If pharmacological stress testing with intravenous dipyridamole for coronary artery disease is considered necessary, then AGGRENOX should be discontinued twenty-four hours prior to testing, otherwise the sensitivity of the intravenous stress test could be limited.
For stroke or TIA patients for whom ASA is indicated to prevent recurrent myocardial infarction (MI) or angina pectoris, the dose of ASA in AGGRENOX has not been proven to provide adequate treatment for these cardiac indications.

Gastrointestinal

PEPTIC ULCER DISEASE
Patients with a history of active peptic ulcer disease should avoid using AGGRENOX, which can cause gastric mucosal irritation, and bleeding, due to the ASA component.
GI side effects include stomach pain, heartburn, nausea, vomiting, diarrhoea, 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.

Hematologic

AGGRENOX should be used with caution in patients with inherited (haemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders, due to the fact that even low doses of ASA can inhibit platelet function leading to an increase in bleeding time.

Hepatic/Biliary/Pancreatic

Due to the ASA component, AGGRENOX should be avoided in patients with severe hepatic insufficiency.

Renal

Due to the ASA component, AGGRENOX should be avoided in patients with severe renal failure (glomerular filtration rate less than 10 mL/min).

Sexual Function/Reproduction

Fertility studies with dipyridamole revealed no evidence of impaired fertility in rats at oral dosages of up to 1250 mg/kg, 156 times the maximum recommended human dose on a mg/kg basis for a 50 kg person (or 35 times on a mg/m2 basis). ASA inhibits ovulation in rats.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies of AGGRENOX in pregnant women. Because animal reproduction studies are not always predictive of human response, AGGRENOX should be given during the first two trimesters of pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Due to the ASA component, AGGRENOX should not be prescribed during the third trimester of pregnancy.
Nursing Women: Dipyridamole and ASA are excreted in human breast milk in low concentrations. Therefore, caution should be exercised when AGGRENOX is administered to a nursing woman.
Pediatrics (< 18 years of age): Safety and effectiveness of AGGRENOX in pediatric patients has not been studied. Therefore, AGGRENOX should not be used in pediatric patients.
ASA 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 ASA in certain viral illnesses.

Monitoring and Laboratory Tests

ASA has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria and prolonged bleeding time. 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/mm^3.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.
A 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 ASA 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. Discontinuation due to adverse events in ESPS2 was 27.8% for AGGRENOX, 28.2% for extended release dipyridamole, 23.2% for ASA, and 23.7% for placebo.
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 those patients treated with placebo.

Table 2: INCIDENCE OF ADVERSE EVENTS IN ESPS2 REPORTED BY > 1% OF PATIENTS DURING AGGRENOX TREATMENT WHERE THE INCIDENCE WAS GREATER THAT THOSE TREATED WITH PLACEBO

	Individual Treatment Group			
	AGGRENOX	**ER-DP Alone**	**ASA Alone**	**placebo**
Total Number of Patients	**N=1650**	**N=1654**	**N =1649**	**N =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%)**
Body System/Preferred Term				
Any Bleeding** Severity of bleeding:***				
Mild	84 (5.1%)	53 (3.2%)	82 (5.0%)	52 (3.2%)
Moderate	33 (2.0%)	18 (1.1%)	33 (2.0%)	15 (0.9%)
Severe	23 (1.4%)	4 (0.2%)	19 (1.2%)	5 (0.3%)
Fatal	4 (0.2%)	2 (0.1%)	1 (0.1%)	2 (0.1%)
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%)
Cardiovascular Disorders, General				
Cardiac Failure	26 (1.6%)	17 (1.0%)	30 (1.8%)	25 (1.5%)
Central & Peripheral Nervous System Disorders				
Headache	647 (39.2%)	634 (38.3%)	558 (33.8%)	543 (32.9%)
Convulsions	28 (1.7%)	15 (0.9%)	28 (1.7%)	26 (1.6%)
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%)	262 (15.9%)	239 (14.5%)
Nausea	264 (16.0%)	254 (15.4%)	210 (12.7%)	232 (14.1%)
Diarrhoea	210 (12.7%)	257 (15.5%)	112 (6.8%)	161 (9.8%)
Vomiting	138 (8.4%)	129 (7.8%)	101 (6.1)	118 (7.2%)
Hemorrhage Rectum	26 (1.6%)	22 (1.3%)	16 (1.0%)	13 (0.8%)
Melena	31 (1.9%)	10 (0.6%)	20 (1.2%)	13 (0.8%)
Haemorrhoids	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%)
Musculo-Skeletal 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%)

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Table 2: INCIDENCE OF ADVERSE EVENTS IN ESPS2 REPORTED BY > 1% OF PATIENTS DURING AGGRENOX TREATMENT WHERE THE INCIDENCE WAS GREATER THAT THOSE TREATED WITH PLACEBO *(cont'd)*

	Individual Treatment Group			
	AGGRENOX	ER-DP Alone	ASA Alone	placebo
Total Number of Patients	N=1650	N=1654	N =1649	N =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%)
Neoplasm				
Neoplasm NOS	28 (1.7%)	16 (1.0%)	23 (1.4%)	20 (1.2%)
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%)
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%)
Anorexia	19 (1.2%)	17 (1.0%)	10 (0.6%)	15 (0.9%)
Somnolence	20 (1.2%)	13 (0.8%)	18 (1.1%)	9 (0.5%)
Red Blood Cell Disorders				
Anaemia	27 (1.6%)	16 (1.0%)	19 (1.2%)	9 (0.5%)
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%)	16 (1.0%)	14 (0.8%)

