# INFORMATION FOR AUTHORS

The Canadian Journal of Neurological Sciences publishes original articles in neurology, neurosurgery and basic neurosciences. Manuscripts are considered for publication with the understanding that they, or the essence of their content, have not been published elsewhere except in abstract form and are not under simultaneous consideration by another journal. A cover letter that states the above must accompany the submission. Articles undergo peer review. Manuscripts should be submitted to: Douglas Zochodne, M.D., Editor, Canadian Journal of Neurological Sciences, 7015 Macleod Trail SW, Suite 709, Calgary, AB, Canada T2H 2K6

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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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• Electronic submission is now available. Papers will be accepted in English or French. Text should be formatted in Microsoft Word (saved as RFT files) or Quark Xpress. Store illustrations as separate files - do NOT integrate them into your text. Export line drawings/vector graphics as TIF, or EPS format. Use Photoshop for processing and retouching scanned half-tone images. Save the original scan and the processed version. Export black and white or colour images as TIF or EPS format in their anticipated size in print. Do NOT send pictures embedded in a Word document.

• Papers will be accepted in English or French. Manuscripts must be double spaced throughout including references, tables and legends for illustrations. Margins of at least 25mm should be left on all sides.

• Scanned line drawings must be digitalized with a resolution of at least 800, better 1000 dpi (dots per inch) after scaling.

• 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.

• Scanned half-tone images should be digitalized with a final resolution of at least 300 dpi, a 12 bit grayscale accuracy and a density range of 2.8. Screen values must lie between 5% and 95%. Scanned color illustrations must be digitalized in RGB mode with a resolution of at least 300 dpi, a 32 bit accuracy and a density range of 2.8.

**To Submit Manuscripts Electronically:**

authorsubmission@cjns.org

• ***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", five copies of the 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 five copies 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.

• ***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.

• ***Review articles*** on selected topics are also published. They are usually invited, but unsolicited reviews will be considered.

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

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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

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See page A-7

# 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**<br>Intravenous infusion |
| **Dosage Form / Strength**<br>Concentrate for solution / 300 mg per 15 mL |
| **Clinically Relevant Nonmedicinal Ingredients**<br>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.

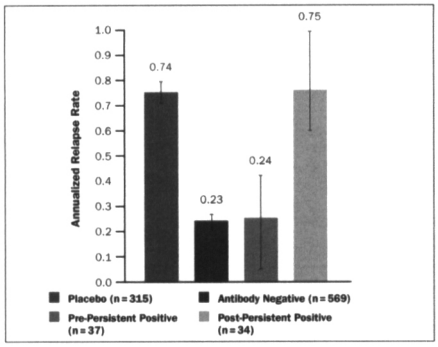
In controlled clinical trials in MS patients, persistent anti-natalizumab antibodies developed in approximately 6% of patients. Antibodies were detected on only one occasion in 4% of patients. Additional infusion-related reactions associated with persistent antibodies included rigors, nausea, vomiting 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 elan

Biogen Idec Canada Inc. 3 Robert Speck Parkway, Suite 300, Mississauga, ON L4Z 2G5.



TYB1039

PAAB



See page A-4, A-5

BRIEF PRESCRIBING INFORMATION

CONSULT FULL PRODUCT MONOGRAPH FOR COMPLETE PRESCRIBING INFORMATION

**Reminyl®**

galantamine hydrobromide tablets

4 mg, 8 mg, 12 mg galantamine base

**Reminyl® ER**

galantamine hydrobromide extended release capsules

8 mg, 16 mg, 24 mg galantamine base

Cholinesterase Inhibitor

## INDICATIONS AND CLINICAL USE

REMINYL (galantamine hydrobromide) and REMINYL ER are indicated for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. REMINYL and REMINYL ER have not been studied in controlled clinical trials for longer than 6 months.

*REMINYL and REMINYL ER should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease.*

**Geriatrics (≥85 years of age):** There is limited safety information for REMINYL and REMINYL ER in this patient population (see **WARNINGS AND PRECAUTIONS**).

**Pediatrics:** No data are available in children. Therefore, the use of REMINYL and REMINYL ER are not recommended in children under 18 years of age.

## CONTRAINDICATIONS

REMINYL and REMINYL ER are contraindicated in patients with known hypersensitivity to galantamine hydrobromide, other tertiary alkaloid derivatives or to any excipients used in the formulation.

## WARNINGS AND PRECAUTIONS

**Carcinogenesis and Mutagenesis** See ***Product Monograph Part II:*** **TOXICOLOGY – Carcinogenicity, Mutagenicity** for discussion on animal data.

**Cardiovascular** Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and heart block. These actions may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction disorders, or to patients taking other drugs concomitantly which significantly slow heart rate. In clinical trials, patients with serious cardiovascular disease were excluded. Caution should be exercised in treating patients with active coronary artery disease or congestive heart failure. It is recommended that REMINYL and REMINYL ER 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.

In randomized controlled trials, bradycardia was reported at 2-3% for galantamine doses up to 24 mg/day compared with <1% for placebo, but was rarely severe and rarely led to treatment discontinuation. No increased incidence of heart block was observed at the recommended doses. Patients treated with galantamine up to 24 mg/day at the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo, 0.7% [2/286]; 4 mg b.i.d., 0.4% [3/692]; 8 mg b.i.d., 1.3% [7/552]; 12 mg b.i.d., 2.2% [6/273]).

A 6-week cardiovascular safety clinical trial (GAL-USA-16; n=139) was performed to investigate the effect of galantamine at doses up to 32 mg/day. This dosing regimen was: 8 mg/day in Week 1, 16 mg/day in Week 2, 24 mg/day in Weeks 3 and 4, and 32 mg/day in Weeks 5 and 6. Heart block/pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients. It should be noted that a forced 1-week dose escalation was used in this study, which is not recommended. Whether these cardiac effects are attenuated by slower titration rates is not known. Particular caution is warranted during titration where the majority of pauses occurred in the above study.

**Metabolism** Cholinesterase inhibitors as well as Alzheimer's disease can be associated with significant weight loss. In controlled clinical trials, the use of REMINYL was associated with weight loss. Weight decrease occurred early during treatment and was related to dose. Weight loss of ≥7% occurred more frequently in patients treated with REMINYL and in female patients than in patients receiving placebo. Where weight loss may be of clinical concern, body weight should be monitored.

**Gastrointestinal** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g. those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). In controlled clinical studies with galantamine, patients with symptomatic peptic ulceration were excluded. Clinical studies of galantamine have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding (see **ADVERSE REACTIONS**).

Galantamine, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting and diarrhea, anorexia and weight loss. These effects appeared more frequently at higher doses (see **ADVERSE REACTIONS**), with nausea and vomiting being more prevalent in women and patients with lower body weight and correspondingly higher plasma drug concentrations. Females are more sensitive to the cholinergic adverse effects associated with cholinesterase inhibitors and in general are more likely to experience nausea and vomiting than are males. In most cases, these effects were of mild to moderate intensity and transient and have resolved during continued REMINYL treatment or upon treatment discontinuation.

**Genitourinary** Although not observed in clinical trials of galantamine, cholinomimetics may cause bladder outflow obstruction.

**Neurologic** Seizures: In placebo-controlled trials with galantamine, cases of seizure were reported; there was no increase in incidence compared with placebo. Although cholinomimetics are believed to have some potential to cause seizures, seizure activity may also be a manifestation of Alzheimer's disease. The risk/benefit of REMINYL and REMINYL ER treatment for patients with a history of seizure disorder must therefore be carefully evaluated.

