INFORMATION FOR AUTHORS

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• Submit five high quality copies of the manuscript and original illustrations. Papers will be accepted in English or French. Text should be formatted in Microsoft Word (saved as RFT files) or Quark Xpress. Manuscripts must be double spaced throughout including references, tables and legends for illustrations. Margins of at least 25mm should be left on all sides.

• After a paper has been reviewed, the author will be requested to submit four copies of the revised manuscript, including illustrations. Supply a CD containing the article *saved in an RTF format*. Identify clearly first author's name, file name, word processing program and version, and system (i.e. PC or Mac). Clearly indicate the order and importance of headings.

• 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 www.icmje.org, but the main points are summarized here. Articles should be submitted under conventional headings of *introduction, methods and materials, results, discussion,* but other headings will be considered if more suitable. Clinical trials must be reported in Consort format (www.cjns.org). Pages of text should be numbered consecutively.

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• Clearly label name and address of corresponding author. Set up a folder with all files and label as Journal Submission, attach and submit to address below.

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• ***A title page*** should identify the title of the article which should be no more than 80 characters including spaces; name of institution(s) from which the work originated; and the name, address, telephone, and fax number of the corresponding author.

• ***Abstract*** Original Articles should be accompanied by an abstract of 250 words or less on a separate page, preferably in English and French, although the Journal will provide translation if required. Abstracts of original articles should consist of four paragraphs headed: *Background (or objective), Methods, Results and Conclusions*. Review articles should be accompanied by an abstract of 150 words or less.

• ***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. An ***Ethics approval statement*** must be provided, if applicable. Temperatures are reported in degrees celsius. English language text may use either British or American spelling, but should be consistent throughout.

• ***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. For any reference cited as "in press", article must accompany the author's manuscript. Do not reference unpublished or "submitted" papers; these can be mentioned in the body of the text and authors must provide a copy of "submitted" manuscripts. Avoid "personal communications" and, if necessary, include them in the body of the text, not among the references. Reference citations should not include unpublished presentations or other non-accessible material. Books or chapter references should also include the place of publication and the name of the publisher. Examples of correct forms of reference follow:

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.

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• ***Illustrations*** *(regular mail)* Submit five original sets of illustrations. We will not return illustrations; therefore, authors should keep negatives for all photographs. Submit high quality glossy black and white photographs preferably 127 x 173 mm (5" x 7"). This includes graphs and diagrams. Do NOT send photocopies of illustrations. Original artwork and radiographs should not be submitted. The additional cost of coloured illustrations must be borne by the author; quotations are available upon request from the Journal office. Identify each figure with a label at the back indicating top, figure number and first author. Letters and arrows applied to the figures to identify particular findings should be professional appliques suitable for publication. Photomicrographs should include a calibration bar with a scale indicated on the figure or in the legend. Legends for illustrations should be typed on a separate page from the illustrations.

• ***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.

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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%)

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

Boehringer Ingelheim (Canada) Ltd.
5180 South Service Rd.,
Burlington, Ontario L7L 5H4

PAAB Member R&D

07/06

See IBC

TYSABRI™ (natalizumab)

Concentrate for solution for intravenous infusion
300 mg/15 mL

THERAPEUTIC CLASSIFICATION:
Selective adhesion molecule inhibitor

TYSABRI should be used by physicians who have sufficient knowledge of multiple sclerosis and who have familiarized themselves with the efficacy/safety profile of the drug.

SUMMARY PRODUCT INFORMATION

Route of Administration Intravenous infusion
Dosage Form / Strength Concentrate for solution / 300 mg per 15 mL
Clinically Relevant Nonmedicinal Ingredients There are no clinically relevant nonmedicinal ingredients. For a complete listing of nonmedicinal ingredients see Dosage Forms, Composition and Packaging section.

DESCRIPTION

TYSABRI™ (natalizumab) is a recombinant humanized $IgG_{4\kappa}$ monoclonal antibody selective for α4-integrin. Natalizumab is produced in murine myeloma cells. The molecular weight of natalizumab is 149 kilodaltons. TYSABRI is supplied as a sterile, colourless, clear to slightly opalescent concentrate for solution for intravenous (IV) infusion.

INDICATIONS AND CLINICAL USE

TYSABRI™ (natalizumab) is indicated as monotherapy (i.e., single disease-modifying agent) for the treatment of patients with the relapsing-remitting form of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations, to decrease the number and volume of active brain lesions identified on magnetic resonance imaging (MRI) scans and to delay the progression of physical disability. TYSABRI is generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, other therapies for multiple sclerosis.

Safety and efficacy in patients with chronic progressive multiple sclerosis, and in geriatric and pediatric patients, have not been established.

The efficacy and safety of TYSABRI for a treatment duration beyond 2 years has not been determined.

TYSABRI should be used by physicians who have sufficient knowledge of multiple sclerosis and who have familiarized themselves with the efficacy/safety profile of TYSABRI.

Geriatrics (>65 years of age)

Clinical studies of TYSABRI did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients.

Pediatrics (<18 years of age)

Safety and effectiveness of TYSABRI in pediatric patients with multiple sclerosis have not been studied.

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.
- Patients who have or have had progressive multifocal leukoencephalopathy (PML).
- Patients who are immunocompromised, including those immunocompromised due to immunosuppressant or antineoplastic therapies, or immunodeficiencies (HIV, leukemias, lymphomas, etc.).

WARNINGS AND PRECAUTIONS

- **Treatment with TYSABRI™ (natalizumab) has been associated with an increased risk of progressive multifocal leukoencephalopathy (PML). PML can cause disability or death (see Warnings and Precautions, Immune; Contraindications; Adverse Reactions).**
- **Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom that may be suggestive of PML. TYSABRI dosing should be withheld immediately at the first sign or symptom suggestive of PML.**

General

Before initiation of treatment with TYSABRI™ (natalizumab), a recent magnetic resonance image (MRI) should be available. This MRI may be helpful in differentiating subsequent MS symptoms from PML. For diagnosis of PML, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended (see Warnings and Precautions, Immune).

Patients who are prescribed TYSABRI should enroll in the Tysabri Care Program™ – a registry of Canadian patients. This program ensures that appropriate physicians and infusion centres are able to prescribe or infuse the product.

TYSABRI has been associated with hypersensitivity reactions, which occurred at an incidence of 4%, including serious systemic reactions (e.g., anaphylaxis), which occurred at an incidence of < 1%. These reactions usually occurred within 2 hours of the start of the infusion. Symptoms associated with these reactions included urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea and chest pain. Generally, these reactions are associated with antibodies to TYSABRI. If a hypersensitivity reaction occurs, discontinue administration of TYSABRI immediately and initiate appropriate therapy.

Although not seen in clinical trials with TYSABRI, there is a potential for aggravation of infection or latent infection becoming activated in patients receiving TYSABRI. In clinical trials, most patients did not interrupt treatment with TYSABRI during an infection (see Adverse Reactions, Infections).

Carcinogenesis and Mutagenesis

No clastogenic or mutagenic effects of natalizumab were observed in the Ames human chromosomal aberration assays. Natalizumab showed no effects on in vitro assays of α4-integrin-positive human tumour line proliferation/cytotoxicity. Xenograft transplantation models in SCID and nude mice with two α4-integrin-positive human tumour lines (leukemia,melanoma) demonstrated no increase in tumour growth rates or metastasis resulting from natalizumab treatment.

Hematologic

TYSABRI induces increases in circulating lymphocytes, monocytes, eosinophils and nucleated red blood cells. During phase 3 clinical trials, cell counts were measured every 12 weeks. The largest cell increases were seen in lymphocytes, which were found to be elevated within 12 weeks after initiating TYSABRI treatment, reaching a plateau by 24 weeks. Although elevated, mean cell counts remained within the normal range. Observed increases persist during TYSABRI exposure, but are reversible, returning to baseline levels usually within 16 weeks after the last dose. Elevations of neutrophils were not observed. TYSABRI also induces mild decreases in hemoglobin levels that are frequently transient. These observations were not associated with clinical symptoms; therefore routine blood monitoring is not required.

Immune

Progressive Multifocal Leukoencephalopathy: Use of TYSABRI has been associated with an increased risk of progressive multifocal leukoencephalopathy (PML). PML can cause severe disability or death.

Cases of PML included patients who were treated with TYSABRI for over 2 years or who received intermittent doses of TYSABRI over an 18-month period. In clinical trials, two cases of PML were observed in 1869 patients with multiple sclerosis treated for a median of 120 weeks; the third case occurred among 1043 patients with Crohn's disease after the patient received 8 doses. These patients were concomitantly exposed to immunomodulators (e.g., interferon beta) or were immunocompromised due to treatment with immunosuppressants (e.g., azathioprine).

The absolute risk for PML in patients treated with TYSABRI cannot be precisely estimated and factors that might increase an individual patient's risk for PML have not been identified. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of TYSABRI will mitigate the disease. There is limited experience beyond 2 years of treatment. The relationship between the risk of PML and the duration of treatment is unknown.

It is unclear whether the risk of PML is increased in MS patients treated with TYSABRI in combination with interferon beta compared to TYSABRI alone. Until more is known, TYSABRI should not be used in combination with other immunosuppressive or immunomodulatory agents, regardless of their class.

Short courses of corticosteroids can be used in combination with TYSABRI. In phase 3 MS clinical trials, concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection in patients treated with TYSABRI as compared with those on placebo.

Healthcare professionals should be alert to any new signs or symptoms that may be suggestive of PML. TYSABRI should be suspended immediately at the first signs or symptoms suggestive of PML and an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain should be performed. Cerebrospinal fluid analysis for JC viral DNA may also be useful to confirm a diagnosis of PML. Pretreatment investigations (e.g., magnetic resonance imaging) may be helpful in the evaluation of patients who may develop signs or symptoms suggestive of PML.

Immunosuppression: The safety and efficacy of TYSABRI in combination with antineoplastic or immunosuppressive agents have not been established. Concurrent use of these agents with TYSABRI may increase the risk of infections, including opportunistic infections. In clinical studies for conditions other than MS, opportunistic infections (e.g., pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellulare, bronchopulmonary aspergillosis and burkholderia cepacia) have been uncommonly observed in patients receiving TYSABRI; some of these patients were receiving concurrent immunosuppressants (see Adverse Reactions). In pivotal clinical trials (1801 and 1802), concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection in patients treated with TYSABRI as compared with placebo.

Immunizations: No data are available on the effects of vaccination in patients receiving TYSABRI. Similarly, no data are available on the secondary transmission of infection by live vaccines in patients receiving TYSABRI.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies of TYSABRI therapy in pregnant women. In premarketing clinical trials, the extent of exposure is very limited. Because animal reproduction studies are not always predictive of human response, this drug should only be used during pregnancy if clearly needed. If a woman becomes pregnant while taking TYSABRI, discontinuation of TYSABRI should be considered.

In reproductive studies in monkeys and guinea pigs, there was no evidence of teratogenic effects or effects on survival or growth of offspring at doses up to 30 mg/kg (7 times the human clinical dose based on body weight comparison). In one of five studies that exposed monkeys or guinea pigs during pregnancy, the number of abortions in treated (30 mg/kg) monkeys was 33% vs. 17% in controls. No effects on abortion rates were noted in any other study. A study in pregnant cynomolgus monkeys treated at 2.3-fold the clinical dose demonstrated natalizumab-related changes in the fetus. These changes included mild anemia, reduced platelet count, increased spleen weights, and reduced liver and thymus weights associated with increased splenic extramedullary hematopoiesis, thymic atrophy and decreased hepatic hematopoiesis. In offspring born to mothers treated with natalizumab at 7-fold the clinical dose, platelet counts were also reduced. This effect was reversed upon clearance of natalizumab. There was no evidence of anemia in these offspring.

Nursing Women: It is unknown if natalizumab is excreted in human milk. Because many drugs are excreted in human milk and the potential for serious adverse reactions is unknown, discontinuation of nursing or TYSABRI should be considered.

Pediatrics (< 18 years): Safety and effectiveness of TYSABRI in pediatric MS patients have not been studied.

Geriatrics (> 65 years): Clinical studies of TYSABRI did not include sufficient numbers of patients to determine whether they respond differently than younger patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Serious adverse drug reactions most frequently reported during treatment with TYSABRI™ (natalizumab) in clinical trials were infections (3.2% vs. 2.6% placebo, including urinary tract infection [0.8% vs. 0.3%] and pneumonia [0.6% vs. 0%]); acute hypersensitivity reactions (1.1% vs. 0.3%, including anaphylaxis/anaphylactoid reaction [0.8% vs. 0%]); depression (1.0% vs. 1.0%, including suicidal ideation [0.6% vs. 0.3%]); and cholelithiasis (1.0% vs. 0.3%) (see Warnings and Precautions, Immune).

The most frequently reported adverse events leading to discontinuation of TYSABRI therapy were urticaria (1%) and other hypersensitivity reactions (1%) (see Warnings and Precautions, General).

In clinical trials, cases of PML have been reported. PML can cause severe disability or death. Two cases occurred in MS patients who were being treated with concomitant interferon beta-1a for more than 2 years. One patient in other clinical trials who had a long history of treatment with immunosuppressants and associated leucopenia also developed PML (see Warnings and Precautions, Immune).

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.