Note: ER-DP = Extended Release Dipyridamole 400 mg/day; ASA = Acetylsalicylic Acid 50 mg/day.
Note: The dosage regimen for all treatment groups is b.i.d.
** Bleeding at any site, reported during follow-up and within 15 days after eventual stroke or treatment cessation.
*** Severity of bleeding: mild = requiring no special treatment; moderate = requiring specific treatment but no blood transfusion; severe = requiring blood transfusion.
Note: NOS = not otherwise specified

Less Common Clinical Trial Adverse Drug Reactions (<1%)
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 ASA are listed below.
Body as a Whole: allergic reaction, fever
Cardiovascular: hypotension, flushing
Central Nervous System: coma, dizziness, paraesthesia
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, abnormal hepatic function
Metabolic & Nutritional Disorders: hyperglycemia, thirst
Platelet, Bleeding and Clotting Disorders: haematoma, gingival bleeding, cerebral hemorrhage, intracranial hemorrhage, subarachnoid hemorrhage
Note: There was one case of pancytopenia recorded in a patient within the AGGRENOX treatment group, from which the patient recovered without discontinuation of AGGRENOX.
Psychiatric Disorders: agitation
Reproductive: uterine hemorrhage
Respiratory: hypernea, asthma, bronchospasm, haemoptysis, pulmonary edema
Special Senses: taste loss
Skin and Appendages Disorders: pruritus, urticaria
Urogenital: renal insufficiency and failure, hematuria

Abnormal Hematologic and Clinical Chemistry Findings
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/mm^3.

Post-Market Adverse Drug Reactions
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 ASA.
Body as a Whole: hypothermia, migraine-like headache (especially at the beginning of treatment)
Cardiovascular: angina pectoris, worsening of symptoms of coronary heart disease
Central Nervous System: cerebral edema
Fluid and Electrolyte: hyperkalemia, metabolic acidosis, respiratory alkalosis
Gastrointestinal: pancreatitis, Reyes Syndrome
Hearing and Vestibular Disorders: hearing loss
Hypersensitivity: acute anaphylaxis, laryngeal edema
Liver and Biliary System Disorders: hepatitis, incorporated into gallstones
Musculoskeletal: rhabdomyolysis
Metabolic & Nutritional Disorders: hypoglycemia, dehydration
Blood, Platelet, Bleeding and Clotting Disorders: prolongation of the prothrombin time, prolongation of bleeding time, increased bleeding during and after surgery, disseminated intravascular coagulation, coagulopathy, thrombocytopenia
Reproductive: prolonged pregnancy and labour, stillbirths, lower birth weight infants, antepartum and postpartum bleeding
Respiratory: tachypnea
Skin and Appendages Disorders: rash, alopecia, angioedema, skin haemorrhages such as contusion, ecchymosis and haematoma
Urogenital: interstitial nephritis, papillary necrosis, proteinuria

DRUG INTERACTIONS

Drug-Drug Interactions

Overview
When AGGRENOX is used in combination with acetylsalicylic acid or with warfarin the statements regarding precautions, warnings and tolerance for these preparations must be observed. Because of the increased risk of bleeding, the concomitant administration of heparin, or warfarin with AGGRENOX should be undertaken with caution. The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3- Established or Potential Drug-Drug Interactions

	Effect	Clinical comment
The following drug interactions are associated with the Dipyridamole component of AGGRENOX:		
ADENOSINE	Dipyridamole has been reported to increase the plasma levels and cardiovascular effects of adenosine.	Adjustment of adenosine dosage may be necessary.
CHOLINESTERASE INHIBITORS	The dipyridamole component of AGGRENOX may counteract the anticholinesterase effect of cholinesterase inhibitors, thereby potentially aggravating myasthenia gravis.	Patients should be advised to consult a physician if any worsening of the disease occurs.
The following drug interactions are associated with the ASA component of AGGRENOX:		
ACETAZOLAMIDE	Due to the ASA component, concurrent use of AGGRENOX and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.	Adjustment of acetazolamide dosage may be necessary.
ALCOHOL USE (CHRONIC)	Gastro-intestinal bleeding may increase when acetylsalicylic acid is administered concomitantly during chronic alcohol use.	Patients should be advised to consult a physician if any signs or symptoms of bleeding occur.
ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS	Due to the indirect effect of the ASA component on the renin-angiotensin conversion pathway, the hyponatremic and hypotensive effects of ACE inhibitors may be diminished by concomitant administration of AGGRENOX.	Patients should be advised to consult a physician if any signs or symptoms of decreased renal function such as oedema, or increase in blood pressure occur.
ANTICOAGULANT THERAPY (HEPARIN AND WARFARIN	Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and effects on platelets. ASA can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. The ASA component of AGGRENOX can increase the anticoagulant activity of heparin, increasing bleeding risk. Acetylsalicylic acid has been shown to enhance the effect of anticoagulants (e.g. coumarin derivatives and heparin) which may result in an increased risk of bleeding.	Patients should be advised to consult a physician if any signs or symptoms of bleeding occur.
ANTIPLATELET DRUGS (CLOPIDOGREL, TICLOPIDINE)	Acetylsalicylic acid has been shown to enhance the effect of antiplatelet drugs (e.g. clopidogrel, ticlopidine) which may result in an increased risk of bleeding.	Patients should be advised to consult a physician if any signs or symptoms of bleeding occur.
ANTICONVULSANTS	The ASA component of AGGRENOX 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. Acetylsalicylic acid has been shown to enhance the effect of valproic acid which may result in an increased risk of rare, but often fatal hepatotoxicity.	Adjustment of phenytoin or valproic acid dosage may be necessary.
BETA BLOCKERS	The hypotensive effects of beta blockers may be diminished by the concomitant administration of AGGRENOX due to inhibition of renal prostaglandins by ASA, leading to decreased renal blood flow, and salt and fluid retention.	Patient should be advised to consult a physician if any signs or symptoms of decreased renal function such as oedema, or increase in blood pressure occur.
CORTICOSTEROIDS	Gastro-intestinal bleeding increase when acetylsalicylic acid is administered concomitantly with corticosteroids.	Patient should be advised to consult a physician if any signs or symptoms of bleeding occur.
DIURETICS	The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of AGGRENOX due to inhibition of renal prostaglandins by ASA, leading to decreased renal blood flow and salt and fluid retention	Patient should be advised to consult a physician if any signs or symptoms of decreased renal function such as oedema occur.
IBUPROFEN	The concomitant administration of ibuprofen in healthy volunteers shortened the platelet aggregation inhibitory effect of ASA.	
METHOTREXATE	The ASA component of AGGRENOX can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renally impaired.	Adjustment of methotrexate dosage may be necessary.
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)	Due to the ASA component, the concurrent use of AGGRENOX with other NSAIDs may increase bleeding or lead to decreased *renal function.* Gastro-intestinal bleeding increases when acetylsalicylic acid is administered concomitantly with NSAIDs.	Patient should be advised to consult a physician if any signs or symptoms of *bleeding occur.*