REMINYL and REMINYL ER have not been studied in patients with moderately severe or severe Alzheimer's disease, non-Alzheimer dementias or individuals with Parkinsonian features. The efficacy and safety of REMINYL and REMINYL ER in these patient populations is unknown.

**Peri-Operative Considerations** Anesthesia: Galantamine, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

**Respiratory** Like other cholinomimetic drugs, REMINYL and REMINYL ER should be prescribed with care for patients with a history of asthma or obstructive pulmonary disease.

**Special Populations**

**Hepatic Impairment:** There is limited information on the pharmacokinetics of galantamine in hepatically impaired patients. It is therefore recommended that dose escalation with REMINYL or REMINYL ER in Alzheimer's disease patients with hepatic impairment be undertaken with caution and under conditions of close monitoring for adverse effects (see **DOSAGE AND ADMINISTRATION**, Special Populations). Since no data are available on the use of REMINYL or REMINYL ER in patients with severe hepatic impairment (Child-Pugh score of 10-15), REMINYL and REMINYL ER are not recommended for this population.

**Renal Impairment:** There is limited information on the pharmacokinetics of galantamine in renally impaired patients. It is therefore recommended that dose escalation with REMINYL or REMINYL ER in Alzheimer's disease patients with renal impairment (creatinine clearance of 9 to 60 mL/min) be undertaken with caution and under conditions of close monitoring for adverse effects (see **DOSAGE AND ADMINISTRATION**, Special Populations). Since no data are available on the use of REMINYL or REMINYL ER in patients with a creatinine clearance of less than 9 mL/min, REMINYL and REMINYL ER are not recommended for this population.

**Geriatrics (≥85 years of age):** In controlled clinical studies, the number of patients aged 85 years or over who received REMINYL at therapeutic doses of 16 or 24 mg/day was 123. Of these patients, 70 received the maximum recommended dose of 24 mg/day. There is limited safety information for REMINYL in this patient population.

Since cholinomimetics as well as Alzheimer's disease can be associated with significant weight loss, caution is advised regarding the use of REMINYL and REMINYL ER in elderly patients with low body weight, especially in those ≥85 years old.

Use in Elderly Patients with Serious Comorbid Disease There is limited information on the safety of galantamine treatment in patients with mild to moderate Alzheimer's disease and serious/significant comorbidity. The use of REMINYL and REMINYL ER 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. Dose escalation in this patient population should proceed with caution.

**Patients with Mild Cognitive Impairment (MCI):** Mortality in Investigational Trials in MCI Two randomized, double-blind, placebo-controlled efficacy and safety studies of 2 years' duration were completed in non-demented subjects with MCI. Individuals with MCI demonstrate isolated memory impairment greater than expected for their age and education, but do not meet current diagnostic criteria for Alzheimer's Disease. In these trials, REMINYL was not shown to be effective in patients with MCI. In the double-blind portion of these two trials, a total of 13 deaths in subjects on REMINYL (n=1026) were recorded and 1 death in subjects on placebo (n=1022); the reason for this difference is currently unknown. This difference in mortality has not been observed in REMINYL studies in Alzheimer's Disease. Approximately half of the REMINYL deaths appeared to have resulted from various vascular causes (myocardial infarction, stroke, and sudden death); other deaths appeared to have resulted from infection, suicide and cancer. There is no evidence of an increased risk of mortality when REMINYL is used in patients with mild to moderate Alzheimer's Disease.

**Pregnant Women:** In a teratology study in which rats were dosed from Day 14 (females) or Day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the MRHD on a mg/m$^2$ basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m$^2$ basis) during the period of organogenesis.

The safety of REMINYL and REMINYL ER in pregnant women has not been established. REMINYL and REMINYL ER should not be used in women of childbearing potential unless, in the opinion of the physician, the potential benefit to the patient justifies the potential risk to the fetus.

**Nursing Women:** It is not known whether galantamine is excreted in human breast milk and therefore REMINYL and REMINYL ER should not be used in nursing mothers.

**Pediatrics:** The safety and effectiveness of REMINYL and REMINYL ER in any illness occurring in pediatric patients have not been established.

## ADVERSE REACTIONS

**Clinical Trial Adverse Drug Reactions** Because clinical trials are conducted under very specific conditions, the adverse drug 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 total of 2287 patients with mild to moderate Alzheimer's disease were treated with REMINYL in Phase III controlled clinical studies using either a 1-week or 4-week dose-escalation period, and 761 patients received REMINYL 24 mg/day, the maximum recommended maintenance dose. The number of patients who completed the studies was 1686 (72%). The mean duration of treatment for all REMINYL groups was 130 days (range 1-214 days).

Adverse Events Leading to Discontinuation Overall, 19% (441/2287) of patients treated with REMINYL discontinued from Phase III controlled clinical trials due to adverse events compared to 8% (98/1159) in the placebo group. For patients treated with REMINYL, the rate of discontinuation due to adverse events was 14% for males and 22% for females.

In the 4-week dose-escalation fixed-dose study (GAL-USA-10), 8% (55/692) of patients treated with REMINYL withdrew due to adverse events compared to 7% (20/286) in the placebo group. During the dose-escalation phase of this study the incidence of discontinuations due to adverse events was 4% for placebo, 5% for REMINYL 16 mg/day and 6% for REMINYL 24 mg/day. During the maintenance phase, 4% of patients who received placebo, 3% of patients who received REMINYL 16 mg/day and 4% of patients who received REMINYL 24 mg/day withdrew from this study due to adverse events.

Table 1.1 shows the most frequent adverse events leading to discontinuation for study GAL-USA-10, in which the recommended 4-week dose-escalation schedule was used.

**Table 1.1: Most frequent adverse events leading to discontinuation in a placebo-controlled, double-blind trial with a 4-week dose-escalation schedule (GAL-USA-10)**

| | Recommended 4-week dose escalation | | |
|---|---|---|---|
| Adverse Events | Placebo (n=286) % | 16 mg/day (n=279) % | 24 mg/day (n=273) % |
| Nausea | <1 | 2 | 4 |
| Vomiting | 0 | 1 | 3 |
| Anorexia | <1 | 1 | <1 |
| Dizziness | <1 | 2 | 1 |
| Syncope | 0 | 0 | 1 |

Most Frequent Adverse Clinical Events Seen in Association with the Use of REMINYL The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate of placebo in study GAL-USA-10, in which the recommended 4-week dose-escalation schedule was used are shown in Table 1.2.

These events were primarily gastrointestinal and tended to occur at a lower rate with 16 mg/day, the initial recommended maintenance dose. Administration of REMINYL with food, the use of anti-emetic medication and ensuring adequate fluid intake may reduce the impact of these events.

**Table 1.2 : Most frequent adverse events in a randomized placebo-controlled clinical trial with a 4-week dose increment during dose-escalation and maintenance phases (GAL-USA-10)**

| | Week 1-12† | | | Week 13-21 | | |
|---|---|---|---|---|---|---|
| Adverse Events | Placebo (n=286) % | 16 mg/day (n=279) % | 24 mg/day (n=273) % | Placebo (n=259) % | 16 mg/day (n=243) % | 24 mg/day (n=241) % |
| Nausea | 5 | 11 | 13 | <1 | 4 | 6 |
| Vomiting | <1 | 5 | 6 | <1 | 2 | 6 |
| Diarrhea | 5 | 9 | 4 | 2 | 5 | 2 |
| Anorexia | 2 | 5 | 5 | 1 | 2 | 5 |

† Dose escalation occurred with 4 weeks per dose increment.