Summary Listing of Adverse Events: In placebo-controlled trials in 1617 patients with multiple sclerosis treated with TYSABRI, the incidence of common events was balanced between the TYSABRI-treated patients and those who received placebo. Adverse events leading to discontinuation of therapy occurred in 5.8% of patients receiving TYSABRI and in 4.8% of patients receiving placebo. Events are listed in Table 1 by body system and frequency of occurrence in the TYSABRI group.

Table 1: All Adverse Events in Placebo-Controlled Studies of MS Occurring with Incidence ≥ 1.0% in TYSABRI Group and >0.5% in TYSABRI Group Than Placebo Group

System Organ Class	Preferred Term	Placebo (n = 1135)	TYSABRI (n = 1617)
Infections and infestations			
	Influenza	146 (12.9%)	225 (13.9%)
	Sinusitis	122 (10.7%)	184 (11.4%)
	Upper respiratory tract infection viral	88 (7.8%)	134 (8.3%)
	Pharyngitis	59 (5.2%)	125 (7.7%)
	Gastroenteritis	21 (1.9%)	56 (3.5%)
	Tonsillitis	23 (2.0%)	51 (3.2%)
	Bladder infection	16 (1.4%)	38 (2.4%)
	Herpes zoster	16 (1.4%)	33 (2.0%)
	Respiratory tract infection	15 (1.3%)	30 (1.9%)
	Gingival infection	6 (0.5%)	18 (1.1%)
Blood and lymphatic system disorders			
	Anemia	14 (1.2%)	30 (1.9%)
Immune system disorders			
	Seasonal allergy	35 (3.1%)	58 (3.6%)
Psychiatric disorders	Depressed mood	16 (1.4%)	37 (2.3%)
Nervous system disorders			
	Headache	436 (38.4%)	634 (39.2%)
	Dysesthesia	23 (2.0%)	42 (2.6%)
	Sinus headache	19 (1.7%)	38 (2.4%)
Cardiac disorders	Tachycardia	9 (0.8%)	23 (1.4%)
Vascular disorders	Hematoma	6 (0.5%)	17 (1.1%)
Respiratory, thoracic and mediastinal disorders			
	Cough	81 (7.1%)	130 (8.0%)
	Sinus congestion	22 (1.9%)	51 (3.2%)
	Epistaxis	13 (1.1%)	28 (1.7%)
Gastrointestinal disorders			
	Abdominal pain	43 (3.8%)	75 (4.6%)
Musculoskeletal and connective tissue disorders			
	Muscle cramp	42 (3.7%)	82 (5.1%)
	Joint swelling	13 (1.1%)	32 (2.0%)
Reproductive system and breast disorders			
	Menstruation irregular	12 (1.1%)	37 (2.3%)
General disorders and administration site conditions			
	Fatigue	305 (26.9%)	445 (27.5%)
	Edema peripheral	25 (2.2%)	62 (3.8%)
	Chest pain	35 (3.1%)	58 (3.6%)
	Rigors	12 (1.1%)	55 (3.4%)
	Weight decreased	11 (1.0%)	27 (1.7%)
Injury, poisoning, procedural complications			
	Limb injury	20 (1.8%)	38 (2.4%)
	Thermal burn	12 (1.1%)	29 (1.8%)

Additional Information

Hypersensitivity: The incidence of hypersensitivity reactions was based on the investigator assessment that the event was urticaria or an allergic reaction, which may have included terms such as urticaria, itch, flushing, hypersensitivity or anaphylactoid reaction. In controlled clinical trials in MS patients, hypersensitivity reactions occurred in up to 4% of patients. Serious systemic hypersensitivity reactions (e.g., anaphylactic/anaphylactoid) occurred in < 1% (study 1801: 5/627) of MS patients. Hypersensitivity reactions usually occurred within two hours of the start of the infusion.

Immunogenicity: Persistent anti-natalizumab antibodies (detected on two occasions at least 6 weeks apart) were associated with decreased efficacy of TYSABRI and an increased incidence of hypersensitivity reactions. The majority of patients who became persistently antibody-positive had developed antibodies by 12 weeks.

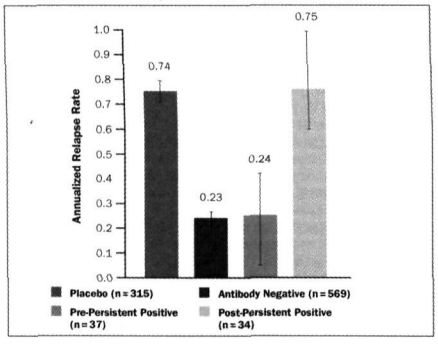
In controlled clinical trials in MS patients, persistent anti-natalizumab antibodies developed in approximately 6% of patients. Antibodies were detected on only one occasion in 4% of patients. Additional infusion-related reactions associated with persistent antibodies included rigors, nausea, vomiting and flushing. Approximately 90% of patients who became persistently antibody-positive in 2-year clinical trials had developed antibodies by 12 weeks.

If, after 3 months of TYSABRI treatment, the presence of persistent antibodies is suspected, antibody testing should be performed. Antibodies may be detected and confirmed with sequential serum antibody tests. Antibodies detected early in the treatment course (e.g., within 6 months) may

be transient and disappear with continued dosing. Repeat testing between 6 weeks and 3 months after the initial positive result is recommended in patients in whom antibodies are detected to confirm that antibodies are persistent. In the presence of persistent antibodies, discontinuation of treatment with TYSABRI should be considered (see Figure 1).

Information regarding the availability and location of testing laboratories may be obtained by contacting Biogen Idec Canada at 1-888-827-2827.

Figure 1: Subject Relapse Rate Prior to and After Antibody Detection – Persistent Positives – Study 1801



Infections: In controlled clinical trials in MS patients, the rate of infection was approximately 1.5 per patient year in both TYSABRI- and placebo-treated patients. The nature of the infections was generally similar in TYSABRI- and placebo-treated patients. The majority of patients did not interrupt TYSABRI therapy during infections, and recovery occurred with appropriate treatment.

In clinical trials, cases of PML have been reported (see Warnings and Precautions, Immune; Adverse Drug Reaction Overview).

In other clinical trials, cases of opportunistic infections have been reported. While a causal role for natalizumab cannot be excluded, it is reasonable to conclude that comorbidities and concomitant medications played an important role in these infections. Should a serious opportunistic infection develop, TYSABRI therapy should be withheld until the infection has been successfully treated (see Warnings and Precautions, Immunosuppression).

Infusion-Related Reactions: An infusion-related reaction was defined in clinical trials as any adverse event occurring within 2 hours of the start of an infusion. These events occurred in 23.1% of MS patients treated with TYSABRI (18.7% placebo). Events reported more commonly with TYSABRI than with placebo included headache, dizziness, fatigue, urticaria, pruritus and rigors.

Malignancies: No differences in incidence rates or the nature of malignancies between TYSABRI- and placebo-treated patients were observed over 2 years of treatment. Should a malignancy develop, TYSABRI therapy should be withheld at least until appropriate treatment has been initiated for the malignancy and the benefit and risks of resuming TYSABRI therapy have been deemed to be acceptable by the treating physician.

Less Common Clinical Trial Adverse Drug Reactions

The incidence of adverse drug reactions experienced by < 1% of subjects in natalizumab group and at least 0.1% higher in natalizumab compared to placebo are listed below:

Blood and lymphatic system disorders: Anemia, thrombocytopenia, leukocytosis

Cardiac disorders: Tachycardia, angina pectoris

Ear and labyrinth disorders: Vertigo

Gastrointestinal disorders: Flatulence, upper abdominal pain, abdominal distention, epigastric discomfort

General disorders and administration site conditions: Feeling hot, peripheral edema, lethargy, feeling abnormal, infusion site erythema, pain, thirst, hyperpyrexia, infusion site pruritus

Immune system disorders: Hypersensitivity, anaphylactoid reaction, anaphylactic reaction

Infections and infestations: Pharyngitis, sinusitis, herpes simplex, herpes zoster, rhinitis infective, bronchial infection, gastroenteritis, skin and subcutaneous tissue abscess, furuncle, pharyngitis streptococcal, bladder infection, breast abscess, dermatitis infected, herpes viral infection, oral infection, pharyngitis viral, tooth infection, urinary tract infection

Injury, poisoning and procedural complications: Overdose

Investigations: Aspartate aminotransferase increased, neutrophil count increased, heart rate increased, neutrophil count decreased, white blood cell count increased, blood test abnormal

Musculoskeletal and connective tissue disorders: Myalgia, muscle cramp, muscle spasms, sensation of heaviness, joint stiffness, muscle tightness, muscle weakness

Neoplasms benign, malignant and unspecified (including cysts and polyps): Cyst

Nervous system disorders: Tremor, paresthesia oral, sensory disturbance, paresis, psychomotor hyperactivity, syncope

Psychiatric disorders: Depression, agitation

Reproductive system and breast disorders: Irregular menstruation

Respiratory, thoracic and mediastinal disorders: Cough, sinus congestion, wheezing, throat irritation

Skin and subcutaneous tissue disorders: Erythema, rash pruritic, acne, pruritus, urticaria, dry skin, onychorrhexis, skin irritation

Vascular disorders: Petechiae, poor venous access, thrombophlebitis, vasodilatation

DRUG INTERACTIONS

Drug-Drug Interactions

If a decision is made to stop treatment with TYSABRI,™ the physician needs to be aware that TYSABRI has pharmacodynamic effects (e.g., increased lymphocyte counts) for approximately 12 weeks following the last dose. For drugs such as interferon and glatiramer acetate, concomitant exposure of this duration was not associated with safety risks in clinical trials. This should be carefully considered on a case-by-case basis and a washout period of TYSABRI might be appropriate.

Should TYSABRI therapy be administered after treatment with another immunosuppressive drug, physicians should consider the half-life of the drug and the potential for persistent immunosuppressive effects of these products when considering if a washout period is needed and, if so, its duration.

TYSABRI should not be diluted with anything other than 0.9% Sodium Chloride Injection, USP.

Drug-Food Interactions

No information is available.

Drug-Laboratory Interactions

TYSABRI induces increases in circulating lymphocytes, monocytes, eosinophils and nucleated red blood cells. Observed increases persist during TYSABRI exposure, but are reversible, returning to baseline levels usually within 16 weeks after the last dose. Elevations of neutrophils are not observed.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- TYSABRI™ (natalizumab) should be administered by a healthcare professional.
- Patients should be observed during the infusion and for 1 hour after the infusion is complete for signs and symptoms of infusion reactions. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction.
- Dilute only with 0.9% Sodium Chloride Injection, USP.

Recommended Dose and Dosage Adjustment

The recommended dose of TYSABRI is 300 mg IV infusion every 4 weeks. Do not administer TYSABRI as an IV push or bolus injection.

Administration

Dilution:

Parenteral Products:

Use aseptic technique when preparing TYSABRI solution for IV infusion. Each vial contains a single dose and is intended for single patient use only.

TYSABRI is a colourless, clear to slightly opalescent concentrate. Inspect the TYSABRI vial for particulate material prior to dilution and administration. If visible particulates are observed and/or the liquid in the vial is discoloured, the vial must not be used. Do not use TYSABRI beyond the expiration date on the carton or vial.

To prepare the solution, withdraw 15 mL of TYSABRI concentrate from the vial using a sterile needle and syringe. Inject the concentrate into 100 mL 0.9% Sodium Chloride Injection, USP. No other IV diluents may be used to prepare the TYSABRI solution.

Gently invert the TYSABRI solution to mix completely. Do not shake. Inspect for particulate material prior to administration.

Following dilution, intravenously infuse TYSABRI solution. If immediate infusion is not possible, store the diluted solution at 2°C to 8°C. If stored at 2°C to 8°C, allow the solution to warm to room temperature prior to infusion and complete the infusion within 8 hours of dilution. DO NOT FREEZE.

Vial Size
15 mL
Volume of Diluent to be Mixed with Concentrate
100 mL 0.9% Sodium Chloride Injection, USP
Approximate Volume for Infusion
115 mL
Diluted Solution Concentration
2.6 mg

Infuse over approximately 1 hour. Observe patients during the infusion and for 1 hour after the infusion is completed for signs and symptoms of infusion reactions.

After the infusion is complete, flush with 0.9% Sodium Chloride Injection, USP. Other medications should not be injected into infusion set side ports or mixed with TYSABRI.

OVERDOSAGE

Safety of doses higher than 300 mg has not been adequately evaluated. The maximum amount of TYSABRI™ (natalizumab) that can be safely administered has not been determined.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TYSABRI™ (natalizumab) is a selective adhesion molecule (SAM) inhibitor and binds to the α4-subunit of human integrin, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils.

Specifically, natalizumab binds to the α4β1-integrin blocking the interaction with its cognate receptor, vascular cell adhesion molecule-1 (VCAM-1), and additional ligands such as osteopontin, and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). Natalizumab blocks the interaction of α4β7-integrin with the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site, and inhibit further recruitment of immune cells into inflamed tissues.

In multiple sclerosis (MS), lesions are believed to occur when activated inflammatory cells, including T-lymphocytes, cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and endothelial cells of the vessel wall. The interaction between α4β1 and its targets is an important component of pathological inflammation in the brain, and disruption of these interactions leads to reduced inflammation. Under normal conditions, VCAM-1 is not expressed in the brain parenchyma. However, in the presence of pro-inflammatory cytokines, VCAM-1 is upregulated on endothelial cells, and possibly on glial cells near the sites of inflammation. In the setting of central nervous system (CNS) inflammation in MS, it is the interaction of α4β1 with VCAM-1, CS-1 and osteopontin that mediates the firm adhesion and transmigration of leukocytes into the brain parenchyma, and may perpetuate the inflammatory cascade in CNS tissue. Blockade of the molecular interactions of α4β1 with its targets reduces inflammatory activity present in the brain in MS and inhibits further recruitment of immune cells into inflamed tissue, thus reducing the formation or enlargement of MS lesions.