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Table 3- Established or Potential Drug-Drug Interactions *(cont'd)*

	Effect	Clinical comment
ORAL HYPOGLYCAEMICS	AGGRENOX may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycaemia.	Patient should be advised to consult a physician if any signs or symptoms of hypoglycaemia occur.
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)	Selective serotonin reuptake inhibitors (SSRIs) may increase the risk of bleeding.	Patient should be advised to consult a physician if any signs or symptoms of bleeding occur.
URICOSURIC AGENTS (PROBENECID AND SULFINPYRAZONE) AND NATRIURETIC AGENTS	The ASA component of AGGRENOX antagonizes the uricosuric action of uricosuric agents. ASA decreased the natriuretic effect of spironolactone in healthy volunteers.	Patient should be advised to consult a physician if any signs or symptoms of decreased renal function such as oedema occur.

Drug-Herb interaction

Pharmacokinetic studies to determine the effect of herb or food have not been conducted with AGGRENOX.

Drug-laboratory interactions

Pharmacokinetic studies to determine the effect of laboratory interactions have not been conducted with AGGRENOX.

Drug-lifestyle interactions

Pharmacokinetic studies to determine the effect of lifestyle have not been conducted with AGGRENOX.

DOSAGE AND ADMINISTRATION

Dosing Considerations

For oral administration.

Recommended Dose and Dosage Adjustment

The recommended dose of AGGRENOX is one capsule twice daily, one in the morning and one in the evening, with or without food.

Administration

The capsules should be swallowed whole without chewing.

OVERDOSAGE

Because of the dose ratio of dipyridamole to ASA, overdosage of AGGRENOX is likely to be dominated by signs and symptoms of dipyridamole overdose. For real or suspected overdose, a Poison Control Center should be contacted immediately. Careful medical management is essential.

DIPYRIDAMOLE

SYMPTOMS

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

TREATMENT

Symptomatic treatment is recommended, possibly including a vasopressor drug. Gastric lavage should be considered. Since dipyridamole is highly protein bound, dialysis is not likely to be of benefit.

ASA

SYMPTOMS

In mild overdosage these may include rapid and deep breathing, nausea, vomiting, vertigo, tinnitus, flushing, sweating, thirst and tachycardia. In more severe cases acid base disturbances including respiratory alkalosis and metabolic acidosis can occur. Severe cases may show fever, hemorrhage, excitement, confusion, convulsion or coma, and respiratory failure.

TREATMENT

It consists of prevention and management of acid-base and fluid and electrolyte disturbances. Renal clearance is increased by increasing urine flow and by alkaline diuresis but care must be taken in this approach not to aggravate further the metabolic acidosis that develops and the hypokalemia. Acidemia should be prevented by administration of adequate sodium containing fluids and sodium bicarbonate. Hypoglycemia is an occasional accompaniment of salicylate overdosage and can be managed by administration of glucose solutions. If a hemorrhagic diathesis is evident, give vitamin K. Haemodialysis may be useful in complex acid base disturbances particularly in the presence of abnormal renal function.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Blood platelets participate actively in the pathogenesis of atherosclerotic lesions and thrombosis which is the principle cause of most strokes and transient ischemic attacks (TIAs). Platelets are believed to adhere to denuded, dysfunctional endothelium and to release mitogenic substances, such as platelet-derived growth factor (PDGF), that foster the lesion's progression to rupture and thrombosis. The antithrombotic action of AGGRENOX is the result of the additive antiplatelet effects of dipyridamole and acetylsalicylic acid (ASA).

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 plasma concentrations (0.5-1.9 µg/mL). This inhibition results in an increase in local concentrations of adenosine which 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 activating factor (PAF), collagen and adenosine diphosphate (ADP). Reduced platelet aggregation reduces platelet consumption towards normal levels.

Dipyridamole also 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).

ASA

ASA inhibits platelet aggregation by irreversible inhibition of platelet cyclo-oxygenase and thus inhibits the generation of thromboxane A2, a powerful inducer of platelet aggregation and vasoconstriction. In studies of platelet activity inhibition, 25 mg ASA was administered b.i.d. to 5 subjects for 2.5 days. Complete inhibition of collagen-induced aggregation was achieved by the 5th dose of ASA, and maximal effect persisted up to 2-3 days following stoppage of drug.s

Pharmacokinetics

There are no significant interactions between ASA and dipyridamole. The kinetics of the components are unchanged by their co-administration as AGGRENOX. AGGRENOX is not interchangeable with the individual components of ASA and dipyridamole.