The majority of these adverse events occurred during the dose-escalation period. Nausea and vomiting, the most frequent adverse events, occurred more frequently at higher doses, lasted 5-7 days in most cases, and the majority of patients had one episode. The incidence of weight loss in this study was, during dose escalation (Weeks 1-12): placebo, 1%; 16 mg/day, 3%; 24 mg/day, 2%; and during the maintenance phase (Weeks 13-21): placebo, <1%; 16 mg/day, 3%; 24 mg/day, 3%.

Dose-escalation should be cautious and maintenance dosing should remain flexible and be adjusted according to individual needs.

Adverse Events Reported in Controlled Trials The reported adverse events in REMINYL trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behaviour and the types of patients treated may differ.

Table 1.3 lists the most common adverse events (adverse events occurring with an incidence of 2% with REMINYL treatment and in which the incidence was greater than with placebo treatment) for four placebo-controlled trials for patients treated with 16 or 24 mg/day of REMINYL. The combined values presented in Table 1.3 were derived from trials using a 1-week or the recommended 4-week dose-escalation period.

**Table 1.3: Adverse events reported in at least 2% of patients with Alzheimer's disease administered REMINYL and at a frequency greater than with placebo (combined 1- and 4-week dose-escalation data)**

| Body System/Adverse Events | Placebo (n=801) % | REMINYL† (n=1040) % |
|---|---|---|
| **Body as a whole – general disorders** | | |
| Fatigue | 3 | 5 |
| Syncope | 1 | 2 |
| **Central & peripheral nervous system disorders** | | |
| Dizziness | 6 | 9 |
| Headache | 5 | 8 |
| Tremor | 2 | 3 |
| **Gastrointestinal system disorders** | | |
| Nausea | 9 | 24 |
| Vomiting | 4 | 13 |
| Diarrhea | 7 | 9 |
| Abdominal pain | 4 | 5 |
| Dyspepsia | 2 | 5 |
| **Heart rate and rhythm disorders** | | |
| Bradycardia | 1 | 2 |
| **Metabolic and nutritional disorders** | | |
| Weight decrease | 2 | 7 |
| **Psychiatric disorders** | | |
| Anorexia | 3 | 9 |
| Depression | 5 | 7 |
| Insomnia | 4 | 5 |
| Somnolence | 3 | 4 |
| **Red blood cell disorders** | | |
| Anemia | 2 | 3 |
| **Respiratory system disorders** | | |
| Rhinitis | 3 | 4 |
| **Urinary system disorders** | | |
| Urinary tract infection | 7 | 8 |
| Hematuria | 2 | 3 |

† Adverse events in patients treated with 16 or 24 mg/day of REMINYL in three placebo-controlled trials with a 1-week dose-escalation period and a 26-week fixed-dose REMINYL treatment, and one placebo-controlled trial with the recommended 4-week dose-escalation period and a 21-week fixed-dose REMINYL treatment are included.

No clinically relevant abnormalities in laboratory values were observed. In a cardiovascular safety clinical trial (GAL-USA-16), pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients during the dose-escalation period (see **WARNINGS AND PRECAUTIONS**).

Most Frequent Adverse Clinical Events Seen in Association with the Use of REMINYL ER

Adverse reactions in clinical trials of once-daily treatment with REMINYL ER extended release capsules were similar to those seen with REMINYL immediate release tablets (see Table 1.4).



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**Table 1.4: Adverse events reported in at least 2% of patients with Alzheimer's disease administered REMINYL or REMINYL ER and at a frequency greater than placebo**

| System Organ Class<br>Preferred Term | Placebo (n=320) % | REMINYL (n=326) % | REMINYL ER (n=319) % |
|---|---|---|---|
| **Body as a whole – general disorders** | | | |
| Injury | 6 | 4 | 8 |
| Edema peripheral | 3 | 2 | 4 |
| Fatigue | 1 | 4 | 4 |
| Syncope | 1 | 1 | 2 |
| Fever | 1 | 2 | 1 |
| Leg pain | 1 | 2 | < 1 |
| **Central & peripheral nervous system disorders** | | | |
| Dizziness | 4 | 7 | 10 |
| Headache | 6 | 6 | 8 |
| Tremor | 0 | 1 | 2 |
| **Gastrointestinal system disorders** | | | |
| Nausea | 5 | 14 | 17 |
| Vomiting | 2 | 9 | 7 |
| Abdominal pain | 2 | 3 | 2 |
| Dyspepsia | 2 | 3 | 2 |
| **Heart rate and rhythm disorders** | | | |
| Bradycardia | 2 | 2 | 3 |
| **Metabolic and nutritional disorders** | | | |
| Weight decrease | 1 | 5 | 4 |
| Hyperglycemia | 1 | 2 | 2 |
| **Musculoskeletal system disorders** | | | |
| Arthralgia | 2 | 2 | 3 |
| Skeletal pain | 1 | 3 | 2 |
| Arthritis | 1 | 1 | 2 |
| Myalgia | 1 | 1 | 2 |
| **Psychiatric disorders** | | | |
| Anorexia | 3 | 7 | 6 |
| Depression | 3 | 5 | 6 |
| Anxiety | 3 | 1 | 4 |
| Somnolence | 2 | 2 | 3 |
| Depression aggravated | 1 | 2 | 2 |
| Aggressive reaction | 1 | 2 | 2 |
| Nervousness | 1 | 2 | 1 |
| **Respiratory system disorders** | | | |
| Rhinitis | 3 | 4 | 4 |
| Pneumonia | 1 | 2 | 2 |
| ***Secondary terms*** | | | |
| Abrasion nos* | 1 | 1 | 2 |
| **Skin and appendages disorders** | | | |
| Rash | 1 | < 1 | 3 |
| **Urinary system disorders** | | | |
| Hematuria | 1 | 1 | 2 |
| Micturition frequency | 1 | 2 | 1 |
| **Vision disorders** | | | |
| Cataract | 1 | 1 | 2 |

* not otherwise specified

**Adverse Events Observed During the GAL-INT-6 Study** **The frequencies of certain cardiovascular-related adverse events, including syncope, hypertension, arrhythmia and bundle branch block were increased in patients treated with galantamine compared to placebo. The increase was due primarily to events that occurred in the subgroup of Alzheimer's patients with concomitant cerebrovascular disease. Patients with Alzheimer's disease and concomitant *cerebrovascular disease who were treated with galantamine experienced* syncope (3%), hypertension (4%), arrhythmia (3%) and bundle branch block (2%), but these events were not reported in the placebo group.**

**In the vascular dementia subgroup syncope was reported for 2% of patients treated with galantamine and 2% of patients treated with placebo; hypertension was reported for 5% of patients treated with galantamine and 2% of patients treated with placebo. Arrhythmia and bundle branch block adverse events were not reported in the vascular dementia subgroup.**

**In the entire study population the most common treatment-emergent adverse events (nausea, dizziness, vomiting, abdominal pain, diarrhea, fatigue and upper respiratory tract infection) were consistent with what has been observed in previous REMINYL studies involving Alzheimer's disease patients (see *Product Monograph Part II:* CLINICAL TRIALS).**

**Other Adverse Events Observed During Clinical Trials** REMINYL has been administered to 3055 patients with Alzheimer's disease during clinical trials worldwide.