Pharmacodynamics

Treatment with TYSABRI (natalizumab) led to an increase in circulating white blood cells and total lymphocytes that was maintained throughout the treatment period. This is due to the ability of natalizumab to inhibit adhesion of leukocytes to endothelial cells and diminish transmigration of these cells from the vascular space into inflamed tissues. These increases were not clinically significant and once treatment was discontinued, counts returned to baseline levels. Consistent with the mechanism of action of natalizumab and the lack of α4 on the surface of this cell type, there was no change in the number of circulating neutrophils.

Pharmacokinetics

Pharmacokinetic values determined after a single 300 mg dose of TYSABRI in healthy subjects are provided in Table 2. Similar values observed in MS patients after a single dose and after 6 months of dosing as monotherapy are given in Table 3. Some accumulation occurs over the 6-month dosing period.

Table 2: Pharmacokinetic Parameters, Single-Dose 300 mg Natalizumab as Intravenous Infusion of 60 minutes

Median Values of Parameter	Study 1805	Study 1806
AUCτ (μg/mL *hr)	19900	21500
C_{max} (μg/mL)	110	94
T_{max} (hrs)	2.98	3.00
$t_{1/2}$ (hr)	224	249
Vdis (mL/kg)	66.6	67.4
CL (mL/hr/kg)	0.212	0.179

Table 3: Summary of Pharmacokinetic Parameters Following 60-Minute 300 mg Natalizumab Infusions Given Monthly in MS Patients (Mean +/- s.d.)

Dose Number	Study	C_{max} (μg/mL)	Minimum (Trough) Conc. (μg/mL)	AUC(last) (μg x hr/mL)	Vd (mL/kg)	CL (mL/hr/kg)	$t_{1/2}$ (hr)
1	C-1801	84.8 ± 22.3	none	17884 ± 9165	77 ± 36	0.23 ± 0.09	249 ± 105
6	C-1801	94.7 ± 34.2	21.3 ± 15.3*	19609 ± 5701	81 ± 43	0.22 ± 0.06	265 ± 98

* Representative of concentration at the end of 6-months dosing (24-week measurement).

Special Populations and Conditions:

Pediatrics: The pharmacokinetics of TYSABRI in pediatric MS patients have not been studied.

Geriatrics: The pharmacokinetics of TYSABRI in MS patients over 65 years of age have not been established.

Hepatic insufficiency: The pharmacokinetics of TYSABRI in patients with hepatic insufficiency have not been studied.

Renal insufficiency: The pharmacokinetics of TYSABRI in patients with renal insufficiency have not been studied.

Gender: Results of a population pharmacokinetics study demonstrated that gender did not influence natalizumab pharmacokinetics.

Race: The effects of race on the pharmacokinetics of TYSABRI have not been studied.

Duration of Effect:

TYSABRI has pharmacodynamic effects (e.g., increased lymphocyte counts) for approximately 12 weeks following the last dose.

STORAGE AND STABILITY

TYSABRI™ (natalizumab) single-use vials must be stored in a refrigerator between 2°C to 8°C. Do not use beyond the expiration date on the carton and vial label. Do not shake or freeze. Protect from light.

If not used immediately, store the TYSABRI solution for infusion at 2°C to 8°C. The administration of TYSABRI solution for infusion must be completed within 8 hours of dilution.

SPECIAL HANDLING INSTRUCTIONS

TYSABRI™ (natalizumab) is for single use only. One vial of TYSABRI should be diluted only with 0.9% Sodium Chloride Injection, USP before use.

Any unused product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TYSABRI™ (natalizumab) concentrate is supplied as 300 mg natalizumab in a sterile, single-use vial free of preservatives.

Each 15 mL dose also contains (pH 6.1):
123 mg sodium chloride, USP/Ph.Eur
17.0 mg sodium phosphate, monobasic, monohydrate, USP
7.24 mg sodium phosphate, dibasic, heptahydrate, USP
3.0 mg polysorbate 80, USP/NF/Ph.Eur
Water for Injection, USP/Ph.Eur

Each package contains one vial.

Product Monograph available on request.

biogen idec™ élan

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See A-8, A-9, A-10, A-11

℞ LYRICA® PREGABALIN

SUMMARY PRODUCT

Classification Analgesic Agent

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsules, 25 mg, 50 mg, 75 mg, 150 mg, 300 mg	Lactose monohydrate *For a complete listing, see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Adults: LYRICA (pregabalin) is indicated for the management of neuropathic pain associated with: • Diabetic peripheral neuropathy and • Postherpetic neuralgia ***Geriatrics (>65 years of age):*** Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see **WARNINGS AND PRECAUTIONS,** *Geriatrics (>65 years of age)*). ***Pediatrics (<18 years of age):*** The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established and its use in this patient population is not recommended (see **WARNINGS AND PRECAUTIONS,** *Pediatrics*).

CONTRAINDICATIONS

Patients who are hypersensitive to pregabalin or to any ingredient in the formulation or component of the container.

WARNINGS AND PRECAUTIONS

Tumorigenic Potential In standard preclinical in vivo lifetime carcinogenicity studies of pregabalin, a high incidence of hemangiosarcoma was identified in two different strains of mice (see **Preclinical Toxicology**). The clinical significance of this finding is uncertain. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans. In clinical studies across various patient populations, comprising 6396 patient-years of exposure in 8666 patients ranging in age from 12 to 100 years, new or worsening-preexisting tumors were reported in 57 patients. The most common malignant tumor diagnosed was skin carcinoma (17 patients) followed by breast *carcinoma (8 patients), prostatic carcinoma (6 patients), carcinoma not otherwise* specified (6 patients) and bladder carcinoma (4 patients). Without knowledge of the background incidence and recurrence in similar populations not treated with LYRICA (pregabalin), it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment. **Ophthalmological Effects** In controlled studies, pregabalin treatment was associated with vision-related adverse events such as blurred vision (amblyopia) (6% pregabalin and 2% placebo) and diplopia (2% pregabalin and 0.5% placebo). Approximately 1% of pregabalin-treated patients discontinued treatment due to vision-related adverse events (primarily blurred vision). Of the patients who did not withdraw, the blurred vision resolved with continued dosing in approximately half of the cases (see **Post-Marketing Adverse Drug Reactions**). Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated, and 2% of placebo-treated patients. At this time, clinical significance of the ophthalmologic findings is unknown. Patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment, including discontinuation of pregabalin, should be considered. More frequent assessments should be considered for patients who are already routinely monitored for ocular conditions. **Peripheral Edema** In controlled clinical trials pregabalin treatment caused peripheral edema in 6% of patients (336/5508) compared with 2% of patients (42/2384) in the placebo group. In these studies, 0.5% (28/5508) of pregabalin patients and 0.2% (4/2384) of placebo patients withdrew due to peripheral edema (see **ADVERSE REACTIONS**, *Peripheral Edema*). In controlled clinical trials of up to 13 weeks in duration of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. In the same trials, peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function. Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA (pregabalin) and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with pregabalin only, and 19% (23/120) of patients who were on both pregabalin and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on pregabalin only; and 7.5% (9/120) of patients on both drugs. As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering LYRICA and these agents. Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, LYRICA should be used with caution in these patients. **Weight Gain** Pregabalin treatment was associated with weight gain. In pregabalin controlled clinical trials of up to 13 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin-treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.2%) withdrew from controlled trials due to weight gain (see **ADVERSE REACTIONS**, *Weight Gain*). Pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender or age. Weight gain was not limited to patients with edema (see **WARNINGS AND PRECAUTIONS, Peripheral Edema**). Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown. Among diabetic patients, pregabalin-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg. While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1c}). **Dizziness and Somnolence** In controlled neuropathic pain studies, pregabalin caused dizziness in 23% of patients (424/1831) compared to 7% in placebo (58/857). Somnolence was experienced by 14% (256/1831) and 4% (33/857) of the patients treated with pregabalin and placebo, respectively. These events begin shortly after the initiation of therapy and generally occur more frequently at higher doses. In these studies, dizziness and somnolence led to withdrawal of 3.5% and 2.6% of the pregabalin-treated patients, respectively. For the remaining patients (359 and 208, respectively) who experienced these events, dizziness and somnolence persisted until the last dose of pregabalin in 43% and 58% of the patients, respectively (see **ADVERSE REACTIONS**, Tables 2 and 4, and **Post-Marketing Adverse Drug Reactions**). Accordingly, patients should be advised not to drive or operate complex machinery or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental and/or motor performance adversely (see **CONSUMER INFORMATION**). **Abrupt or Rapid Discontinuation** Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache and diarrhea. Pregabalin should be tapered gradually over a minimum of one week rather than discontinued abruptly (see **ADVERSE REACTIONS**, *Adverse Events Following Abrupt or Rapid Discontinuation*). **Sexual Function/Reproduction** Impairment of Male Fertility Preclinical Data In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3-4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. In addition, adverse effects on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD. In a fertility study in which female rats were given pregabalin (500, 1250 or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established. The clinical significance of female fertility findings in animals is unknown. Human Data In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin 600 mg/day for 3 months (one complete sperm cycle). Pregabalin did not exhibit significant detrimental effects on the reproductive function of healthy male subjects, as measured by semen analysis, when compared with placebo (n=16). However, due to the small sample size and short-term exposure to pregabalin (only one complete sperm cycle), no conclusions can be made regarding possible reproductive effects of pregabalin during long-term exposure. Effects on other male reproductive parameters in humans have not been adequately studied. **Special Populations** *Renal* Because pregabalin is eliminated primarily by renal excretion, *the dose of pregabalin should be adjusted as noted for elderly patients with* renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**). *Adjustment of Dose in Renally-Impaired Patients* In patients with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Table in **DOSAGE AND ADMINISTRATION, Dosing Considerations**). **Preclinical Data** Pregabalin was not teratogenic in mice, rats or rabbits. Pregabalin induced fetal toxicity in rats and rabbits at ≥39 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day [$AUC_{(0-24)}$ of 123 µg•hr/mL]. In the prenatal-postnatal toxicity study, pregabalin induced offspring developmental toxicity in rats at ≥5 times the maximum recommended human exposure. No developmental effects occurred at 2 times the maximum recommended human exposure (see **PRODUCT MONOGRAPH**). **Human Data** *Pregnant Women* There are no adequate and well-controlled studies in pregnant women. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Labour and Delivery* The effects of pregabalin on labour and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥47 times the mean human exposure [$AUC_{(0-24)}$ of 123 µg•hr/mL] at the maximum recommended clinical dose of 600 mg/day (see **PRODUCT MONOGRAPH**). *Nursing Women* It is not known if pregabalin is excreted in human breast milk; however, it is present in the milk of rats. Because of the potential for adverse reactions in nursing infants from pregabalin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see **PRODUCT MONOGRAPH**). *Pediatrics (<18 years of age)* The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established. *Geriatrics (>65 years of age)* Of the 1831 patients who received pregabalin in neuropathic pain studies, 528 were 65 to 74 years of age, and 452 were 75 years of age or older. No significant differences in efficacy were observed between these patients and younger patients. Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function. In general, the incidence of adverse events did not increase with age. *Creatine Kinase Elevations* Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin-treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur. *Laboratory Changes, Decreased Platelet Count* Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of 20 x 10^3/µL, compared to 11 x 10^3/µL in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and <150 x 10^3/µL. In randomized controlled trials, pregabalin was not associated with an increase in bleeding related adverse events. *ECG Changes, PR Interval Prolongation* Pregabalin treatment was associated with mild PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3-6 msec at pregabalin doses ≥300 mg/day. This mean change difference was not associated with an increased risk of PR increase ≥25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse events of second or third degree AV block. *Information for Patients* **Dizziness and Somnolence** Patients should be counseled that LYRICA (pregabalin) may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental, visual and/or motor performance adversely. **Visual Disturbances** Patients should be counseled that LYRICA may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician (see **WARNINGS AND PRECAUTIONS, Ophthalmologic Effects**). **Abrupt or Rapid Discontinuation** Patients should be advised to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache or diarrhea. **Edema and Weight Gain** Patients should be counseled that LYRICA may cause edema and weight gain. Patients should be advised that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure. **Muscle Pain, Tenderness or Weakness** Patients should be instructed to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Concomitant Treatment with CNS Depressants, Alcohol** Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence. Patients should be told to avoid consuming alcohol while taking LYRICA, as LYRICA may potentiate the impairment of motor skills and sedation of alcohol. **Pregnant Woman** Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast-feeding or intend to breast-feed during therapy. **Animal Studies in Male Reproduction** In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity (see **WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction**). The clinical significance of this finding is uncertain; however, men being treated with LYRICA who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. **Skin** Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with LYRICA. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with LYRICA was observed in clinical trials (see **PRODUCT MONOGRAPH**). Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LYRICA. **Preclinical Toxicology** *Carcinogenesis* A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000 or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. In an investigative study in female B6C3F1 mice, chronic treatment (24 months) with pregabalin at 1000 mg/kg caused an increased incidence of hemangiosarcoma, consistent with previous studies, but not at 50 or 200 mg/kg. Discontinuation of treatment after 12 months at 1000 mg/kg did not significantly reduce the incidence of hemangiosarcoma at 24 months. Evidence of carcinogenicity was not seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150 or 450 mg/kg in males and 100, 300 or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD. The clinical significance in humans of this finding in mice is unknown. *Mutagenesis* Pregabalin is not genotoxic based on results of a battery of in vitro and in vivo tests. Pregabalin was not mutagenic in bacteria or in mammalian cells in vitro, was not clastogenic in mammalian systems in vitro and in vivo, and did *not induce unscheduled DNA synthesis in mouse or rat hepatocytes.* ***Dermatopathy*** Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies. **Ocular lesions** Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) ≥2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year. The clinical significance of this finding in rats is unknown. **Monitoring and Laboratory Tests** Routine therapeutic drug monitoring or clinical laboratory testing is not required for patients treated with LYRICA (pregabalin) (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview **Clinical Trial Adverse Drug Reactions** In all controlled and uncontrolled trials, more than 8666 patients have received LYRICA (pregabalin), with 83% of exposure at dosages of 300 mg/day or above and 32% at dosages of 600 mg/day or higher. Approximately 4010 patients had at least 6 months of exposure, 2415 had at least 1 year of exposure, and 939 had at least 2 years of exposure to pregabalin. In controlled trials, 1831 patients with neuropathic pain received pregabalin. *Most Common Adverse Events in All Controlled Clinical Studies of Neuropathic Pain* The most commonly observed adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: dizziness, somnolence, peripheral edema and dry mouth. Adverse events were usually mild to moderate in intensity. *Discontinuation Due to Adverse Events* In all controlled studies, the discontinuation rate due to adverse events was 14% *for patients receiving pregabalin and 7% for patients receiving placebo. The most* common reasons for discontinuation due to adverse events (≥2%) in the pregabalin treatment groups were dizziness and somnolence. Other adverse events that led to withdrawal more frequently in the pregabalin group than the placebo group were ataxia (1%) and asthenia, confusion, headache and nausea (<1% each). In controlled neuropathic pain studies, the discontinuation rate due to adverse events was 11% for pregabalin and 5% for placebo. The most common reasons for discontinuation due to adverse events (≥2%) in the pregabalin treatment groups were dizziness and somnolence. Other adverse events that led to withdrawal more frequently in the pregabalin group than the placebo group were confusion (1%) and asthenia, peripheral edema and ataxia (<1% each). *Incidence of Adverse Events in Controlled Clinical Studies of Neuropathic Pain* In summaries of adverse events, investigator's terms for individual adverse events have been grouped into a smaller number of standardized categories using the COSTART IV dictionary. The prescriber should be aware that the percentages in Table 1 through Table 6 cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied. *Adverse Events From Controlled Clinical Studies of Neuropathic Pain* Diabetic Peripheral Neuropathy Table 1 lists all adverse events, regardless of causality, occurring in ≥2% of patients with neuropathic pain associated with diabetic peripheral neuropathy receiving pregabalin for at least one of the pregabalin groups, and for which the incidence was greater than in the placebo group. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of mild or moderate. In these studies, 979 patients received pregabalin and 459 patients received placebo for up to 13 weeks.