DIPYRIDAMOLE

Absorption: The dissolution and absorption of dipyridamole from AGGRENOX capsules is independent of the pH of the gastrointestinal tract. Peak plasma levels are achieved in 1.5-2 hours after administration. The absolute bioavailability of dipyridamole from AGGRENOX is about 70%. With a daily maintenance dose of 400 mg of the extended release formulation, peak plasma levels at steady state are between 1.5-3 µg/mL and trough levels are between 0.4-0.8 µg/mL.

Pharmacokinetic studies to determine the effect of food have not been conducted with AGGRENOX.

Distribution: Due to its high lipophilicity, dipyridamole distributes to many organs; however it has been shown that the drug does not cross the blood brain barrier to any significant extent.

Metabolism: Dipyridamole is metabolized in the liver. In plasma, about 80% of the total amount is present as parent compound and 20% as monoglucuronide.

Excretion: 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%). The dominant half-life for elimination after oral or intravenous administration is about 40 minutes.

Special Populations and Conditions

Geriatrics: Plasma concentrations (determined as area under the curve, AUC) of dipyridamole in healthy elderly subjects (> 65 years) are about 30-50% higher than in subjects younger than 55 years, on treatment with AGGRENOX. The difference is caused mainly by reduced clearance.

Hepatic Insufficiency: Patients with mild to severe hepatic insufficiency show no change in plasma concentrations of dipyridamole compared to healthy volunteers, but show an increase in the pharmacologically inactive monoglucuronide metabolite. Dipyridamole can be dosed without restriction as long as there is no evidence of liver failure.

Renal Insufficiency: Renal excretion of dipyridamole is very low (about 5%). In patients 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.

ASA

Absorption: The rate of absorption of ASA from the gastrointestinal tract is dependent on the dosage form, the presence or absence of food, gastric pH, and other physiologic factors. Since ASA produces its pharmacodynamic effect via the irreversible acetylating of platelets, the time course of its pharmacodynamic activity is not dependent on the pharmacokinetics of ASA but rather on the lifespan of the platelets (approximately 8-10 days). Therefore, small differences in the pharmacokinetics of ASA, such as variations in its absorption rate or in elimination, are largely irrelevant to its pharmacologic activity with chronic administration. ASA 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 ASA. Peak plasma levels of ASA are achieved 0.5-1 hour after administration of a 50 mg ASA daily dose from AGGRENOX (given as 25 mg b.i.d.). Peak mean plasma concentration at steady state is 319 ng/mL (175-463 ng/mL).

Distribution: ASA is poorly bound to plasma proteins and its apparent volume of distribution is low (10 L). At low plasma 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; OVERDOSAGE)

Metabolism: ASA is rapidly hydrolyzed in plasma to salicylic acid, with a half-life of 15-30 minutes. Plasma levels of ASA are essentially undetectable 1-2 hours after dosing and peak salicylic acid concentrations occur within 1-2 hours of administration of ASA. 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.

Excretion: The elimination of salicylic acid follows first order kinetics at lower doses, with a resultant half-life of approximately 2-3 hours. 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) Following therapeutic doses, about 10% is excreted as salicylic acid and 75% as salicyluric acid, in urine.

Special Populations and Conditions

Hepatic Insufficiency: Due to the ASA component, AGGRENOX is to be avoided in patients with severe hepatic insufficiency.

Renal Insufficiency: Due to the ASA component, AGGRENOX is to be avoided in patients with severe renal failure (glomerular filtration rate less than 10 mL/min).

STORAGE AND STABILITY

Store at 15 to 30°C.

SPECIAL HANDLING INSTRUCTIONS

Protect from excessive moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each hard gelatine capsule contains 200 mg dipyridamole as extended release pellets (a mixture of two release rate pellets), and 25 mg ASA as an immediate release sugar coated tablet.

AGGRENOX is available as a hard gelatine capsule, with a red cap and an ivory-coloured body, containing yellow extended release pellets incorporating dipyridamole and a round white tablet incorporating immediate-release ASA. The capsule body is imprinted in red with the Boehringer Ingelheim logo and with "01A".

Non-medicinal ingredients (in alphabetical order): acacia, aluminium stearate, colloidal silicon dioxide, corn starch, dimethicone, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide, and triacetin.

The capsule shell contains gelatine, red iron oxide and yellow iron oxide, titanium dioxide and water.

AGGRENOX is supplied in polypropylene tubes containing 60 capsules.

Aggrenox®

ASA /Extended Release Dipyridamole

Boehringer Ingelheim

www.boehringer-ingelheim.ca

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PAAB Member R&D

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THE CNSF CELEBRATES ITS

60TH

ANNIVERSARY IN 2008!

The Canadian Neurological Association was established in 1948. The founding meeting was held in Montreal and was attended by Wilder Penfield, Allan Waters, Walter Hyland, Jean Saucier, Francis McNaughton and Roma Amyot.

The first general meeting of the Association was held at the Royal York Hotel in Toronto and was attended by 38 prospective members from across the country. The Association was established to represent neurology, neurosurgery and neurobiology and Dr. Wilder Penfield was named first president. In 1949, the Association was renamed the Canadian Neurological Society.

In 1965, the Canadian Neurological Society, representing both neurologists and neurosurgeons, was dissolved and two new Societies were formed representing two distinct disciplines – the new Canadian Neurological Society for neurologists and the Canadian Neurosurgical Society for neurosurgeons. A liaison committee, with executive officers from the two Societies, was formed to administer conjoint activities. This committee was important in planning the first annual joint meeting held in 1965 – the first Canadian Congress of Neurological Sciences.