A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's disease received galantamine 24 mg/day, the maximum recommended maintenance dose. About 1000 patients received galantamine for at least one year and approximately 200 patients received galantamine for two years. To establish the rate of adverse events, data from all patients for any dose of REMINYL in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All events occurring in approximately 0.1% of patients are included, except for those already listed elsewhere in labelling, WHO terms too general to be informative, or relatively minor events. Events are classified by body system and listed using the following definitions: *frequent adverse events* - those occurring in at least 1/100 patients; *infrequent adverse events* - those occurring in 1/100 to 1/1000 patients; *rare* - those occurring in 1/1000 to 1/10000 patients; *very rare* - those occurring in fewer than 1/10000 patients. These adverse events are not necessarily related to REMINYL treatment and in most cases were observed *at a similar frequency in placebo-treated patients in the controlled studies.*

Body as a Whole – General Disorders: *Frequent*: chest pain, asthenia, fever, malaise. Cardiovascular System Disorders: *Frequent*: hypertension; *Infrequent*: postural hypotension, hypotension, dependent edema, cardiac failure, myocardial ischemia or infarction. Central & Peripheral Nervous System Disorders: *Infrequent*: vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia, leg cramps, tinnitus, transient ischemic attack or cerebrovascular accident. Gastrointestinal System Disorders: *Frequent*: flatulence; *Infrequent*: gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; *Rare*: esophageal perforation. Heart Rate & Rhythm Disorders: *Infrequent*: AV block, palpitation, atrial arrhythmias including atrial fibrillation and supraventricular tachycardia, QT prolonged, bundle branch block, T-wave inversion, ventricular tachycardia; *Rare*: severe bradycardia. Metabolic & Nutritional Disorders: *Infrequent*: hyperglycemia, alkaline phosphatase increased, NPN increased. Platelet, Bleeding & Clotting Disorders: *Infrequent*: purpura, epistaxis, thrombocytopenia. Psychiatric Disorders: *Infrequent*: apathy, paroniria, paranoid reaction, libido increased, delirium; *Rare*: suicidal ideation, suicide attempt. Urinary System Disorders: *Frequent*: incontinence; *Infrequent*: hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi.

**Post-Market Adverse Drug Reactions** Other adverse events from post-approval controlled and uncontrolled clinical trials and post-marketing experience observed in patients treated with REMINYL include:

Body as a Whole – General Disorders: dehydration (including rare, severe cases leading to renal insufficiency and renal failure). Central & Peripheral Nervous System Disorders: behavioural disturbances including agitation, aggression and hallucinations. Gastrointestinal: upper and lower GI bleeding. Metabolic & Nutritional Disorders: hypokalemia.

Some of these adverse events may be attributable to cholinomimetic properties of REMINYL or in some cases may represent manifestations or exacerbations of the underlying disease processes common in the elderly population.

## DRUG INTERACTIONS

**Overview** Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine so no single pathway appears predominant. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine. CYP2D6 was involved in the formation of O-desmethyl-galantamine, whereas CYP3A4 mediated the formation of galantamine-N-oxide.

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 the clinical trials received neuroleptics, antidepressants or anticonvulsants, there is thus limited information concerning the interaction of REMINYL and REMINYL ER with these drugs.

### Drug-Drug Interactions

Effect of Other Drugs on the Metabolism of Galantamine Pharmacokinetic studies to assess the potential of galantamine for interaction with cimetidine, ranitidine, ketoconazole, erythromycin, paroxetine, warfarin and digoxin were limited to short-term, mostly single-dose studies in young healthy volunteers. Similar studies in elderly patients were not done.

*In vitro* CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of galantamine. CYP3A4 mediates the formation of galantamine-N-oxide, whereas CYP2D6 is involved in the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged in urine, no single pathway appears predominant.

*In vivo Cimetidine and Ranitidine:* Galantamine was administered as a single dose of 4 mg on Day 2 of a 3-day treatment with either cimetidine (800 mg daily; n=6 males and 6 females) or ranitidine (300 mg daily; n=6 males and 6 females). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the pharmacokinetics of galantamine.

*Ketoconazole:* Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg b.i.d. for 4 days, increased the AUC of galantamine by 30% when subjects were treated with galantamine 4 mg b.i.d. for 8 days (n=8 males and 8 females).

*Erythromycin:* Erythromycin, a moderate inhibitor of CYP3A4 at a dose of 500 mg q.i.d. for 4 days increased the AUC of galantamine by 10% when subjects received galantamine 4 mg b.i.d. for 6 days (n=8 males and 8 females).

*Paroxetine:* Paroxetine, a strong inhibitor of CYP2D6, increased the AUC of 4 mg b.i.d., 8 mg b.i.d. and 12 mg b.i.d. galantamine by 40%, 45% and 48%, respectively, in 16 healthy volunteers (8 males and 8 females) who *received galantamine together with 20 mg/day paroxetine.*

Effect of Galantamine on the Metabolism of Other Drugs

*In vitro* Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low.

*In vivo Warfarin:* Galantamine at 12 mg b.i.d. had no effect on the pharmacokinetics of R- and S-warfarin (25 mg single dose) or on the prothrombin time (n=16 males). The protein binding of warfarin was unaffected by galantamine.

*Digoxin:* Galantamine at 12 mg b.i.d. had no effect on the steady-state pharmacokinetics of digoxin (0.375 mg once daily) when they were co-administered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia (n=8 males and 8 females).

*Nicotinic Receptor Modulation*

Single *in vitro* applications of galantamine dose-dependently modulate the *effect on nicotinic receptors, having a positive allosteric (sensitizing) effect at* concentrations below 0.28 µg/mL (1 µM) and an inhibitory effect at higher concentrations. Chronic *in vitro* or *in vivo* studies on nicotinic receptor modulation have not been conducted.

It is unknown whether galantamine has an effect on the pharmacodynamic action of other drugs that act on cholinergic nicotinic receptors.

**Drug-Food Interactions** Interactions with food have not been established.

**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

**REMINYL (galantamine hydrobromide) and REMINYL ER are not indicated for use in patients with mild cognitive impairment (see WARNINGS AND PRECAUTIONS, Special Populations, Patients with Mild Cognitive Impairment (MCI), Mortality in Investigational Trials in MCI).**

*REMINYL and REMINYL ER should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease.*

REMINYL tablets should be administered twice a day, preferably with morning and evening meals.

REMINYL ER extended release capsules should be administered once daily in the morning, preferably with food. Patients and caregivers should be advised to ensure adequate fluid intake during treatment.

### Dosing Considerations

- Concomitant Treatment: In patients treated with potent CYP2D6 or CYP3A4 inhibitors, dose reductions can be considered.
- Special Populations: Dosage adjustments may be required for elderly patients (>85 years old) with low body weight (especially females), and patients with hepatic and/or renal impairment.
- Missed Dose: The missed dose should be taken at the next scheduled dose. Doses should not be doubled. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

### Recommended Dose and Dosage Adjustment

The dosage of REMINYL shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16-24 mg/day. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of REMINYL might provide additional benefit for some patients.

The recommended starting dose is 8 mg/day. The dose should be increased to the initial maintenance dose of 16 mg/day after 4 weeks. If this initial maintenance dose is well tolerated, a further increase to 24 mg/day may be considered only after a minimum of 4 weeks at 16 mg/day.

The abrupt withdrawal of REMINYL or REMINYL ER in those patients who had been receiving doses in the effective range was not associated with an increased frequency of adverse events in comparison with those continuing to receive the same doses of that drug. The beneficial effects of REMINYL and REMINYL ER are lost, however, when the drug is discontinued.

Special Populations Dose escalation for elderly patients (> 85 years old) with low body weight (especially females) or serious comorbid diseases should be undertaken with particular caution.