Table 1. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-*Controlled Studies in Neuropathic Pain Associated with Diabetic* Peripheral Neuropathy (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

		Pregabalin (mg/day)			
Body System Preferred Term	Placebo (n = 459) %	75 (n = 77) %	150 (n = 212) %	300 (n = 321) %	600 (n = 369) %
Body as a whole					
Infection	6.1	3.9	7.5	8.4	4.6

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Body System Preferred Term	Placebo (n = 459) %	Pregabalin (mg/day) 75 (n = 77) %	150 (n = 212) %	300 (n = 321) %	600 (n = 369) %
Asthenia	2.4	3.9	1.9	4.4	7.3
Pain	3.9	5.2	4.2	2.5	4.9
Accidental injury	2.8	5.2	2.4	2.2	5.7
Back pain	0.4	0.0	2.4	1.2	1.9
Chest pain	1.1	3.9	1.4	1.2	1.6
Face edema	0.4	0.0	0.9	0.9	2.2
Digestive system					
Dry mouth	1.1	2.6	1.9	4.7	6.5
Constipation	1.5	0.0	2.4	3.7	6.0
Diarrhea	4.8	5.2	2.8	1.9	3.0
Flatulence	1.3	2.6	0.0	2.2	2.7
Vomiting	1.5	1.3	0.9	2.2	1.1
Hemic and lymphatic system					
Ecchymosis	0.2	2.6	0.5	0.6	0.3
Metabolic and nutritional disorders					
Peripheral edema	2.4	3.9	6.1	9.3	12.5
Weight gain	0.4	0.0	4.2	3.7	6.2
Edema	0.0	0.0	1.9	4.0	1.9
Hypoglycemia	1.1	1.3	3.3	1.6	1.1
Nervous system					
Dizziness	4.6	7.8	9.0	23.1	29.0
Somnolence	2.6	3.9	6.1	13.1	16.3
Neuropathy	3.5	9.1	1.9	2.2	5.4
Ataxia	1.3	6.5	0.9	2.2	4.3
Vertigo	1.1	1.3	1.9	2.5	3.5
Confusion	0.7	0.0	1.4	2.2	3.3
Euphoria	0.0	0.0	0.5	3.4	1.6
Thinking abnormal[a]	0.0	1.3	0.0	0.9	3.0
Abnormal gait	0.0	1.3	0.0	0.6	2.7
Reflexes decreased	1.7	3.9	0.5	1.2	1.4
Amnesia	0.2	2.6	0.9	0.0	2.2
Hypesthesia	0.7	2.6	0.0	0.0	0.8
Hyperalgesia	0.2	2.6	0.0	0.0	0.3
Respiratory system					
Dyspnea	0.7	2.6	0.0	1.9	1.9
Skin and appendages					
Pruritus	1.3	2.6	0.0	0.9	0.0
Special senses					
Blurred vision[b]	1.5	2.6	1.4	2.8	1.5
Conjunctivitis	0.2	2.6	1.4	0.6	0.3

a Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slow thinking.

b Investigator term; summary level term is amblyopia.

Discontinuation in Controlled Clinical Studies of Diabetic Peripheral Neuropathy Approximately 9% of patients receiving pregabalin and 4% receiving placebo discontinued from controlled diabetic peripheral neuropathy studies due to adverse events. The adverse events most commonly leading to discontinuation are presented in Table 2.

Table 2. Adverse Events Most Frequently (≥2% of patients) Leading to Discontinuation in Placebo-Controlled Studies in Patients with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

	Number (%) of Patients				
		Pregabalin (mg/day)			
COSTART Preferred Term	Placebo (n = 459)	75 (n = 77)	150 (n = 212)	300 (n = 321)	600 (n = 369)
Dizziness	2 (0.4)	0 (0.0)	3 (1.4)	6 (1.9)	21 (5.7)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.6)	15 (4.1)

Postherpetic Neuralgia Table 3 lists all adverse events, regardless of causality, occurring in ≥2% of patients with neuropathic pain associated with postherpetic neuralgia receiving pregabalin for at least one of the pregabalin groups, and for which the incidence was greater than in the placebo group. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of mild or moderate. In these studies, 852 patients received pregabalin and 398 patients received placebo for up to 13 weeks.

Table 3. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

Body System Preferred Term	Placebo (n = 398) %	Pregabalin (mg/day) 75 (n = 84) %	150 (n = 302) %	300 (n = 312) %	600 (n = 154) %
Body as a whole					
Infection	3.5	14.3	8.3	6.4	2.6
Headache	5.3	4.8	8.9	4.5	8.4
Pain	3.8	4.8	4.3	5.4	4.5
Asthenia	4.0	3.6	5.0	2.6	5.2
Accidental injury	1.5	3.6	2.6	3.2	5.2
Flu syndrome	1.3	1.2	1.7	2.2	1.3
Face edema	0.8	0.0	1.7	1.3	3.2
Malaise	1.0	2.4	0.3	0.6	0.0
Cardiovascular system					
Vasodilatation	1.3	2.4	1.0	0.6	0.0
Digestive system					
Dry mouth	2.8	7.1	7.0	6.1	14.9
Constipation	2.3	3.6	4.6	5.4	5.2
Diarrhea	4.0	2.4	4.3	3.5	4.5
Flatulence	1.0	2.4	1.3	1.6	3.2
Vomiting	0.8	1.2	0.7	2.9	2.6
Metabolic and nutritional disorders					
Peripheral edema	3.5	0.0	7.9	15.7	16.2
Weight gain	0.3	1.2	1.7	5.4	6.5
Edema	1.3	0.0	1.0	2.2	5.8
Hyperglycemia	0.8	2.4	0.3	0.0	0.0
Nervous system					
Dizziness	9.3	10.7	17.9	31.4	37.0
Somnolence	5.3	8.3	12.3	17.9	24.7
Ataxia	0.5	1.2	2.0	5.4	9.1
Abnormal gait	0.5	0.0	2.0	3.8	7.8
Confusion	0.3	1.2	2.3	2.9	6.5
Thinking abnormal[a]	1.5	0.0	1.7	1.3	5.8
Incoordination	0.0	2.4	1.7	1.3	2.6
Amnesia	0.0	0.0	1.0	1.3	3.9
Speech disorder	0.0	0.0	0.3	1.3	3.2
Insomnia	1.8	0.0	0.7	2.2	0.0
Euphoria	0.0	2.4	0.0	1.3	1.3
Nervousness	0.5	0.0	1.0	0.3	2.6
Tremor	1.5	1.2	0.0	1.0	2.6
Hallucinations	0.0	0.0	0.3	0.3	3.2
Hyperesthesia	0.3	2.4	0.3	0.0	1.3
Respiratory system					
Bronchitis	0.8	0.0	1.3	1.0	2.6
Pharyngitis	0.8	0.0	2.6	0.6	0.6
Rhinitis	1.8	1.2	0.7	0.6	3.2
Skin and appendages					
Rash	3.0	2.4	2.0	2.9	5.2
Special senses					
Blurred vision[b]	2.5	1.2	5.0	5.1	9.1
Diplopia	0.0	0.0	1.7	1.9	3.9
Abnormal vision	0.3	0.0	1.0	1.6	5.2
Urogenital system					
Urinary tract infection	1.5	0.0	2.3	1.6	3.2

a Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slow thinking.

b Investigator term; summary level term is amblyopia.

Discontinuation in Controlled Clinical Studies of Postherpetic Neuralgia Approximately 14% of patients receiving pregabalin and 7% receiving placebo discontinued from controlled postherpetic neuralgia studies due to adverse events. The adverse events most commonly leading to discontinuation are presented in Table 4.

Table 4. Adverse Events Most Frequently (≥2% of patients) Leading to Discontinuation in Placebo-Controlled Studies in Patients with Neuropathic Pain Associated with Postherpetic Neuralgia

	Number (%) of Patients				
		Pregabalin (mg/day)			
COSTART Preferred Term	Placebo (n = 398)	75 (n = 84)	150 (n = 302)	300 (n = 312)	600 (n = 154)
Dizziness	3 (0.8)	0 (0.0)	11 (3.6)	12 (3.8)	12 (7.8)
Somnolence	1 (0.3)	0 (0.0)	6 (2.0)	12 (3.8)	10 (6.5)
Confusion	1 (0.3)	0 (0.0)	2 (0.7)	5 (1.6)	8 (5.2)
Peripheral edema	1 (0.3)	0 (0.0)	2 (0.7)	5 (1.6)	5 (3.2)
Ataxia	0 (0.0)	0 (0.0)	1 (0.3)	5 (1.6)	4 (2.6)
Abnormal gait	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)	4 (2.6)
Hallucinations	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	4 (2.6)
Dry mouth	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.6)

Incidence of Most Common Dose-Related Treatment-Emergent Adverse Events Most common dose-related treatment-emergent adverse events are presented in Table 5 (diabetic peripheral neuropathy) and Table 6 (postherpetic neuralgia).

Table 5. Incidence (%) of Most Common Dose-Related Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Adverse Event Preferred Term	Placebo (n = 459) %	Pregabalin (mg/day) 75 (n = 77) %	150 (n = 212) %	300 (n = 321) %	600 (n = 369) %
Dizziness	4.6	7.8	9.0	23.1	29.0
Somnolence	2.6	3.9	6.1	13.1	16.3
Peripheral edema	2.4	3.9	6.1	9.3	12.5
Asthenia	2.4	3.9	1.9	4.4	7.3
Dry mouth	1.1	2.6	1.9	4.7	6.5
Weight gain	0.4	0.0	4.2	3.7	6.2
Constipation	1.5	0.0	2.4	3.7	6.0
Blurred vision[a]	1.5	2.6	1.4	2.8	5.7

a Investigator term; summary level term is amblyopia.

Table 6. Incidence (%) of Most Common Dose-Related Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Postherpetic Neuralgia

Adverse Event Preferred Term	Placebo (n = 398) %	Pregabalin (mg/day) 75 (n = 84) %	150 (n = 302) %	300 (n = 312) %	600 (n = 154) %
Dizziness	9.3	10.7	17.9	31.4	37.0
Somnolence	5.3	8.3	12.3	17.9	24.7
Peripheral edema	3.5	0.0	7.9	15.7	16.2
Dry mouth	2.8	7.1	7.0	6.1	14.9
Blurred vision[a]	2.5	1.2	5.0	5.1	9.1
Ataxia	0.5	1.2	2.0	5.4	9.1
Weight gain	0.3	1.2	1.7	5.4	6.5
Abnormal gait	0.5	0.0	2.0	3.8	7.8

a Investigator term; summary level term is amblyopia.