In subsequent years, the two Societies were joined by the Canadian EEG Society (later named the Canadian Society of Clinical Neurophysiologists) and the Canadian Association of Child Neurology.

In 1990, the Canadian Congress of Neurological Sciences was formally incorporated with a Board of Directors representing each of the four member Societies, with a permanent Secretariat Office in Calgary. In 2006, the name was changed to the Canadian Neurological Sciences Federation (CNSF).

The CNSF Today

This unique partnership of neurologists, neurosurgeons, clinical neurophysiologists and child neurologists continues to hold a combined annual Congress in June every year. Additionally, the CNSF now publishes the Canadian Journal of Neurological Sciences, the 'Journal'.

A Board of Directors governs the CNSF. The Board consists of two members (the President and Vice President) from each of the four Societies, the President and two Vice-Presidents of the Board who are appointed from the general membership of the four Societies, one Neurology or Neurosurgery resident (alternating), the immediate Past-Chair of the Board (non-voting), and the CNSF CEO (non-voting).

The CNSF has approximately 1,100 members and eight full-time staff in the Secretariat Head Office.

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MICARDIS® (telmisartan)

40 mg and 80 mg Tablets
THERAPEUTIC CLASSIFICATION:
Angiotensin II AT_1 Receptor Blocker

INDICATIONS AND CLINICAL USE

MICARDIS® (telmisartan) is indicated for the treatment of mild to moderate essential hypertension.
MICARDIS® may be used alone or in combination with thiazide diuretics.
The safety and efficacy of concurrent use with angiotensin converting enzyme inhibitors have not been established. Information on the use of telmisartan in combination with beta blockers is not available.

CONTRAINDICATIONS

MICARDIS® (telmisartan) is contraindicated in patients who are hypersensitive to any components of this product (see Composition).

WARNINGS

Pregnancy:
Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and mortality when administered to pregnant women. If pregnancy is detected, MICARDIS® (telmisartan) should be discontinued as soon as possible. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and nonnatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of MICARDIS® as soon as possible unless it is considered life-saving for the mother. Rarely, probably less often than once in every thousand pregnancies, no alternative to an angiotensin II AT_1 receptor antagonist will be found. In these rare cases, the physician should apprise mothers of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra amniotic environment. If oligohydramnios is observed, contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of in utero exposure to an angiotensin II AT_1 receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion may be required as a means of reversing hypertension and/or substituting for disordered renal function. Telmisartan is not removed from plasma by hemodialysis. No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses of up to 45 mg/kg/day with saline supplementation. In rabbits, fetotoxicity (total resorptions) associated with maternal toxicity (reduced body weight gain, mortality) was observed at the highest dose level (45 mg/kg/day). In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 50 mg/kg/day in late gestation and during lactation were observed to produce adverse effects in rat fetuses and neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Significant levels of telmisartan were present in rat milk and rat fetuses' blood during late gestation.

Hypotension:
In patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting, symptomatic hypotension may occur after initiation of therapy with MICARDIS®. These conditions should be corrected prior to administration of MICARDIS®. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

PRECAUTIONS

General:
Hepatic Impairment: As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency have reduced clearance of telmisartan. Three-to four-fold increases in C_{max} and AUC were observed in patients with liver impairment as compared to healthy subjects. MICARDIS® (telmisartan) should be used with caution in these patients (see DOSAGE AND ADMINISTRATION).
Renal Impairment: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely acute renal failure and/or death. There is no experience with long-term use of MICARDIS® (telmisartan) in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. In susceptible patients, concomitant diuretic use may further increase the risk. Use of telmisartan should include appropriate assessment of renal function in these types of patients.
Valvular Stenosis: There is concern on theoretical grounds that patients with aortic stenosis might be at a particular risk of decreased coronary perfusion, because they do not develop as much afterload reduction.
Hyperkalemia: Drugs such as MICARDIS® that affect the renin-angiotensin-aldosterone system can cause hyperkalemia. Monitoring of serum potassium in patients at risk is recommended. Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to a greater risk of an increase in serum potassium.
Use in Nursing Mothers: It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Use in Children: Safety and effectiveness in pediatric patients have not been established.
Use in the Elderly: Of the total number of patients receiving MICARDIS® (telmisartan) in clinical studies, 551 (18.6%) were 65 to 74 years of age and 130 (4.4%) were 75 years or older. No overall age-related differences were seen in the adverse effect profile, but greater sensitivity in some older patients cannot be ruled out.
Effects on Ability to Drive and Use Machines: No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery, it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

Drug Interactions:
Warfarin: MICARDIS® (telmisartan) administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR). Coadministration of MICARDIS® also did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, hydrochlorothiazide or ibuprofen. For digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is recommended that digoxin plasma levels be monitored when initiating, adjusting or discontinuing MICARDIS®.
Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Therefore, serum lithium level monitoring is advisable during concomitant use.

ADVERSE EVENTS

MICARDIS® (telmisartan) has been evaluated for safety in 27 clinical trials involving 7,968 patients. Of these 7,968 patients, 5,788 patients were treated with MICARDIS® monotherapy including 1,058 patients treated for ≥1 year and 1,395 patients treated in placebo-controlled trials. In 3,400 patients, discontinuation of therapy due to adverse events was required in 2.8% of MICARDIS® patients and 6.1% placebo patients. The following potentially serious adverse reactions have been reported rarely with telmisartan in controlled clinical trials: syncope and hypotension. In placebo-controlled trials, no serious adverse event was reported with a frequency of greater that 0.1% in MICARDIS®-treated patients.