*Hepatic Impairment* Galantamine plasma levels may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), based on pharmacokinetic modelling, dosing with REMINYL tablets should begin with 4 mg once daily in *the morning, preferably with food, for at least 1 week. Then the dosage should* be increased to 4 mg twice a day for at least 4 weeks. For REMINYL ER extended release capsules, based on pharmacokinetic modelling, dosing should begin with 8 mg every other day in the morning, preferably with food, for at least 1 week. Then the dosage should be increased to 8 mg once daily for at least 4 weeks. In these patients, daily doses should not exceed a total of 16 mg/day. Since no data are available on the use of REMINYL or REMINYL ER in patients with severe hepatic impairment (Child-Pugh score of 10-15), REMINYL and REMINYL ER are not recommended for this population (see **WARNINGS AND PRECAUTIONS**).

*Renal Impairment* For patients with renal impairment (creatinine clearance of 9 to 60 mL/min), dose escalation should proceed cautiously and the maintenance dose should generally not exceed 16 mg/day. Since no data are available on the use of REMINYL or REMINYL ER in patients with a creatinine clearance less than 9 mL/min, REMINYL and REMINYL ER are not recommended for this population (see **WARNINGS AND PRECAUTIONS**).

In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

## OVERDOSAGE

**Symptoms** Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

In a postmarketing report, one patient who had been taking 4 mg of galantamine daily inadvertently ingested eight 4 mg tablets (32 mg total) on the tenth day of treatment. Subsequently, she developed bradycardia, QT prolongation, ventricular tachycardia and torsades de pointes accompanied by a brief loss of consciousness for which she required hospital treatment. ECG obtained just prior to initiation of galantamine treatment was normal. Two additional cases of accidental ingestion of 32 mg (nausea, vomiting, and dry mouth; nausea, vomiting, and substernal chest pain) and one of 40 mg (vomiting), resulted in brief hospitalizations for observation with full recovery. One patient, who was prescribed 24 mg/day and had a history of hallucinations over the previous two years, mistakenly received 24 mg twice daily for 34 days and developed hallucinations requiring hospitalization. Another patient, who was prescribed 16 mg/day, inadvertently ingested 160 mg and experienced sweating, vomiting, bradycardia, and near-syncope one hour later, which necessitated hospital treatment. His symptoms resolved within 24 hours.

**Treatment** *Galantamine has a plasma half-life of approximately 7-8 hours.* It is recommended that, in case of asymptomatic overdose, no further dose of REMINYL or REMINYL ER should be administered and the patient should be monitored.

As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous *system, and the neuromuscular junction. In addition to muscle weakness or* fasciculations, some or all of the following signs of cholinergic crisis may develop: severe nausea, vomiting, gastrointestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Tertiary anticholinergics such as atropine may be used as an antidote for galantamine overdosage. Intravenous atropine sulphate titrated to effect is *recommended at an initial dose of 0.5 to 1.0 mg i.v. with subsequent doses* based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics. It is not known whether galantamine and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included hypoactivity, tremors, clonic convulsions, salivation, lacrimation, chromodacryorrhea, mucoid feces, and dyspnea.

## DOSAGE FORMS

### Dosage Forms

REMINYL (galantamine hydrobromide), expressed as galantamine base, is available as film-coated tablets in the following strengths: **4 mg** galantamine as off-white, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G4" on the other side; **8 mg** galantamine as pink, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G8" on the other side; **12 mg** galantamine as orange-brown, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G12" on the other side.

REMINYL ER (galantamine hydrobromide) extended release capsules contain white to off-white pellets. The following strengths are available: **8 mg** galantamine as white opaque capsules imprinted with "G 8"; **16 mg** galantamine as pink opaque capsules imprinted with "G 16"; **24 mg** galantamine as caramel opaque capsules imprinted with "G 24".

Product Monograph available upon request.

JANSSEN-ORTHO

Member R&D PhRMA

19 Green Belt Drive, Toronto, Ontario M3C 1L9



ROBP053286E



See OBC

# PrLYRICA® 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<br>*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, 652 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<br>Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg<br>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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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%).

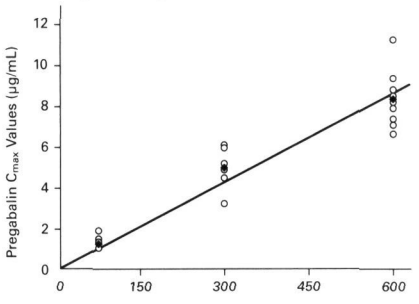
**Table 8. Pregabalin Mean (CV%[a]) Steady-State Pharmacokinetic Parameter Values in Healthy Volunteers**

| 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 (O) 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**

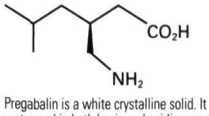
Each capsule of LYRICA (pregabalin) contains 25, 50, 75, 150 or 300 mg pregabalin, lactose monohydrate, maize starch and talc. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate 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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**LIPITOR**
atorvastatin calcium
tablets

***power** you can **trust***™

**PrLIPITOR (atorvastatin calcium) 10 mg, 20 mg, 40 mg and 80 mg tablets**

**THERAPEUTIC CLASSIFICATION:** Lipid Metabolism Regulator

**ACTIONS AND CLINICAL PHARMACOLOGY**

Please refer to the Product Monograph for complete ACTIONS AND CLINICAL PHARMACOLOGY information.

**INDICATIONS AND CLINICAL USE**

**Hypercholesterolemia**

LIPITOR (atorvastatin calcium) is indicated as an adjunct to lifestyle changes, including diet (at least equivalent to the Adult Treatment Panel III (ATP III) TLC diet), for the reduction of elevated total cholesterol (total-C), LDL-C, TG and apolipoprotein B (apo B) in hyperlipidemic and dyslipidemic conditions, when response to diet and other nonpharmacological measures alone has been inadequate, including:

Primary hypercholesterolemia (Type IIa); Combined (mixed) hyperlipidemia (Type IIb), including familial combined hyperlipidemia, regardless of whether cholesterol or triglycerides are the lipid abnormality of concern; Dysbetalipoproteinemia (Type III); Hypertriglyceridemia (Type IV); Familial hypercholesterolemia (homozygous and heterozygous). For homozygous familial hypercholesterolemia, LIPITOR should be used as an adjunct to treatments such as LDL apheresis, or as monotherapy if such treatments are not available; an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age with heterozygous familial hypercholesterolemia, if after an adequate trial of diet therapy the following findings are still present:

a. LDL-C remains ≥4.9 mmol/L (190 mg/dL) or
b. LDL-C remains ≥4.1 mmol/L (160 mg/dL) and:
   - there is a positive family history of premature cardiovascular disease or
   - two or more other CVD risk factors are present in the pediatric patient

LIPITOR also raises HDL-cholesterol and therefore lowers the LDL-C/HDL-C and total-C/HDL-C ratios in patients with primary hypercholesterolemia and combined (mixed) hyperlipidemia (Fredrickson Type IIa and IIb dyslipidemia). In pooled data from 24 controlled clinical trials, LIPITOR raised HDL-C levels 5%-7% in primary hypercholesterolemic (Type IIa) patients and 10%-15% in mixed (Type IIb) dyslipidemic patients.