Adverse Events Following Abrupt or Rapid Discontinuation Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache and diarrhea. Pregabalin should be tapered gradually over a minimum of one week rather than discontinued abruptly (see **WARNINGS AND PRECAUTIONS, Abrupt or Rapid Discontinuation**). **Drug Abuse and Dependence/Liability** In a study of recreational users (n=15) of sedative/hypnotic drugs, including alcohol, a single dose of LYRICA (pregabalin) 450 mg received subjective ratings of "good drug effect", "high", and "liking" to a degree that was similar to a single dose of diazepam 30 mg. In controlled clinical studies in over 5500 patients, 4% of LYRICA-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse event. However, in clinical trials of diabetic peripheral neuropathy, euphoria was reported as an adverse event by 1.8% of LYRICA-treated patients and 0% of placebo-treated patients, and in clinical trials of postherpetic neuralgia, euphoria was reported as an adverse event by 0.9% of LYRICA-treated patients and 0% of placebo-treated patients. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea suggestive of physical dependence (see **WARNINGS AND PRECAUTIONS, Abrupt or Rapid Discontinuation**). Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behaviour). *Other Events Observed During the Premarketing Evaluation of LYRICA* Following is a list of treatment-emergent adverse events reported during premarketing assessment of LYRICA in clinical trials (over 8600 adult subjects) except those already listed in the previous tables or elsewhere in labeling. In the tabulations that follow, a COSTART-based dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 8600 adult individuals exposed to multiple doses of LYRICA who experienced an event of the type cited on at least 1 occasion while receiving LYRICA. It is important to emphasize that although the events reported occurred during treatment with LYRICA, they were not necessarily caused by it. **Less Common Clinical Trial Adverse Drug Reactions (<2%)** Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body System	Adverse Events
Body as a whole	
Frequent	Flu syndrome, back pain, allergic reaction, fever, generalized edema
Infrequent	Neck pain, neoplasm, cellulitis, cyst, chills, malaise, overdose, moniliasis, hernia, viral infection, photosensitivity reaction, pelvic pain, abdomen enlarged, abscess, neck rigidity, lab test abnormal, drug level increased, carcinoma, sepsis, suicide attempt, reaction unevaluable
Rare	Infection fungal, unexpected benefit, chills and fever, body odor, drug level decreased, halitosis, hangover effect, injection site reaction, hormone level altered, hypothermia, infection bacterial, injection site hemorrhage, intentional overdose, mucous membrane disorder, accidental overdose, adenoma, anaphylactoid reaction, ascites, chest pain substernal, death, sarcoidosis, sudden death, immune system disorder, increased drug effect, injection site pain, Lupus Erythematosus syndrome, medication error, sarcoma, shock, tolerance decreased
Cardiovascular	
Frequent	Hypertension, vasodilatation
Infrequent	Palpitation, migraine, tachycardia, peripheral vascular disorder, electrocardiogram abnormal, cardiovascular disorder, angina pectoris, congestive heart failure, hemorrhage, myocardial infarct, hypotension, postural hypotension, ventricular extrasystoles, atrial fibrillation, coronary artery disorder, bradycardia, cerebrovascular accident, arrhythmia, cerebral ischemia, vascular disorder, sinus bradycardia, myocardial ischemia, bundle branch block, AV block first degree, arteriosclerosis, deep thrombophlebitis, phlebitis, arterial anomaly, heart failure, pulmonary embolus, retinal vascular disorder, varicose vein
Rare	Heart arrest, vascular anomaly, occlusion, supraventricular tachycardia, atrial arrhythmia, atrial flutter, cerebral infarct, coronary occlusion, thrombophlebitis, thrombosis, cardiomegaly, extrasystoles, pallor, AV block, AV block second degree, cardiomyopathy, peripheral gangrene, QT interval prolonged, retinal artery occlusion, supraventricular extrasystoles, cerebral hemorrhage, digitalis intoxication, ventricular arrhythmia, aortic stenosis, bigeminy, cerebrovascular disorder, left heart failure, ventricular tachycardia, AV block complete, carotid occlusion, carotid thrombosis, cor pulmonale, embolus lower extremity, endocarditis, heart block, increased capillary fragility, intracranial aneurysm, nodal tachycardia, QT interval shortened, retinal vein thrombosis, ST elevated, T inverted, vascular headache, vasculitis
Digestive system	
Frequent	Nausea, diarrhea, anorexia, gastrointestinal disorder
Infrequent	Gastroenteritis, tooth disorder, periodontal abscess, colitis, gastritis, liver function tests abnormal, increased salivation, thirst, nausea and vomiting, rectal disorder, gingivitis, dysphagia, stomatitis, mouth ulceration, cholelithiasis, rectal hemorrhage, gastrointestinal hemorrhage, glossitis, tooth caries, abnormal stools, cholecystitis, melena, oral moniliasis, esophagitis, tongue disorder, cheilitis, tongue edema
Rare	Eructation, pancreatitis, stomach ulcer, ulcerative stomatitis, esophageal stenosis, fecal incontinence, gum hemorrhage, intestinal obstruction, enteritis, peptic ulcer, enterocolitis, gum hyperplasia, hepatomegaly, liver fatty deposit, tenesmus, biliary pain, fecal impaction, jaundice, periodontitis, ulcerative colitis, aphthous stomatitis, cholestatic jaundice, gastrointestinal carcinoma, hemorrhagic gastritis, hepatitis, liver tenderness,

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Body System	Adverse Events
	nausea, vomiting and diarrhea, salivary gland enlargement, stomach atony, bloody diarrhea, cardiospasm, duodenal ulcer, gamma glutamyl transpeptidase increased, hematemesis, hepatoma, intestinal perforation, intestinal stenosis, intestinal ulcer, leukoplakia of mouth, necrotizing pancreatitis, pancreas disorder, pseudomembranous colitis, sialadenitis, stomach ulcer hemorrhage, tongue discoloration
Endocrine system	
Infrequent	Diabetes mellitus, hypothyroidism
Rare	Goiter, prolactin increased, thyroid disorder, gonadotropic follicle stim hormone increase, hyperthyroidism, thyroiditis, adrenal insufficiency, parathyroid disorder, thyroid carcinoma, thyroid neoplasia, virilism
Hemic and lymphatic	
Infrequent	Anemia, leukopenia, thrombocytopenia, lymphadenopathy, hypochromic anemia, leukocytosis, eosinophilia
Rare	Lymphocytosis, petechia, iron deficiency anemia, cyanosis, lymphedema, polycythemia, lymphoma like reaction, megaloblastic anemia, splenomegaly, purpura, thrombocythemia, thrombocytopenic purpura, chronic leukemia, coagulation disorder, erythrocytes abnormal, leukemoid reaction, lymphangitis, macrocytic anemia, pancytopenia, prothrombin decreased, rupture of spleen, sedimentation rate increased
Metabolic and nutritional	
Infrequent	Hyperglycemia, SGPT increased, hypoglycemia, hypokalemia, hypercholesteremia, SGOT increased, weight loss, hyperlipemia, amylase increased, hyperuricemia, alkaline phosphatase increased, creatinine increased, hyponatremia, gout, dehydration, BUN increased, healing abnormal
Rare	Hypercalcemia, hyperkalemia, hypocalcemia, bilirubinemia, alcohol intolerance, hypoglycemic reaction, ketosis, calcium disorder, hypochloremia, hypomagnesemia, hypoproteinemia, NPN increased, uremia, acidosis, avitaminosis, enzymatic abnormality, gamma globulins increased, hypernatremia, hypophosphatemia, lactic acidosis, obesity
Musculoskeletal system	
Frequent	Arthralgia, myalgia, arthritis, leg cramps, myasthenia
Infrequent	Tendon disorder, arthrosis, joint disorder, bone disorder, tenosynovitis, bursitis, tendinous contracture, osteoporosis, tendon rupture, bone pain
Rare	Rheumatoid arthritis, osteomyelitis, rhabdomyolysis, myopathy, muscle atrophy, myositis, pyogenic arthritis, bone neoplasm, musculoskeletal congenital anomaly, pathological fracture
Nervous system	
Frequent	Insomnia, anxiety, libido decreased, depersonalization, hypertonia, neuropathy
Infrequent	Reflexes decreased, sleep disorder, abnormal dreams, hostility, hallucinations, hyperkinesia, personality disorder, dysarthria, hyperesthesia, hypokinesia, circumoral paresthesia, libido increased, neuralgia, vestibular disorder, aphasia, movement disorder, hyperalgesia, apathy, hypotonia, convulsion, facial paralysis, psychosis
Rare	Drug dependence, neuritis, paranoid reaction, CNS depression, CNS neoplasia, manic reaction, neurosis, extrapyramidal syndrome, meningitis, hemiplegia, reflexes increased, akathisia, delirium, paralysis, withdrawal syndrome, brain edema, CNS stimulation, dyskinesia, encephalopathy, foot drop, grand mal convulsion, hypalgesia, peripheral neuritis, psychotic depression, addiction, arachnoiditis, cerebellar syndrome, cogwheel rigidity, dementia, dystonia, Guillain-Barre syndrome, intracranial hemorrhage, multiple sclerosis, myelitis, schizophrenic reaction, subarachnoid hemorrhage, torticollis
Respiratory system	
Frequent	Sinusitis, rhinitis, dyspnea, cough increased, pneumonia, lung disorder
Infrequent	Asthma, epistaxis, laryngitis, voice alteration, respiratory disorder, sputum increased
Rare	Apnea, emphysema, aspiration pneumonia, hyperventilation, lung edema, pleural disorder, atelectasis, hemoptysis, hiccup, hypoxia, laryngismus, lung fibrosis, pleural effusion, lung function decreased, pulmonary hypertension, yawn, bronchiectasis, bronchiolitis, carcinoma of lung, hypoventilation, laryngeal neoplasia, nasal septum disorder, pneumothorax
Skin and appendages	
Infrequent	Pruritus, sweating, skin disorder, acne, dry skin, alopecia, skin ulcer, herpes simplex, urticaria, nail disorder, eczema, herpes zoster, skin benign neoplasm, fungal dermatitis, maculopapular rash, vesiculobullous rash, skin carcinoma, furunculosis, skin discoloration, skin hypertrophy, psoriasis, seborrhea, hirsutism
Rare	Skin nodule, angioedema, cutaneous moniliasis, skin atrophy, exfoliative dermatitis, pustular rash, ichthyosis, skin melanoma, subcutaneous nodule, sweating decreased, hair disorder, lichenoid dermatitis, melanosis, miliaria, purpuric rash, skin necrosis, Stevens Johnson syndrome
Special sense	
Frequent	Eye disorder, conjunctivitis, otitis media
Infrequent	Retinal disorder, tinnitus, eye pain, cataract specified, dry eyes, taste perversion, ear pain, lacrimation disorder, ear disorder, deafness, eye hemorrhage, photophobia, glaucoma, vitreous disorder, corneal lesion, otitis externa, refraction disorder, blepharitis, retinal edema, taste loss, abnormality of accommodation
Rare	Hyperacusis, keratitis, mydriasis, parosmia, ptosis, retinal hemorrhage, color blindness, retinal depigmentation, retinal detachment, corneal opacity, corneal ulcer, iritis, night blindness, optic atrophy, retinal degeneration, cataract NOS, scleritis, strabismus, anisocoria, blindness, exophthalmos, keratoconjunctivitis, ophthalmoplegia, papilledema
Urogenital system	
Frequent	Anorgasmia
Infrequent	Urinary frequency, urinary incontinence, cystitis, abnormal ejaculation, urination impaired, dysuria, metrorrhagia, hematuria, vaginal moniliasis, prostatic disorder, vaginitis, dysmenorrhea, urinary urgency, kidney calculus, breast pain, menstrual disorder, amenorrhea, menorrhagia, kidney function abnormal, nephritis, urine abnormality, vaginal hemorrhage, urinary retention, urinary tract disorder, leukorrhea, breast neoplasm, menopause, oliguria, polyuria, albuminuria, pyuria
Rare	Breast carcinoma, penis disorder, papanicolau smear suspicious, fibrocystic breast, prostatic carcinoma, uterine fibroids enlarged, acute kidney failure, creatinine clearance decreased, nephrosis, nocturia, polycystic kidney, bladder carcinoma, breast enlargement, cervicitis, cervix disorder, female lactation, glycosuria, gynecomastia, hypomenorrhea, kidney pain, mastitis, pyelonephritis, kidney failure, breast abscess, epididymitis, orchitis, prostate neoplasia, prostatic specific antigen increase, salpingitis, urogenital disorder, urolithiasis, uterine disorder, vulvovaginal disorder, balanitis, bladder calculus, calcium crystalluria, cervix neoplasm, dyspareunia, endometrial carcinoma, endometrial disorder, glomerulitis, hydronephrosis, ovarian cancer, unintended pregnancy, urethral pain, urethritis, urogenital anomaly, urogenital neoplasia, uterine hemorrhage