ALL CLINICAL TRIALS

The adverse drug events listed below have been accumulated from 27 clinical trials including 5,788 hypertensive patients treated with telmisartan. Adverse events have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100, >1/10); uncommon (≥1/1.000, <1/100); rare (≥1/10.000, <1/1.000); very rare (<1/10.000).
Body as a Whole, General: Common: Back pain (e.g. sciatica), chest pain, influenza-like symptoms, symptoms of infection (e.g. urinary tract infections including cystitis), fatigue, conjunctivitis. Uncommon: Abnormal vision, sweating increased.
Cardiovascular System: Common: Edema, palpitation.
Central and Peripheral Nervous System: Very common: Headache. Common: Dizziness, insomnia. Uncommon: Vertigo.
Gastro-Intestinal System: Common: Abdominal pain, diarrhea, dyspepsia, nausea, constipation, gastritis. Uncommon: Dry mouth, flatulence.
Musculo-Skeletal System: Common: Arthralgia, cramps in legs or leg pain, myalgia, arthritis, arthrosis. Uncommon: Tendinitis like symptoms.
Psychiatric System: Common: Anxiety, depression, nervousness.
Respiratory System: Common: Upper respiratory tract infections including pharyngitis and sinusitis, bronchitis, coughing, dyspnea, rhinitis.
Skin and Appendages Systems: Common: Skin disorders like eczema, rash.

CLINICAL LABORATORY FINDINGS

Hemoglobin: Infrequently, a decrease in hemoglobin has been observed which occurs more often during treatment with telmisartan than with placebo.

PLACEBO-CONTROLLED TRIALS

The overall incidence of adverse events reported with MICARDIS® (41.4%) was usually comparable to placebo (43.9%) in placebo-controlled trials. Adverse events occurring in 1% or more of 1,395 hypertensive patients treated with MICARDIS® monotherapy in placebo-controlled clinical trials, regardless of drug relationship, include the following:

Adverse Event, by System	MICARDIS® Total n=1,395 %	Placebo n=583 %
Body as a Whole		
Back pain	2.7	0.9
Chest pain	1.3	1.2
Fatigue	3.2	3.3
Influenza-like symptoms	1.7	1.5
Pain	3.5	4.3
Central & Peripheral Nervous System		
Dizziness	3.6	4.6
Headache	8.0	15.6
Somnolence	0.4	1.0
Gastrointestinal System		
Diarrhea	2.6	1.0
Dyspepsia	1.6	1.2
Nausea	1.1	1.4
Vomiting	0.4	1.0
Musculoskeletal System		
Myalgia	1.1	0.7
Respiratory System		
Coughing	1.6	1.7
Pharyngitis	1.1	0.3
Sinusitis	2.2	1.9
Upper respiratory tract infection	6.5	4.6
Heart Rate and Rhythm Disorders		
ECG abnormal specific	0.2	1.0
Palpitation	0.6	1.0
Cardiovascular Disorders, General		
Hypertension	1.0	1.7
Oedema peripheral	1.0	1.2

The incidence of adverse events was not dose-related and did not correlate with the gender, age, or race of patients.
In addition, the following adverse events, with no established causality, were reported at an incidence of <1% in placebo-controlled clinical trials.
Autonomic Nervous Systems Disorders: sweating increased.
Body as a Whole: abdomen enlarged, allergy, cyst nos, fall, fever, leg pain, rigors, syncope.
Cardiovascular Disorders, General: hypotension, hypotension-postural, leg edema.
Central & Peripheral Nervous System Disorders: hypertonia, migraine-aggravated, muscle contraction-involuntary.
Gastrointestinal System Disorders: anorexia, appetite increased, flatulence, gastrointestinal disorder nos, gastroenteritis, gastroesophageal reflux, melena, mouth dry, abdominal pain.
Heart Rate & Rhythm Disorders: arrhythmia, tachycardia.
Metabolic & Nutritional Disorders: diabetes mellitus, hypokalemia.
Musculoskeletal System Disorders: arthritis, arthritis aggravated, arthrosis, bursitis, fascitis plantar, tendinitis.
Myo Endo Pericardial & Valve Disorders: myocardial infarction.
Psychiatric Disorders: nervousness.
Red Blood Cell Disorders: anemia.
Reproductive Disorders, Female: vaginitis.
Resistance Mechanism Disorders: abscess, infection, bacterial, moniliasis genital, otitis media.
Respiratory System Disorders: bronchospasm, epistaxis, pneumonia, bronchitis.
Skin & Appendage Disorders: rash, skin dry.
Urinary System Disorders: dysuria, hematuria, micturition disorder, urinary tract infection.
Vascular (Extracardiac) Disorders: cerebrovascular disorder, purpura.
Vision Disorders: vision abnormal.
Clinical Laboratory Findings:
In placebo-controlled clinical trials involving 1,041 patients treated with MICARDIS® monotherapy, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of MICARDIS®.
Creatinine, Blood Urea Nitrogen: Increases in BUN (≥11.2 mg/dL) and creatinine (≥0.5 mg/dL) were observed in 1.5% and 0.6% of MICARDIS®-treated patients; the corresponding incidence was 0.3% each for placebo-treated patients. These increases occurred primarily with MICARDIS® in combination with hydrochlorothiazide. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.
Hemoglobin, Hematocrit: Clinically significant changes in hemoglobin and hematocrit (<10 mg/dL and <30% respectively) were rarely observed with MICARDIS® treatment and did not differ from rates in placebo-treated patients. No patients discontinued therapy due to anemia.
Serum Uric Acid: An increase in serum uric acid (≥2.7 mg/dL) was reported in 1.7% of patients treated with MICARDIS® and in 0.0% of patients treated with placebo. Clinically significant hyperuricemia (≥10 mEg/L) was observed in 2.3% of patients with MICARDIS® with 0.4% reported in patients at baseline. Increases in serum acid were primarily observed in patients who received MICARDIS® in combination with hydrochlorothiazide. No patient was discontinued from treatment due to hyperuricemia.
Liver Function Tests: Clinically significant elevations in AST and ALT (>3 times the upper limit of normal) occurred in 0.1% and 0.5% respectively of patients treated with MICARDIS® compared to 0.8% and 1.7% of patients receiving placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.
Serum Potassium: Marked laboratory changes in serum potassium (≥+/- 1.4 mEg/L) occurred rarely and with a lower frequency in MICARDIS®-treated patients (0.3%, 0.1%, respectively) than in placebo patients (0.6%, 0.3%, respectively). Clinically significant changes in potassium (that exceed 3 mEg/L were found in 0.6% of MICARDIS®-treated patients, with 0.5% of these reported at baseline. The corresponding rates for placebo-treated patients were 0.6% and 0.8%.
Cholesterol: In placebo-controlled trials, marked increases in serum cholesterol were reported in a total of 6 telmisartan-treated patients (0.4%) and no placebo patients. Two of these patients were followed over time; in both cases cholesterol values reverted to baseline levels. Serum elevations in cholesterol were reported as adverse events in 11 of 3,445 patients (0.3%) in all clinical trials. There were no reported cases of hypercholesterolemia in telmisartan-treated patients in placebo-controlled trials.