In clinical trials, LIPITOR (10 to 80 mg/day) significantly improved lipid profiles in patients with a wide variety of hyperlipidemic and dyslipidemic conditions. In 2 dose-response studies in mildly to moderately hyperlipidemic patients (Fredrickson Types IIa and IIb), LIPITOR reduced the levels of total cholesterol (29-45%), LDL-C (39-60%), apo B (32-50%), TG (19-37%), and increased high density lipoprotein cholesterol (HDL-C) levels (5-9%). Comparable responses were achieved in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, combined hyperlipidemia, including familial combined hyperlipidemia and patients with non-insulin dependent diabetes mellitus. In patients with hypertriglyceridemia (Type IV), LIPITOR (10 to 80 mg daily) reduced TG (25-56%) and LDL-C levels (23-40%). LIPITOR has not been studied in conditions where the major abnormality is elevation of chylomicrons (TG levels >11 mmol/L), i.e., Types I and V.

In an open-label study in patients with dysbetalipoproteinemia (Type III), LIPITOR (10 to 80 mg daily) reduced total-C (40-57%), TG (40-56%) and IDL-C + VLDL-C levels (34-58%).

In an open-label study in patients with homozygous familial hypercholesterolemia (FH), LIPITOR (10 to 80 mg daily) reduced mean LDL-C levels (22%). In a pilot study, LIPITOR 80 mg/day showed a mean LDL-C lowering of 30% for patients not on plasmapheresis and of 31% for patients who continued plasmapheresis. A mean LDL-C lowering of 35% was observed in receptor defective patients and of 19% in receptor negative patients.

Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevations in plasma lipid levels (*e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease and alcoholism*), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C and TG. For patients with TG <4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

LDL-C (mmol/L) = total-C - [(0.37 x (TG) + HDL-C)]
LDL-C (mg/dL) = total-C - [(0.2 x (TG) + HDL-C)]'

For patients with TG levels >4.52 mmol/L (>400 mg/dL), this equation is less accurate and LDL-C concentrations should be measured directly or by ultracentrifugation.

Patients with high or very high triglyceride levels, i.e., >2.2 mmol/L (200 mg/dL) or >5.6 mmol/L (500 mg/dL), respectively, may require triglyceride-lowering therapy (fenofibrate, bezafibrate or nicotinic acid) alone or in combination with LIPITOR.

**In general, combination therapy with fibrates must be undertaken cautiously and only after risk-benefit analysis** (see **WARNINGS – Muscle Effects; PRECAUTIONS – Pharmacokinetic Interaction Studies and Potential Drug Interactions**).

Elevated serum triglycerides are most often observed in patients with the metabolic syndrome (abdominal obesity, atherogenic dyslipidemia [elevated triglycerides, small dense LDL particles and low HDL-cholesterol], insulin resistance with or without glucose intolerance, raised blood pressure and prothrombic and proinflammatory states).

(For the treatment of specific dyslipidemias, refer to the Report of the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias or to the US NCEP Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III], under **REFERENCES**).

When drugs are prescribed, attention to therapeutic lifestyle changes (reduced intake of saturated fats and cholesterol, weight reduction, increased physical activity, ingestion of soluble fibres) should always be maintained and reinforced.

**Prevention of Cardiovascular Disease**

LIPITOR is indicated to reduce the risk of myocardial infarction in adult hypertensive patients without clinically evident coronary heart disease, but with at least 3 additional risk factors for coronary heart disease such as: age ≥55 years, male sex, smoking, type 2 diabetes, left ventricular hypertrophy, other specified abnormalities on ECG, microalbuminuria or proteinuria, ratio of plasma total cholesterol to HDL-C ≥6 or premature family history of coronary heart disease.

LIPITOR is also indicated to reduce the risk of myocardial infarction and stroke in adult patients with type 2 diabetes mellitus and hypertension without clinically evident coronary heart disease, but with other risk factors such as age ≥55 years, retinopathy, albuminuria or smoking.

**CONTRAINDICATIONS**

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see **WARNINGS**).

Pregnancy and nursing women: Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). LIPITOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the possible harm. If the patient becomes pregnant while taking LIPITOR, the drug should be discontinued immediately and the patient apprised of the potential harm to the fetus. Atherosclerosis being a chronic process, discontinuation of lipid metabolism regulating drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia (see **PRECAUTIONS – Use in Pregnancy, Use in Nursing Mothers**).

**WARNINGS**

**Pharmacokinetic Interactions**

The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Atorvastatin is metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this enzyme (see **WARNINGS – Muscle Effects; PRECAUTIONS – Pharmacokinetic Interaction Studies and Potential Drug Interactions, Cytochrome P-450-mediated Interactions**).

**Muscle Effects**

Effects on skeletal muscle such as myalgia, myopathy and very rarely, rhabdomyolysis have been reported in patients treated with LIPITOR. **Very rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria, have been reported with LIPITOR and other HMG-CoA reductase inhibitors.**

Myopathy, defined as muscle pain or muscle weakness in conjunction with increases in creatine kinase (CK) values to >10 times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CK. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. LIPITOR therapy should be discontinued if markedly elevated CK levels are measured or myopathy is diagnosed or suspected.

**Predisposing Factors for Myopathy/Rhabdomyolysis:** LIPITOR, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with predisposing factors for myopathy/rhabdomyolysis. Such factors include:

Personal or family history of hereditary muscular disorders; Previous history of muscle toxicity with another HMG-CoA reductase inhibitor; Concomitant use of a fibrate or niacin; Hypothyroidism; Alcohol abuse; Excessive physical exercise; Age >70 years; Renal impairment; Hepatic impairment; Diabetes with hepatic fatty change; Surgery and trauma; Frailty; Situations where an increase in plasma levels of active ingredient may occur.

LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as sepsis, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders and uncontrolled seizures).

LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, clarithromycin, niacin (nicotinic acid), azole antifungals or nefazodone. As there is no experience to date with the use of LIPITOR given concurrently with these drugs, with the exception of pharmacokinetic studies conducted in healthy subjects with erythromycin and clarithromycin, the benefits and risks of such combined therapy should be carefully considered (see **PRECAUTIONS – Pharmacokinetic Interaction Studies and Potential Drug Interactions**).

**Hepatic Effects**

In clinical trials, persistent increases in serum transaminases >3 times the upper limit of normal occurred in <1% of patients who received LIPITOR. When the dosage of LIPITOR was reduced, or when drug treatment was interrupted or discontinued, serum transaminase levels returned to pretreatment levels. The increases were generally not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of LIPITOR without clinical sequelae.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients measurements should be repeated promptly and then performed more frequently.

**If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to >3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued.**

**LIPITOR, as well as other HMG-CoA reductase inhibitors, should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.** Active liver disease or unexplained transaminase elevations are contraindications to the use of LIPITOR; if such a condition should develop during therapy, the drug should be discontinued.

**PRECAUTIONS**

**General**

Before instituting therapy with LIPITOR (atorvastatin calcium), an attempt should be made to control elevated serum lipoprotein levels with appropriate diet, exercise, and weight reduction in overweight patients, and to treat other underlying medical problems (see **INDICATIONS AND CLINICAL USE**). Patients should be advised to inform subsequent physicians of the prior use of LIPITOR or any other lipid-lowering agents.

**Effect on the Lens**

Current long-term data from clinical trials do not indicate an adverse effect of atorvastatin on the human lens.

**Effect on Ubiquinone ($CoQ_{10}$) Levels**

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. *It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with* borderline congestive heart failure.

**Effect on Lipoprotein (a)**

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) lipoprotein concentrations. Present knowledge suggests the importance of high Lp(a) levels as an emerging risk factor for coronary heart disease. It is thus desirable to maintain and reinforce lifestyle changes in high risk patients placed on atorvastatin therapy.

**Hypersensitivity**

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, LIPITOR should be discontinued if hypersensitivity is suspected.