Comparison of Gender and Race The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race. *Peripheral Edema* Incidence of peripheral edema in controlled neuropathic pain studies was 10.4% in the pregabalin group compared with 2.9% in the placebo group. In clinical trials, these events of peripheral edema were dose-related, mostly mild to moderate in intensity and rarely led to withdrawal. Peripheral edema was not associated with cardiovascular complications such as hypertension or congestive heart failure and there was no evidence of hemodilution or changes in any laboratory parameters indicative of underlying organ dysfunction (see **WARNINGS AND PRECAUTIONS, Peripheral Edema**). *Weight Gain* In the controlled neuropathic pain studies, patients on pregabalin had a higher incidence (5.9%) of weight gain as defined by a ≥7% increase from baseline weight as compared with the placebo group (1.6%). The mean change in the pregabalin group was an increase of 1.5 kg compared with 0.2 kg in the placebo group; few patients (0.1%) withdrew due to weight gain. This weight gain was dose-related, and not associated with clinically important changes in blood pressure or cardiovascular adverse events. There was no relationship between baseline body mass index and the incidence of ≥7% weight gain in the controlled trials. Based on the results of a controlled study of reproductive function in healthy male volunteers, the ≥7% weight gain on pregabalin appeared to be reversible. In this study, there were no reports of peripheral edema (see **WARNINGS AND PRECAUTIONS, Weight Gain**). **Abnormal Hematologic and Clinical Chemistry Findings** In all controlled trials, 1.0% of patients on pregabalin and 0.5% of placebo patients had an increase in creatine kinase of >3x upper limit of normal. Renal dysfunction was generally not associated with the elevated creatine kinase in these patients. Mean changes in creatine kinase ranged from 9.6 to 26.3 U/L for pregabalin-treated patients and 4.8 U/L for the placebo patients (see **DOSAGE AND ADMINISTRATION**, Patients with Renal Impairment). Routine therapeutic drug monitoring or clinical laboratory testing is not required for patients treated with LYRICA (see **WARNINGS AND PRECAUTIONS**). **Post-Marketing Adverse Drug Reactions** The worldwide post-marketing experience to date with LYRICA is consistent with the clinical program. The most frequently reported adverse events from spontaneous post-marketing reports for LYRICA are shown below. There are insufficient data to support an estimate of their incidence or to establish causation. **Eye disorders:** diplopia, vision blurred, visual disturbance. There have also been rare reports of accommodation disorder, eyelid edema and eye redness (see **WARNINGS AND PRECAUTIONS, Ophthalmological Effects**). **Gastrointestinal disorders:** diarrhea, dry mouth, nausea, vomiting **General disorders and administration site conditions:** fatigue, feeling abnormal, pain **Nervous system disorders:** ataxia, coordination abnormal, dizziness, dysarthria, headache, memory impairment, paresthesia, somnolence, speech disorder, tremor (see **WARNINGS AND PRECAUTIONS, Dizziness and Somnolence**). **Psychiatric disorders:** confusional state, depression, insomnia, psychotic disorder. There have been rare reports of psychotic disorders in patients receiving pregabalin. **Renal and urinary disorders:** urinary retention **Respiratory, thoracic and mediastinal disorders:** dyspnea **Skin and subcutaneous tissue disorders:** pruritus

DRUG INTERACTIONS

Overview Since pregabalin is predominately excreted unchanged in the urine, *undergoes negligible metabolism in humans (<2% of a dose recovered in urine as* metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, LYRICA (pregabalin) is unlikely to produce, or be subject to, pharmacokinetic interactions. *Pharmacokinetic* **In Vitro Studies:** In vitro drug metabolism studies revealed that pregabalin at concentrations which were, in general, 10-fold greater than observed in Phase 2/3 clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. **In Vivo Studies:** The drug interaction data described in this section were obtained from studies involving healthy adults, patients with epilepsy, and patients with chronic pain disorders. **Carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate** In vitro and in vivo studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no clinically significant pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs. **Tiagabine:** The results of a population pharmacokinetic analysis indicated that in patients with partial seizures tiagabine had no clinically significant effect on pregabalin clearance. **Gabapentin:** The pharmacokinetics of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single dose administration of 100 mg pregabalin and 300 mg gabapentin, and in 18 healthy subjects following concomitant multiple dose administration of 200 mg pregabalin q8h and 400 mg gabapentin q8h. Gabapentin pharmacokinetics following single and multiple dose administration were unaltered by pregabalin coadministration. The rate of pregabalin absorption was reduced by approximately 26% (single dose administration) and 18% (multiple dose administration) based on lower C_{max} values; however, the extent of pregabalin absorption was unaffected by gabapentin coadministration. **Oral Contraceptives:** Pregabalin coadministration (200 mg TID) had no effect on the steady state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 µg, respectively) in healthy subjects. **Lorazepam:** Multiple dose administration of pregabalin (300 mg BID) in healthy subjects had no effect on the rate and extent of lorazepam single dose pharmacokinetics and single dose administration of lorazepam (1 mg) had no clinically significant effect on the steady state pharmacokinetics of pregabalin. **Oxycodone:** Multiple dose administration of pregabalin (300 mg BID) in healthy subjects had no effect on the rate and extent of oxycodone single dose pharmacokinetics. Single dose administration of oxycodone (10 mg) had no clinically significant effect on the steady state pharmacokinetics of pregabalin. **Ethanol:** Multiple dose administration of pregabalin (300 mg BID) in healthy subjects had no effect on the rate and extent of ethanol single dose pharmacokinetics and single dose administration of ethanol (0.7 g/kg) had no clinically significant effect on the steady state pharmacokinetics of pregabalin. **Diuretics, Oral Hypoglycemics, and Insulin:** A population pharmacokinetic analysis in patients with chronic pain showed no clinically significant effect on pregabalin clearance with the concomitant use of diuretics, oral hypoglycemics, and insulin. *Pharmacodynamic* Multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. Pregabalin may potentiate the effects of ethanol and lorazepam. **Drug-Food Interactions** The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. *However, administration of pregabalin with food has no clinically relevant effect on* the total amount of pregabalin absorbed. Therefore, pregabalin can be taken with or without food. **Drug-Herb Interactions** LYRICA (pregabalin) has no known drug/herb interactions. **Drug-Laboratory Interactions** LYRICA (pregabalin) has no known drug/laboratory test interactions.

DOSAGE AND ADMINISTRATION

Dosing Considerations ***Patients with Impaired Renal Function*** **Pregabalin is primarily eliminated from the systemic circulation by renal excretion as unchanged drug. In patients with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Dosage Adjustment Based on Renal Function, below).** In accordance with current clinical practice, if LYRICA (pregabalin) has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week (see **WARNINGS AND PRECAUTIONS, Abrupt or Rapid Discontinuation**). **Adults: Neuropathic pain associated with diabetic peripheral neuropathy** The recommended starting dose for LYRICA is 150 mg/day, given in two or three divided doses (75 mg BID or 50 mg TID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week. For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg twice a day, BID) can be used. However, in clinical trials, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced markedly higher rates of adverse events and discontinued the trial more frequently. **Neuropathic pain associated with postherpetic neuralgia** The recommended starting dose for LYRICA is 150 mg/day, given in two or three divided doses (75 mg BID or 50 mg TID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week. For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg twice a day, BID) can be used. However, in clinical trials, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced markedly higher rates of adverse events and discontinued the trial more frequently. **Dosage Adjustment Based on Renal Function** LYRICA is primarily eliminated by renal excretion. Therefore, the dose should be adjusted for patients with reduced renal function. Pregabalin clearance is directly proportional to creatinine clearance. Therefore, dosing adjustment should be based on creatinine clearance (CL_{Cr}), as indicated in Table 7. To use this dosing table, an estimate of the patient's creatinine clearance (CL_{Cr}) in mL/min is needed. CL_{Cr} in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

$$CL_{Cr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

Pregabalin is effectively removed from plasma by hemodialysis. Over a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients receiving hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table 7).

Table 7. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CL_{Cr}) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a]			Dose Regimen
≥60	150	300	600	BID or TID
30-60	75	150	300	BID or TID
15-30	25-50	75	150	QD or BID
<15	25	25-50	75	QD
Supplementary dosage following hemodialysis (mg)[b]				
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg				

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.
a Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.
b Supplementary dose is a single additional dose.

Geriatrics (>65 years): Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function. ***Pediatrics (<18 years of age):*** The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established and its use in this patient population is not recommended. **Administration** LYRICA (pregabalin) is given orally with or without food (see **ACTION AND CLINICAL PHARMACOLOGY**).

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans The highest known dose of pregabalin received in the clinical development program was 15,000 mg in 1 patient. The types of adverse events experienced by patients who received an overdose were not clinically different from other patients receiving recommended doses of pregabalin. **Treatment or Management of Overdose** There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin. **Hemodialysis** Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action *Pharmacodynamics* LYRICA (pregabalin) binds with high affinity to the alpha$_2$-delta protein (a calcium channel subunit) of brain tissues and has analgesic, antiepileptic and anxiolytic activity. Pregabalin is known chemically as (S)-3-(aminomethyl)-5-methylhexanoic acid. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally-related to pregabalin indicate that selective binding to the alpha$_2$-delta protein is required for analgesic, antiepileptic and anxiolytic action in animal models. In vitro, pregabalin reduces the release of several neurotransmitters, suggesting a modulatory action on calcium channel function. Pregabalin does not mimic

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ADVERTISERS INDEX

GABA at $GABA_A$ or $GABA_B$ receptors, nor does it augment $GABA_A$ responses like benzodiazepines or barbiturates. In contrast to vascular calcium channel blockers, pregabalin does not alter systemic blood pressure or cardiac function. Various in vitro and in vivo results differentiate pregabalin from GABA uptake inhibitors or GABA transaminase inhibitors. In addition, pregabalin does not block sodium channels, it is not active at opiate receptors, it does not alter cyclooxygenase enzyme activity, it is not a serotonin agonist, it is not a dopamine antagonist, and it is not an inhibitor of dopamine, serotonin or noradrenaline reuptake. Pregabalin treatment reduces pain-related behavior in neuropathic animal models of diabetes, peripheral nerve damage or chemotherapeutic insult and in a model of musculoskeletal-associated pain. Pregabalin given intrathecally prevents pain-related behaviors and reduces pain-related behavior caused by spinally administered agents, suggesting that it acts directly on tissues of the spinal cord or brain. **Pharmacokinetics** All pharmacological actions following pregabalin administration are due to the activity of the parent compound; pregabalin is not appreciably metabolized in humans. Mean steady-state plasma pregabalin concentration-time profiles following 75, 300 and 600 mg/day given in equally divided doses every 8 hours (TID) and 600 mg/day given in equally divided doses every 12 hours (BID) are shown in Table 8. Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (<20%).

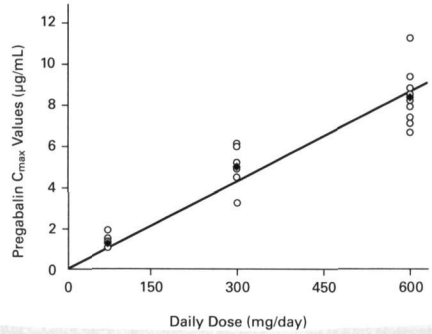
Table 8. Pregabalin Mean (CV%[a]) Steady-State Pharmacokinetic Parameter Values in Healthy Volunteers

Dose (mg)	Regimen	Daily Dose (mg/day)	n	C_{maxss} (µg/mL)	t_{max} (hr)	C_{minss} (µg/mL)	$AUC_{(0-t)}$ (µg•hr/mL)	$t_{1/2}$ (hr)	$C_{L/F}$ (mL/min)
25	TID[b]	75	8	1.39	0.9	0.45	6.7	5.9	64.1
				-19.5	-34.2	-25	-18.3	-17.3	-16.1
100	TID	300	6	5.03	0.8	1.94	25.2	6.3	68.9
				-21.3	-31	-33.6	-23	-19.6	-20.9
200	TID	600	11	8.52	0.9	3.28	41.7	6.3	81
				-14.8	-22.2	-29.2	-12.8	-13.6	-11.7
300	BID[c]	600	8	9.07	1.4	2.6	59	6.7	85.1
				-10.5	-57.1	-15.5	-6.4	-16.2	-6.4

C_{maxss}: Steady-state peak plasma concentration.
t_{max}: Time of peak plasma concentration at steady state.
C_{minss}: Steady-state trough plasma concentration
$AUC_{(0-t)}$: Area under the plasma concentration-time curve during one dosing interval at steady state
$t_{1/2}$: Elimination half-life
$C_{L/F}$: Oral clearance
a: Percent coefficient of variation
b: Total daily dose given in equally divided doses every 8 hours
c: Total daily dose given in equally divided doses every 12 hours

Absorption: Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1.5 hours following both single- and multiple-dose administration. Pregabalin oral bioavailability is ≥90% and is independent of dose. C_{max} (Figure 1) and AUC values increase proportionally following single- and multiple-dose administration. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple dose pharmacokinetics are predictable from single-dose data.

Figure 1. Individual and Mean Steady-State Pregabalin C_{max} Values Following 75, 300 and 600 mg/day Given in Equally Divided Doses TID (q8h) to Healthy Volunteers[a]



a: Solid line is the regression line going through the origin; individual (○) and mean (◆) values.