POST-MARKETING EXPERIENCE

Since the introduction of telmisartan in the market, cases of erythema, pruritus, faintness, insomnia, depression, stomach upset, vomiting, hypotension, bradycardia, tachycardia, dyspnoea, eosinophilia, thrombocytopenia, weakness and lack of efficacy have been reported rarely. As with other angiotensin II antagonists rare cases of angio-oedema, pruritis, rash and urticaria have been reported.
Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and/or tachycardia. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

DOSAGE AND ADMINISTRATION

The recommended dose of MICARDIS® (telmisartan) is 80 mg once daily.
The antihypertensive effect is present within 2 weeks and maximal reduction is generally attained after four weeks. If additional blood pressure reduction is required, a thiazide diuretic may be added.
No initial dosing adjustment is necessary for elderly patients or for patients with renal impairment, but greater sensitivity in some older individuals cannot be ruled out. Markedly reduced telmisartan plasma levels were observed in patients on hemodialysis.
For patients with hepatic impairment, a starting dose of 40 mg is recommended (see PRECAUTIONS, Hepatic Impairment). MICARDIS® should be taken consistently with or without food.

Composition:
MICARDIS® Tablets contain the following inactive ingredients: sodium hydroxide, meglumine, povidone, sorbitol, and magnesium stearate.

Stability and Storage Recommendations:
MICARDIS® Tablets are hygroscopic and require protection from moisture. Tablets are packaged in blisters and should be stored at room temperature, 15 to 30°C (59-86°F).
Tablets should not be removed from blisters until immediately prior to administration.

AVAILABILITY OF DOSAGE FORMS

MICARDIS® is available as white, oblong-shaped, uncoated tablets containing telmisartan 40 mg or 80 mg. Tablets are marked with the Boehringer Ingelheim logo on one side, and on the other side, with a decorative score and either 51H or 52H for the 40 mg and 80 mg strengths, respectively.
MICARDIS® Tablets 40 mg are individually blister sealed in cartons of 28 tablets as 4 cards containing 7 tablets each.
MICARDIS® Tablets 80 mg are individually blister sealed in cartons of 28 tablets as 4 cards containing 7 tablets each.

Product Monograph available upon request.

References:

1. Mallion JM *et al.* ABPM Comparison of the Antihypertensive Profiles of the Selective Angiotensin II Receptor Antagonists Telmisartan and Losartan in Patients With Mild-to-Moderate Hypertension. *Journal of Human Hypertension* 1999;13(10):657-664. **2.** Lacourcière Y, *et al.* A Multicenter, 14-Week Study of Telmisartan and Ramipril in Patients With Mild-to-Moderate Hypertension Using Ambulatory Blood Pressure Monitoring. *American Journal of Hypertension* 2006;19:104-112. **3.** MICARDIS® Product Monograph, Boehringer Ingelheim (Canada) Ltd. October 2005. **4.** Cozaar® Product Monograph, E.I. du Pont de Nemours and Company. **5.** Diovan® Product Monograph, Novartis. **6.** Avapro™ Product Monograph (Canada), Sanofi-Synthelabo. **7.** Atacand® Product Monograph, AstraZeneca Pharma Inc. **8.** Teveten® Product Monograph, Solvay Pharma Inc.