**Use in Pregnancy**

**LIPITOR is contraindicated during pregnancy** (see **CONTRAINDICATIONS**).

There are no data on the use of LIPITOR during pregnancy. LIPITOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking LIPITOR, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

**Use in Nursing Mothers**

In rats, milk concentrations of atorvastatin are similar to those in plasma. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see **CONTRAINDICATIONS**).

**Pediatric Use**

Safety and effectiveness of LIPITOR in patients 10-17 years of age (N=140) with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months duration in adolescent boys and postmenarchal girls. Patients treated with LIPITOR had a safety and tolerability profile generally similar to that of placebo. Doses >20 mg have not been studied in this patient population.

LIPITOR had no effect on growth or sexual maturation in boys and in girls. The effects on menstrual cycle were not assessed [see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** for **Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)**].

Adolescent females should be counselled on appropriate contraceptive methods while on LIPITOR therapy (see **CONTRAINDICATIONS; PRECAUTIONS – Use in Pregnancy**). LIPITOR has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.

Doses of LIPITOR up to 80 mg/day for 1 year have been evaluated in 8 pediatric patients with homozygous familial hypercholesterolemia.

**Geriatric Use**

Treatment experience in adults 70 years or older (N=221) with doses of LIPITOR up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially.

Elderly patients may be more susceptible to myopathy (see **WARNINGS – Muscle Effects – Predisposing Factors for Myopathy/Rhabdomyolysis**).

**Renal Insufficiency**

Plasma concentrations and LDL-C lowering efficacy of LIPITOR was shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of LIPITOR should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously (see **WARNINGS – Muscle Effects; PRECAUTIONS – Pharmacokinetic Interaction Studies and Potential Drug Interactions**). Refer also to **DOSAGE AND ADMINISTRATION**.

**Endocrine Function**

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with atorvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g., ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

**Pharmacokinetic Interaction Studies and Potential Drug Interactions**

Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying diseases and use of concomitant medications (see **PRECAUTIONS – Geriatric Use, Renal Insufficiency; Patients with Severe Hypercholesterolemia**).

**Concomitant Therapy with Other Lipid Metabolism Regulators:** Based on post-marketing surveillance, gemfibrozil, fenofibrate, other fibrates and lipid-lowering doses of niacin (nicotinic acid) may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone (see **WARNINGS – Muscle Effects**). Therefore, combined drug therapy should be approached with caution.

**Bile Acid Sequestrants:**

Patients with mild to moderate hypercholesterolemia: LDL-C reduction was greater when LIPITOR 10 mg and colestipol 20 g were coadministered (-45%) than when either drug was administered alone (-35% for LIPITOR and -22% for colestipol).

Patients with severe hypercholesterolemia: LDL-C reduction was similar (-53%) when LIPITOR 40 mg and colestipol 20 g were coadministered when compared to LIPITOR 80 mg alone. Plasma concentration of atorvastatin was lower (approximately 26%) when LIPITOR 40 mg plus colestipol 20 g were coadministered compared with LIPITOR 40 mg alone. However, the combination drug therapy was less effective in lowering triglycerides than LIPITOR monotherapy in both types of hypercholesterolemic patients.

When LIPITOR is used concurrently with colestipol or any other resin, an interval of at least 2 hours should be maintained between the two drugs, since the absorption of LIPITOR may be impaired by the resin.

**Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (nicotinic acid):** Although there is limited experience with the use of LIPITOR given concurrently with fibric acid derivatives and niacin, the benefits and risks of such combined therapy should be carefully considered. The risk of myopathy during treatment with drugs in this class, including atorvastatin, is increased with concurrent administration (see **WARNINGS – Muscle Effects**).

**Coumarin Anticoagulants:** LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

**Digoxin:** In healthy subjects, digoxin pharmacokinetics at steady-state were not significantly altered by coadministration of digoxin 0.25 mg and LIPITOR 10 mg daily. However, digoxin steady-state concentrations increased approximately 20% following coadministration of digoxin 0.25 mg and LIPITOR 80 mg daily. Patients taking digoxin should be monitored appropriately.

**Antihypertensive agents (amlodipine):** In clinical studies, LIPITOR was used concomitantly with antihypertensive agents without evidence to date of clinically significant adverse interactions. In healthy subjects, atorvastatin pharmacokinetics were not altered by the coadministration of LIPITOR 80 mg and amlodipine 10 mg at steady state.

**(quinapril):** In a randomized, open-label study in healthy subjects, steady-state quinapril dosing (80 mg QD) did not significantly affect the pharmacokinetic profile of atorvastatin tablets (10 mg QD).

**Oral Contraceptives and Hormone Replacement Therapy:** Coadministration of LIPITOR with an oral contraceptive containing 1 mg norethindrone and 35 µg ethinyl estradiol increased plasma concentrations (AUC levels) of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive. In clinical studies, LIPITOR was used concomitantly with estrogen replacement therapy without evidence of clinically significant adverse interactions.

**Antacids:** Administration of aluminum and magnesium based antacids, such as Maalox® TC Suspension, with LIPITOR decreased plasma concentrations of LIPITOR by approximately 35%. LDL-C reduction was not altered but the triglyceride-lowering effect of LIPITOR may be affected.

**Cimetidine:** Administration of cimetidine with LIPITOR did not alter plasma concentrations or the LDL-C lowering efficacy of LIPITOR, however, the triglyceride-lowering effect of LIPITOR was reduced from 34% to 26%.

**Cytochrome P-450-mediated Interactions:** Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4. Erythromycin, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as grapefruit juice, some macrolide antibiotics (i.e., erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (i.e., itraconazole, ketoconazole), protease inhibitors, or the antidepressant nefazodone, may have the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including LIPITOR. Caution should thus be exercised with concomitant use of these agents (see **WARNINGS – Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS – Renal Insufficiency, Endocrine Function; DOSAGE AND ADMINISTRATION**).

**Terfenadine:** In healthy subjects, coadministration of maximum doses of atorvastatin (80 mg) and terfenadine (120 mg), a CYP 3A4 substrate, was shown to produce a modest increase in terfenadine AUC. The QTc interval remained unchanged. However, since an interaction between these two drugs cannot be excluded in patients with predisposing factors for arrhythmia, (e.g., pre-existing prolonged QT interval, severe coronary artery disease, hypokalemia), caution should be exercised when these agents are coadministered (see **WARNINGS – Pharmacokinetic Interactions; DOSAGE AND ADMINISTRATION**).

**Antipyrine:** Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme (cytochrome P-450) system. LIPITOR had no effect on the pharmacokinetics of antipyrine, thus interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

**Macrolide Antibiotics (azithromycin, clarithromycin, erythromycin):** In healthy adults, coadministration of LIPITOR (10 mg QD) and azithromycin (500 mg QD) did not significantly alter the plasma concentrations of atorvastatin. However, coadministration of atorvastatin (10 mg QD) with erythromycin (500 mg QID) or clarithromycin (500 mg BID), which are both CYP 3A4 inhibitors, increased plasma concentrations of atorvastatin by approximately 40% and 80%, respectively (see **WARNINGS – Muscle Effects**).

**Protease Inhibitors (nelfinavir mesylate):** In healthy adults, coadministration of nelfinavir mesylate (1250 mg BID), a known CYP 3A4 inhibitor, and atorvastatin (10 mg QD) resulted in increased plasma concentrations of atorvastatin. AUC and $C_{max}$ of atorvastatin were increased by 74% and 122% respectively.