Distribution: In preclinical studies, pregabalin has been shown to readily cross the blood brain barrier in mice, rats and monkeys. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood-brain barrier. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is not bound to plasma proteins. At clinically efficacious doses of 150 and 600 mg/day, the average steady-state plasma pregabalin concentrations were approximately 1.5 and 6.0 µg/mL, respectively. **Metabolism:** Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits or monkeys. **Excretion:** Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean $t_{1/2}$ is 6.3 hours. Pregabalin elimination is proportional to creatinine clearance. Pregabalin clearance is reduced in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). **Special Populations and Conditions** Pregabalin undergoes negligible metabolism, is not bound to plasma proteins and is eliminated predominately as unchanged drug by renal excretion. Clinically important differences in pregabalin pharmacokinetics due to race and gender have not been observed and are not anticipated. **Pediatrics:** Pharmacokinetics of pregabalin have not been studied in paediatric patients. **Geriatrics:** Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). **Gender:** A population pharmacokinetic analysis of the Phase 2/3 clinical program showed that the relationship between daily dose and pregabalin drug exposure is similar between genders when adjusted for gender-related differences in creatinine clearance. **Race:** A population pharmacokinetic analysis of the Phase 2/3 clinical program showed that the relationship between daily dose and pregabalin drug exposure is similar among Caucasians, Blacks and Hispanics. **Renal Insufficiency:** Because renal elimination is the major elimination pathway, dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified (see **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Store at 15°C-30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

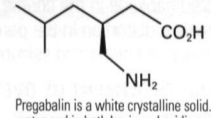
Each capsule of LYRICA (pregabalin) contains 25, 50, 75, 150 or 300 mg pregabalin, lactose monohydrate, maize starch and talc. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid, which may not be present. The markings on the capsules are in black ink, which contains shellac, black iron oxide, propylene glycol, potassium hydroxide and water.

Capsules are packaged in HDPE bottles containing 60 capsules, and PVC/aluminum blisters.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: pregabalin
Chemical name: (S)-3-(aminomethyl)-5-methylhexanoic acid
Molecular formula: $C_8H_{17}NO_2$
Molecular mass: 159.23
Structural formula:



Physicochemical properties: Pregabalin is a white crystalline solid. It is soluble in water and in both basic and acidic aqueous solutions.

Product Monograph available upon request.

Last revised: June 3, 2005.

References: 1. LYRICA Product Monograph, Pfizer Canada Inc., June 2005. **2.** Freynhagen R *et al.* Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. *Pain* 2005; 115:254-63. **3.** Data on file, Pfizer Canada Inc., study 1008-96. **4.** van Seventer R *et al.* Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. *Clin Med Res Opin* 2006; 22(2):375-84.

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See page A-3 (English) A-5 (French)

nabilone
CESAMET®
Symptom Control

THERAPEUTIC CLASSIFICATION
Antiemetic Agent

ACTION
NCESAMET (nabilone) is a synthetic cannabinoid with antiemetic properties which have been found to be of value in the management of some patients with nausea and vomiting associated with cancer chemotherapy. It also has sedative and psychotropic effects.

After oral administration, comparable peak plasma levels of nabilone and of its carbinol metabolite were attained within 2 hours. The combined plasma concentrations of nabilone and of its carbinol metabolite accounted for, at most, 10 to 20% of the total radiocarbon concentration in plasma. The plasma half-life of nabilone was approximately 2 hours, while that of the total radiocarbon was of the order of 35 hours.

Of the two major possible metabolic pathways, stereo-specific enzymatic reduction and direct enzymatic oxidation, the latter appears to be the more important in man.

The drug and its metabolites are eliminated mainly in the feces (approximately 65%) and to a lesser extent in the urine (approximately 20%). The major excretory pathway is the biliary system.

INDICATIONS
NCESAMET is indicated for the management of severe nausea and vomiting associated with cancer chemotherapy.

CONTRAINDICATIONS
NCESAMET is contraindicated in patients with known sensitivity to marijuana or other cannabinoid agents, and in those with a history of psychotic reactions.

WARNINGS
NCESAMET should be used with extreme caution in patients with severe liver dysfunction and in those with a history of non-psychotic emotional disorders.

NCESAMET should not be taken with alcohol, sedatives, hypnotics, or other psychotomimetic substances.

NCESAMET should not be used during pregnancy, in nursing mothers or in pediatric patients, since its safety under these conditions has not been established.

PRECAUTIONS
Since NCESAMET will often impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car and operating machinery, the patient should be warned accordingly and should not be permitted to drive or engage in dangerous tasks until the effects of nabilone are no longer present.

Adverse psychiatric reactions can persist for 48 to 72 hours following cessation of treatment.

Since NCESAMET elevates supine and standing heart rates and causes postural hypotension, it should be used with caution in the elderly and in patients with hypertension or heart disease.

Drug Interactions: Potential interactions between NCESAMET, and diazepam; sodium secobarbital; alcohol; or codeine, were evaluated. The depressant effects of the combinations were additive. Psychomotor function was particularly impaired with concurrent use of diazepam.

ADVERSE REACTIONS
The most frequently observed adverse reactions to nabilone and their incidences reported in the course of clinical trials were as follows: drowsiness (66.0%), vertigo (58.8%), psychological high (38.8%), dry mouth (21.6%), depression (14.0%), ataxia (12.8%), blurred vision (12.8%), sensation disturbance (12.4%), anorexia (7.6%), asthenia (7.6%), headache (7.2%), orthostatic hypotension (5.2%), euphoria (4.0%) and hallucinations (2.0%).

The following adverse reactions were observed in less than 1% of the patients who were administered nabilone in the course of the clinical trials: tachycardia, tremors, syncope, nightmares, distortion in the perception of time, confusion, dissociation, dysphoria, psychotic reactions and seizures.

SYMPTOMS AND TREATMENT OF OVERDOSE
Signs and Symptoms: Signs and symptoms which might be expected to occur are psychotic episodes including hallucinations, anxiety reactions, respiratory depression and coma (experience with cases of overdosage of more than 10 mg/day has not yet been reported).

Treatment: Overdosage may be considered to have occurred, even at prescribed dosages, if disturbing psychiatric symptoms are present. In these cases, the patient should be observed in a quiet environment and supportive measures, including reassurance, should be used. Subsequent doses should be withheld until patients have returned to their baseline mental status; routine dosing may then be resumed if clinically indicated. In such instances, a lower initiating dose is suggested.

If psychotic episodes occur, the patient should be managed conservatively, if possible. For moderate psychotic episodes and anxiety reactions, verbal support and comforting may be sufficient. In more severe cases, antipsychotic drugs may be useful; however, the utility of antipsychotic drugs in cannabinoid psychosis has not been systematically evaluated. Support for their use is drawn from limited experience using antipsychotic agents to manage cannabis overdoses. Because of the potential for drug-drug interactions (eg, additive CNS depressant effects due to nabilone and chlorpromazine), such patients should be closely monitored.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

The use of forced diuresis, peritoneal dialysis, hemodialysis, charcoal hemoperfusion, or cholestyramine has not been reported. In the presence of normal renal function, most of a dose of nabilone is eliminated through the biliary system.

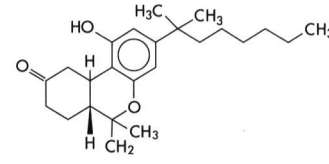
Treatment for respiratory depression and comatose state consists in symptomatic and supportive therapy. Particular attention should be paid to the occurrence of hypothermia. If the patient becomes hypotensive, consider fluids, inotropes, and/or vasopressors.

DOSAGE AND ADMINISTRATION
The usual adult dosage of NCESAMET (nabilone) is 1 mg or 2 mg twice a day. The first dose should be given the night before initiating administration of chemotherapeutic medication. The second dose is usually administered 1 to 3 hours before chemotherapy. If required, administration of NCESAMET can be continued up to 24 hours after the chemotherapeutic agent is given. The maximum recommended daily dose is 6 mg in divided doses.

NCESAMET® is available in a 0.5 mg strength for dose adjustment within the therapeutic range. Dose adjustment may be required for the purposes of response and tolerance in individual patients. Overdosage may occur even at prescribed dosages, if disturbing psychiatric symptoms are present. In these cases, the patient should be observed in a quiet environment and supportive measures, including reassurance, should be used. Subsequent doses should be withheld until patients have returned to their baseline mental status; routine dosing may then be resumed if clinically indicated. In such instances, a lower initiating dose is suggested.

NCESAMET contains nabilone in a capsule dosage form and is intended only for oral administration.

STRUCTURAL FORMULA AND CHEMISTRY



Molecular Formula: $C_{24}H_{36}O_3$
Molecular Weight: 372
U.S.A.N: Nabilone
Chemical Name: (+)-trans-3-(1,1-dimethyl-heptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo(b,d),pyran-9-one.
Description: White crystalline powder

Composition

Each 1 mg NCESAMET® capsule contains 1 mg of nabilone, starch, povidone, gelatin, FD&C blue #2 (indigo carmine), red iron oxide and titanium dioxide.

Each 0.5 mg NCESAMET® capsule contains: 0.5 mg of nabilone, starch, povidone, gelatin, titanium dioxyde, D&C red # 33, D&C yellow # 10, FD&C red # 40.

Stability and storage Recommendations
Store at controlled room temperature at 15-30°C.

AVAILABILITY
NCESAMET® 1 mg capsule: each capsule contains 1 mg of nabilone and are available in bottles of 20 capsules.

NCESAMET® 0.5 mg capsule: each capsule contains 0.5 mg of nabilone and are available in bottles of 50 capsules.

NCESAMET legally is considered to be a narcotic and is subject to the controls which apply to those drugs.

Product Monograph available upon request

VALEANT
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PAAB

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See page A-15

Once-a-day

Aricept®

donepezil HCl 5 & 10 mg tablets

Once-a-day

Aricept RDT®

donepezil HCl 5 & 10 mg tablets
rapidly disintegrating tablets

PHARMACOLOGIC CLASSIFICATION Cholinesterase Inhibitor **INDICATIONS AND CLINICAL USE ARICEPT** (donepezil hydrochloride) is indicated for the symptomatic treatment of patients with mild-to-moderate dementia of the Alzheimer's type. Efficacy of **ARICEPT** in patients with mild-to-moderate Alzheimer's disease was established in two 24-week and one 54-week placebo-controlled trials. **ARICEPT** tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. **CONTRAINDICATIONS ARICEPT** (donepezil hydrochloride) is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. **WARNINGS AND PRECAUTIONS *Cardiovascular:*** Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials in Alzheimer's disease, most patients with serious cardiovascular conditions were excluded. Patients such as those with controlled hypertension (DBP<95 mmHg), right bundle branch blockage and pacemakers were included. Therefore, caution should be taken in treating patients with active coronary artery disease and congestive heart failure. Syncopal episodes have been reported in association with the use of **ARICEPT.** It is recommended that **ARICEPT** should not be used in patients with cardiac conduction abnormalities (except for right bundle branch block) including "sick sinus syndrome" and those with unexplained syncopal episodes. ***Gastrointestinal:*** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), including high doses of acetylsalicylic acid (ASA), should be monitored for symptoms of active or occult gastrointestinal bleeding. Clinical studies of **ARICEPT** have shown no increase relative to placebo in the incidence of either peptic ulcer disease or gastrointestinal bleeding (see **ADVERSE REACTIONS** section). **ARICEPT,** as a predictable consequence of its pharmacological properties, has been shown to produce, in controlled clinical trials in patients with Alzheimer's disease, diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg dose than with the 5 mg dose. In most cases, these effects have usually been mild and transient, sometimes lasting 1 to 3 weeks, and have resolved during continued use of **ARICEPT** (see **ADVERSE REACTIONS** section). Treatment with the 5 mg/day dose for 4–6 weeks prior to increasing the dose to 10 mg/day is associated with a lower incidence of gastrointestinal intolerance. ***Genitourinary:*** Although not observed in clinical trials of **ARICEPT,** cholinomimetics may cause bladder outflow obstruction. ***Hepatic:*** There is limited information regarding the pharmacokinetics of **ARICEPT** in hepatically impaired Alzheimer's disease patients. Close monitoring for adverse effects in patients with hepatic disease being treated with **ARICEPT** is therefore recommended. ***Neurologic:*** **Seizures:** Some cases of seizures have been reported with the use of **ARICEPT** in clinical trials and from spontaneous Adverse Reaction reporting. Cholinomimetics can cause a reduction of seizure threshold, increasing the risk of seizures. However, seizure activity may also be a manifestation of Alzheimer's disease. The risk/benefit of **ARICEPT** treatment for patients with a history of seizure disorder must therefore be carefully evaluated. **ARICEPT** has not been studied in patients with Parkinsonian features. The efficacy and safety of **ARICEPT** in these patients are unknown. ***Peri-Operative Considerations:*** **Anesthesia: ARICEPT,** as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. ***Renal:*** There is limited information regarding the pharmacokinetics of **ARICEPT** in renally impaired Alzheimer disease patients. Close monitoring for adverse effects in patients with renal disease being treated with **ARICEPT** is therefore recommended. ***Respiratory:*** Because of their cholinomimetic action, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **ARICEPT** has not been studied in patients under treatment for these conditions and should therefore be used with particular caution in such patients. ***Special Populations:*** **Pregnant and Nursing Women:** The safety of **ARICEPT** during pregnancy and lactation has not been established and therefore, it should not be used in women of childbearing potential or in nursing mothers unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus or the infant. Teratology studies conducted in pregnant rats at doses of up to 16 mg/kg/day and in pregnant rabbits at doses of up to 10 mg/kg/day did not disclose any evidence for a teratogenic potential of **ARICEPT. Pediatrics:** There are no adequate and well-controlled trials to document the safety and efficacy of **ARICEPT** in any illness occurring in children. Therefore, **ARICEPT** is not recommended for use in children. **Geriatrics (≥85 years of age):** In controlled clinical studies with 5 and 10 mg of **ARICEPT,** 536 patients were between the ages of 65 to 84, and 37 patients were aged 85 years or older. In Alzheimer's disease patients, nausea, diarrhea, vomiting, insomnia, fatigue and anorexia increased with dose and age and the incidence appeared to be greater in female patients. Since cholinesterase inhibitors as well as Alzheimer's disease can be associated with significant weight loss, caution is advised regarding the use of **ARICEPT** in low body-weight elderly patients, especially in those ≥85 years old. **Use in Elderly Patients with Comorbid Disease:** There is limited safety information for **ARICEPT** in patients with mild-to-moderate Alzheimer's disease and significant comorbidity. The use of **ARICEPT** in Alzheimer's disease patients with chronic illnesses common among the geriatric population should be considered only after careful risk/benefit assessment and include close monitoring for adverse events. Caution is advised regarding the use of **ARICEPT** doses above 5 mg in this patient population. **ADVERSE REACTIONS Adverse Drug Reaction Overview: *Alzheimer's Disease:*** A total of 747 patients with mild-to-moderate Alzheimer's disease were treated in controlled clinical studies with **ARICEPT** (donepezil hydrochloride). Of these patients, 613 (82%) completed the studies. The mean duration of treatment for all **ARICEPT** groups was 132 days (range 1–356 days). ***Adverse Events Leading to Discontinuation:*** The rates of discontinuation from controlled clinical trials of **ARICEPT** due to adverse events for the **ARICEPT** 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received the 10 mg/day dose after only a 1-week initial treatment with 5 mg/day **ARICEPT** was higher at 13%. The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal From Controlled Clinical Trials by Dose Group