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FÉDÉRATION DES SCIENCES NEUROLOGIQUES DU CANADA

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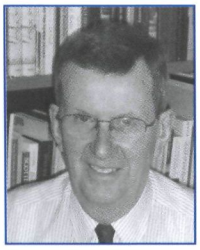

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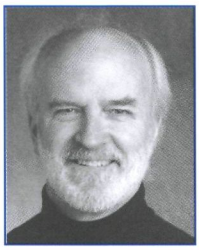

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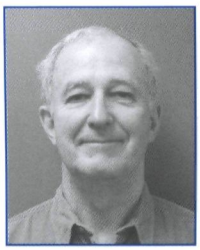

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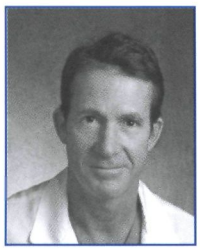

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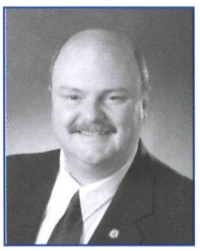

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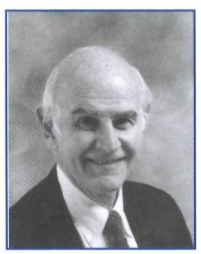

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CNSF - *Canadian Neurological Sciences Federation;* NSFC - *Neurological Sciences Foundation of Canada;* CNS - *Canadian Neurological Society;* CNSS - *Canadian Neurosurgical Society;* CSCN - *Canadian Society of Clinical Neurophysiologists;* CACN - *Canadian Association of Child Neurology;* CBANHC - *Canadian Brain and Nerve Health Coalition*

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PrAGGRENOX® PROVIDES STRONG DEFENSE AGAINST A SECOND STROKE

- **AGGRENOX® prevented *twice* as many strokes vs. ASA alone[1,2,3*]**
  - 22.1% additional stroke protection over ASA (p=0.008)[2†]
  - 36.8% greater stroke protection vs. placebo (p<0.001)[2†]
- **Proven safety profile[2]**
- **ASA/extended release dipyridamole is recommended as first-line secondary stroke prevention therapy in:**
  - Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy[4]
  - European Stroke Initiative (EUSI)[5]
  - UK Royal College Physician Guidelines[6]

* Randomized, double-blind, placebo-controlled trial, 6,602 patients with history of TIA or ischemic stroke. AGGRENOX® 50 mg ASA + 400 mg extended release dipyridamole per day (b.i.d. dosing) n=1,650, ASA 50 mg per day (25 mg b.i.d.) n=1,649, placebo n=1,649, extended release dipyridamole 400 mg per day (200 mg b.i.d.) n=1,654. For every 1,000 patients treated for two years, AGGRENOX® prevented 58 strokes vs. only 29 for ASA, compared to placebo.[1,2,3]

† Percentage of patients experiencing a stroke within two years: AGGRENOX® 9.5%, ASA 12.5%, placebo 15.2%.[2]

AGGRENOX® is indicated for the prevention of stroke in patients who have had a previous stroke or a transient ischemic attack (TIA).

The overall discontinuation rate due to adverse events was 27.8% for AGGRENOX®, 23.2% for ASA, and 23.7% for placebo.

AGGRENOX® is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products; patients with the syndrome of asthma, rhinitis and nasal polyps; and in patients with hypersensitivity to dipyridamole, ASA, or any of the other product components.

AGGRENOX® contains approximately 23 mg sucrose and 106 mg of lactose per maximum recommended daily dose. Patients with rare hereditary problems of fructose intolerance and/or galactose intolerance (e.g. galactosaemia) should not take this medicine.

If a patient is to undergo elective surgery, consideration should be given to discontinue AGGRENOX® 10 days prior to surgery, to allow for the reversal of effect.

The use of AGGRENOX® may increase the risk of bleeding such as skin haemorrhage, gastrointestinal bleeding and intracerebral haemorrhage. The addition of other antiplatelet agents (e.g. Clopidogrel, Ticlopidine) to AGGRENOX® may further increase the risk of serious bleeding and is not recommended.

Due to the ASA component of AGGRENOX® should be: avoided in patients with severe hepatic insufficiency or severe renal failure, avoided in patients with a history of active peptic ulcer disease, and used with caution in patients with inherited or acquired bleeding disorders, nursing mothers, patients taking selective serotonin reuptake inhibitors (SSRIs) or corticosteroids, or in patients who consume three or more alcoholic drinks per day.

AGGRENOX® should not be used in paediatric patients or during the third trimester of pregnancy.

AGGRENOX® 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).

The most common adverse events with AGGRENOX® was headache (39.2% vs. 33.8% for ASA and 32.9% for placebo), dyspepsia (18.4% vs. 18.1% for ASA, and 16.7% for placebo), abdominal pain (17.5% vs. 15.9% for ASA and 14.5% for placebo), nausea (16.0% vs. 12.7% for ASA and 14.1% for placebo), and diarrhea (12.7% vs. 6.8% for ASA and 9.8% for placebo). When headache occurred it was particularly evident in the first month of therapy. 8.9% of patients discontinued due to headache, 66% of these discontinued within the first month.

Discontinuation rates due to headache were 2.8% and 2.1% in the placebo and ASA group respectively.

Consult Prescribing Information for complete details.

References: **1.** Diener HC, *et al.* European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *Journal of the Neurological Sciences* 1996;143:1-13. **2.** AGGRENOX® Product Monograph. Boehringer Ingelheim (Canada) Ltd. July 2006. **3.** Diener HC, *et al.* European Stroke Prevention Study 2. Efficacy and Safety Data. *Journal of the Neurological Sciences* 1997;151:S1-S77. **4.** Albers GW, Amarenco P, Easton DJ, Sacco RL, Teal P. Antithrombotic and Thrombolytic Therapy for Ischemic Stroke. Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *CHEST* 2004;126:483S-512S.

5. European Stroke Initiative (EUSI) Executive Committee, and EUSI Writing Committee. EUSI Recommendations for Stroke Management – Update 2003. *Cerebrovascular Dis* 2003;16:311-337.
6. Royal College of Physicians of London. National Clinical Guidelines for Stroke, June 2004.

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ASA /Extended Release Dipyridamole

Challenging the benchmark in secondary stroke prevention[1,4,5,6]

For brief prescribing information see pages A-12, A-13, A-14

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