Dose Group	Placebo	5 mg/day ARICEPT	10 mg/day ARICEPT
Number of Patients Randomized	**355**	**350**	**315**
Events / % Discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT: The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by **ARICEPT's** cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued **ARICEPT** treatment without the need for dose modification. There is evidence to suggest that the frequency of these common adverse events may be affected by the duration of treatment with an initial 5 mg daily dose prior to increasing the dose to 10 mg/day. An open label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients received a 5 mg/day dose for 6 weeks prior to initiating treatment with 10 mg/day. The rates of common adverse events were lower than those seen in controlled clinical trial patients who received 10 mg/day after only a 1-week initial treatment period with a 5 mg daily dose, and were comparable to the rates noted in patients treated only with 5 mg/day. See Table 2 for a comparison of the most common adverse events following 1- and 6-week initial treatment periods with 5 mg/day **ARICEPT.**

Table 2. Comparison of Rates of Adverse Events in Patients Treated with 10 mg/day after 1 and 6 Weeks of Initial Treatment with 5 mg/day

	No Initial treatment	1-Week Initial treatment with 5 mg/day		6-Week Initial treatment with 5 mg/day
Adverse Event	**Placebo (n=315)**	**5 mg/day (n=311)**	**10 mg/day (n=315)**	**10 mg/day (n=269)**
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle Cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

Clinical Trial Adverse Drug Reactions: The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behaviour and the kinds of patients treated may differ. Table 3 lists treatment-emergent signs and symptoms (TESS) that were reported in at least 2% of patients from placebo-controlled clinical trials who received **ARICEPT** and for which the rate of occurrence was greater for **ARICEPT** than placebo-assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age.

Table 3: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving ARICEPT and at a Higher Frequency than Placebo-Treated Patients

Body System / Adverse Events	Placebo (n=355)	ARICEPT (n=747)	Body System / Adverse Events	Placebo (n=355)	ARICEPT (n=747)
Percent of Patients with any Adverse Event	72	74	**Metabolic and Nutritional**		
Body as a Whole			Weight Decrease	1	3
Headache	9	10	**Musculoskeletal System**		
Pain, various locations	8	9	Muscle Cramps	2	6
Accident	6	7	Arthritis	1	2
Fatigue	3	5	**Nervous System**		
Cardiovascular System			Insomnia	6	9
Syncope	1	2	Dizziness	6	8
Digestive System			Depression	<1	3
Nausea	6	11	Abnormal Dreams	0	3
Diarrhea	5	10	Somnolence	<1	2
Vomiting	3	5	**Urogenital**		
Anorexia	2	4	Frequent Urination	1	2
Hemic and Lymphatic Systems					
Ecchymosis	3	4			

Long-Term Safety: Patients were exposed to **ARICEPT** in 2 open-label extension studies (n=885) of over 2 years. In 1 of the studies, 763 patients who previously completed 1 of 2 placebo-controlled studies of 15 or 30 weeks duration continued to receive **ARICEPT** and were evaluated for safety and neuropsychological evaluations for up to 152 weeks; the safety profile of **ARICEPT** in this extension study remained consistent with that observed in placebo-controlled trials. Following 1 and 2 years of treatment, 76% (n=580) and 49% (n=374) of these patients, respectively, were still receiving therapy (cumulative Weeks 48 and 108). ***Postmarket Adverse Drug Reactions:*** Voluntary reports of adverse events temporally associated with **ARICEPT** that have been received since market introduction, that are not listed above, and for which there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, pancreatitis, and rash. **Vascular dementia:** The initial safety profile from controlled clinical trials in Vascular dementia patients indicates that the rate of occurrence of adverse events overall was higher in Vascular dementia patients (91%) than in Alzheimer's disease patients (75%), however this was seen in both **ARICEPT**-treated subjects, and placebo-treated subjects, and may relate to the greater number of comorbid medical conditions in the Vascular dementia population. A comparison of the Alzheimer's disease and Vascular dementia studies shows that the type of **ARICEPT**-associated adverse events was similar in the 2 patient populations. A total of 827 patients with Vascular dementia were treated in controlled clinical studies with **ARICEPT.** Of these patients, 639 (77%) completed the studies. The mean duration of treatment for all **ARICEPT** groups was 152 days (range 1–428 days). In controlled clinical trials in Vascular dementia patients, the rates of discontinuation due to adverse events were 10.6 % for **ARICEPT** 5 mg and 19% for **ARICEPT** 10 mg compared to 9.9% for placebo. The most common adverse event leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, was nausea. Other less common events leading to discontinuation include cerebrovascular accident, confusion, dizziness, diarrhea and vomiting. The most common serious adverse events were cerebrovascular accident (3.4%) and pneumonia (1.6%). The most common adverse events were infection (14.4%), diarrhea (13.9%), accidental injury (13.0%) and nausea (11.3%). Most adverse events were judged by the investigator to be mild to moderate in intensity and not related to study medication. **DRUG INTERACTIONS Concomitant Use with Other Drugs: *Use with Anticholinergics:*** Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. ***Use with Cholinomimetics and Other Cholinesterase Inhibitors:*** A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. ***Use with Other Psychoactive Drugs:*** Few patients in controlled clinical trials received neuroleptics, antidepressants or anticonvulsants. There is thus limited information concerning the interaction of **ARICEPT** with these drugs. **Drug-Drug Interactions** Pharmacokinetic studies, limited to short-term, single-dose studies in young subjects evaluated the potential of **ARICEPT** for interaction with theophylline, cimetidine, warfarin and digoxin administration. No significant effects on the pharmacokinetics of these drugs were observed. Similar studies in elderly patients were not done. ***Drugs Highly Bound to Plasma Proteins:*** Drug displacement studies have been performed in vitro between donepezil, a highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil at concentrations of 0.3 - 10 µg/mL did not affect the binding of furosemide (5 µg/mL), digoxin (2 ng/mL) and warfarin (3 µg/mL) to human albumin. Similarly, the binding of donepezil to human albumin was not affected by furosemide, digoxin and warfarin. ***Effect of ARICEPT on the Metabolism of Other Drugs:*** In vitro studies show a low rate of donepezil binding to CYP 3A4 and CYP 2D6 isoenzymes (mean Ki about 50-130 µM), which, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interferences. In a pharmacokinetic study involving 18 healthy volunteers, the administration of **ARICEPT** at a dose of 5 mg/day for 7 days had no clinically significant effect on the pharmacokinetics of ketoconazole. No other clinical trials have been conducted to investigate the effect of **ARICEPT** on the clearance of drugs metabolized by CYP 3A4 (eg, cisapride, terfenadine) or by CYP 2D6 (eg, imipramine). It is not known whether **ARICEPT** has any potential for enzyme induction. ***Effect of Other Drugs on the Metabolism of ARICEPT:*** Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism in vitro. In a pharmacokinetic study, 18 healthy volunteers received 5 mg/day **ARICEPT** together with 200 mg/day ketoconazole for 7 days. In these volunteers, mean donepezil plasma concentrations were increased by about 30%-36%. Inducers of CYP 2D6 and CYP 3A4 (eg, phenytoin, carbamazepine, dexamethasone, rifampin and phenobarbital) could increase the rate of elimination of **ARICEPT.** Pharmacokinetic studies demonstrated that the metabolism of **ARICEPT** is not significantly affected by concurrent administration of digoxin or cimetidine. **Drug-Food Interactions:** Food does not have an influence on the rate and extent of donepezil hydrochloride absorption. **Drug-Herb Interactions:** Interactions with herbal products have not been established. **Drug-Laboratory Interactions:** Interactions with laboratory tests have not been established. **DOSAGE AND ADMINISTRATION Dosing considerations: ARICEPT** (donepezil hydrochloride) or **ARICEPT RDT** should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. **Recommended Dose and Dosage Adjustment: *Adults:*** The recommended initial dose of **ARICEPT** or **ARICEPT RDT** is 5 mg taken once daily. Therapy with the 5 mg dose should be maintained for 4-6 weeks before considering a dose increase, in order to avoid or decrease the incidence of the most common adverse reactions to the drug (see **ADVERSE REACTIONS** section) and to allow plasma levels to reach steady state. Based on clinical judgement, the 10 mg daily dose may be considered following 4–6 weeks of treatment at 5 mg/day. The maximum recommended dose is 10 mg taken once daily. Following initiation of therapy or any dosage increase, patients should be closely monitored for adverse effects. ***Special Populations:*** Adverse events are more common in individuals of low body weight, in patients ≥85 years old and in females. It is recommended that **ARICEPT** be used with caution in these patient populations. In elderly women of low body weight, the dose should not exceed 5 mg/day. In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision. **ARICEPT** should be taken once daily in the morning or evening. It may be taken with or without food. **Administration: ARICEPT** tablets should be swallowed whole with water. **ARICEPT RDT** should be placed on the tongue and allowed to disintegrate before swallowing with water. **AVAILABILITY OF DOSAGE FORMS ARICEPT** is supplied as film-coated tablets containing 5 mg (white tablets) or 10 mg (yellow tablets) of donepezil hydrochloride. The name **ARICEPT** and the strength are embossed on each tablet. **ARICEPT** is available in high-density polyethylene (HDPE) bottles of 30 tablets and in blister strips boxed as 28 tablets (combination of 2 strips of 14 tablets). **ARICEPT RDT** is supplied as uncoated rapidly disintegrating tablets containing 5 mg (white tablets) or 10 mg (yellow tablets) of donepezil hydrochloride. The name **ARICEPT** and the strength are embossed on each tablet. **ARICEPT RDT** is available in blister strips boxed as 28 tablets. **STORAGE AND STABILITY: ARICEPT RDT** should not be removed from blisters until immediately prior to administration.

Product Monograph available upon request.

References:

1. Seltzer B *et al.* Efficacy of donepezil in early-stage Alzheimer disease. *Arch Neurol* 2004;61:1852-1856.
2. Rogers SL *et al.* A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998;50:136-145.

Pfizer

Member R&D PAAB

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See OBC, A-12, A-13

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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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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PrAggrenox®
ASA /Extended Release Dipyridamole

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

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For brief prescribing information see pages A-19, A-20, A-21

Helping him make connections[1,2†‡]

CHOOSE ARICEPT®

ARICEPT is indicated for the symptomatic treatment of patients with mild-to-moderate dementia of the Alzheimer's type. ARICEPT does not change the underlying course of the disease.

The most common adverse events with ARICEPT 10 mg/d after proper dose escalation include nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue and anorexia (occurring in at least 5% of patients). These events are usually mild and transient, resolving with continued ARICEPT treatment without the need for dose modification.

† In a 24-week, randomized, double-blind, placebo-controlled study of ARICEPT in 153 mild AD patients (MMSE 21-26). Patients received either ARICEPT 5 mg/d for the first 6 weeks and 10 mg/d thereafter, (n=96), or placebo (n=57). 37% of ARICEPT-treated patients experienced a 4 point ADAS-cog improvement and 10% experienced a 7 point improvement versus 16% and 7% respectively with placebo.

‡ In a 24-week, multicentre, randomized, double-blind, placebo-controlled trial, 473 patients were randomized to receive ARICEPT 5 mg/d, ARICEPT 10 mg/d or placebo. Following the 24-week, double-blind phase, all patients underwent a 6-week, single-blind placebo washout. Patients treated with either dose of ARICEPT demonstrated significantly less decline on the CIBIC-plus versus placebo (CIBIC-plus value at endpoint for ARICEPT 5 mg/d and 10 mg/d were 4.15 and 4.07 respectively versus 4.51 with placebo, p=0.0047 and p<0.0001).

Product Monograph available on request.

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rapidly disintegrating tablets

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First Alzheimer's Therapy in Canada

For brief prescribing information see page A-29

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