**Patients with Severe Hypercholesterolemia**

Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) are associated with increased plasma levels of atorvastatin. **Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors** (see **WARNINGS – Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS – Pharmacokinetic Interaction Studies and Potential Drug Interactions; DOSAGE AND ADMINISTRATION**).

**Drug/Laboratory Test Interactions**

LIPITOR may elevate serum transaminase and creatine kinase levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with LIPITOR, cardiac and noncardiac fractions of these enzymes should be determined.

**ADVERSE REACTIONS**

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies (placebo-controlled and active-controlled comparative studies with other lipid-lowering agents) involving 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to LIPITOR. Of these 2502 patients, 1721 were treated for at least 6 months and 1253 for 1 year or more.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of LIPITOR and reported to be possibly, probably or definitely drug related include constipation, diarrhea, dyspepsia, flatulence, nausea, headache, pain, myalgia and asthenia.

The following additional adverse events were reported in clinical trials (not all have been associated with a causal relationship to LIPITOR therapy): muscle cramps, myositis, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, impotence, hyperglycemia and hypoglycemia.

**Heterozygous Familial Hypercholesterolemia in Pediatric Patients (ages 10-17 years)**

In a 26-week controlled study in boys and postmenarchal girls (n=187, where 140 patients received LIPITOR), the safety and tolerability profile of LIPITOR 10 to 20 mg daily was similar to that of placebo. The adverse events reported in ≥1% of patients were abdominal pain, depression and headache (see **PRECAUTIONS – Pediatric Use**).

**Laboratory Changes and Adverse Events**

The criteria for clinically significant laboratory changes were >3 X the upper limit of normal (ULN) for liver enzymes, and >5 X ULN for creatine kinase. A total of 8 unique subjects met one or more of these criteria during the double-blind phase. Hence, the incidence of patients who experienced abnormally high enzymatic levels (AST/ALT and creatine kinase) was >4% (8/187).

Five atorvastatin and one placebo subjects had increases in CK >5 X ULN during the double-blind phase; two of the five atorvastatin-treated subjects had increases in CK >10 X ULN. Two subjects had clinically significant increases in ALT.

**Post-Market Adverse Drug Reaction:** The following adverse events have also been reported during post-marketing experience with LIPITOR, regardless of causality assessment: Very rare reports: severe myopathy with or without rhabdomyolysis (see **WARNINGS – Muscle Effects; PRECAUTIONS – Renal Insufficiency, Pharmacokinetic Interaction Studies and Potential Drug Interactions**). Isolated reports: Gynecomastia, thrombocytopenia, arthralgia and allergic reactions including urticaria, angioneurotic edema, anaphylaxis and bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis) and fatigue. These may have no causal relationship to atorvastatin.

**Abnormal Hematologic and Clinical Chemistry Findings**

Ophthalmologic observations: see **PRECAUTIONS**.

Laboratory Tests: Increases in serum transaminase levels have been noted in clinical trials (see **PRECAUTIONS**).

**DOSAGE AND ADMINISTRATION**

Patients should be placed on a standard cholesterol-lowering diet [at least equivalent to the Adult Treatment Panel III (ATP III) TLC diet] before receiving LIPITOR, and should continue on this diet during treatment with LIPITOR. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with LIPITOR, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed.

Primary Hypercholesterolemia and Combined (Mixed) Dyslipidemia, Including Familial Combined Hyperlipidemia

The recommended starting dose of LIPITOR is 10 or 20 mg once daily, depending on the patient's LDL-C reduction required (see Tables 1 and 2). Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of LIPITOR is 10 to 80 mg once daily. Doses can be given at any time of the day, with or without food, and should preferably be given in the evening. A significant therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 2-4 weeks. The response is maintained during chronic therapy. Adjustments of dosage, if necessary, should be made at intervals of 2 to 4 weeks. The maximum dose is 80 mg/day.

TABLE 1. Dose-Response in Patients With Mild-to-Moderate Hypercholesterolemia (Mean Percent Change from Baseline)[a]

| Lipid Parameter | LIPITOR Dose (mg/day) | | | |
|---|---|---|---|---|
| | 10 (N=22) | 20 (N=20) | 40 (N=21) | 80 (N=23) |
| Total-C: 7.1 mmol/L[b] (273 mg/dL)[b] | -29 | -33 | -37 | -45 |
| LDL-C: 4.9 mmol/L[b] (190 mg/dL)[b] | -39 | -43 | -50 | -60 |

[a] Results are pooled from 2 dose-response studies
[b] Mean baseline values

The dosage of LIPITOR should be individualized according to the baseline LDL-C, total-C/HDL-C ratio and/or TG levels to achieve the recommended target lipid values at the lowest dose needed to achieve the LDL-C target (see Recommendations for the Management of Dyslipidemia and the Prevention of Cardiovascular Disease [Canada], summarized below in Table 2, and/or the Third Report of the US National Cholesterol Education Program [NCEP Adult Treatment Panel III]), and the patient's response. Lipid levels should be monitored periodically and, if necessary, the dose of LIPITOR adjusted based on target lipid levels recommended by guidelines.

TABLE 2. Canadian Recommendations for the Target Lipid Values Based on Level of Risk

| Risk Category | Target Levels | | |
|---|---|---|---|
| | LDL-C level (mmol/L) | | Total-C/HDL-C ratio |
| High[†] (10-year risk of CAD ≥20%, or a history of diabetes mellitus[††] or any atherosclerotic disease) | <2.5 | **and** | <4.0 |
| Moderate (10-year risk 11%-19%) | <3.5 | **and** | <5.0 |
| Low[†††] (10-year risk ≤10%) | <4.5 | **and** | <6.0 |

Note: LDL-C = low-density lipoprotein cholesterol.

[†] Apolipoprotein B can be used as an alternative measurement, particularly for follow-up of patients treated with statins. An optimal level of apolipoprotein B in a patient at high risk is <0.9 g/L, in a patient at moderate risk <1.05 g/L and in a patient at low risk <1.2 g/L.
[††] Includes patients with chronic kidney disease and those undergoing long-term dialysis.
[†††] In the 'very low' risk stratum, treatment may be deferred if the 10-year estimate of cardiovascular disease is <5% and the LDL-C level is <5.0 mmol/L.

Severe Dyslipidemias

In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (Type III), higher dosages (up to 80 mg/day) may be required (see **WARNINGS – Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS – Pharmacokinetic Interaction Studies and Potential Drug Interactions**).

**Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)**

In this population, the recommended starting dose of LIPITOR is 10 mg/day; the maximum recommended dose is 20 mg/day (doses >20 mg/day have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines; **INDICATIONS AND CLINICAL USE**). Adjustments should be made at intervals of 4 weeks or more.

NCEP (National Cholesterol Education Program) Pediatric Panel Guidelines: Classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

| Category | Total-C (mmol/L [mg/dL]) | LDL-C (mmol/L [mg/dL]) |
|---|---|---|
| Acceptable | <4.4 [170] | <2.8 [110] |
| Borderline | 4.4-5.1 [170-199] | 2.8-3.3 [110-129] |
| High | ≥5.2 [200] | ≥3.4 [130] |

**Concomitant Therapy**

See **PRECAUTIONS – Drug/Laboratory Test Interactions**.

**Dosage in Patients With Renal Insufficiency**

See **PRECAUTIONS**.

**AVAILABILITY OF DOSAGE FORMS**

LIPITOR (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg, 40 mg and 80 mg atorvastatin per tablet.

1. Friedewald WT, *et al. Clin Chem* 1972;18(6):489-502.

For a copy of the Product Monograph or full Prescribing Information, please contact:

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See page A-6

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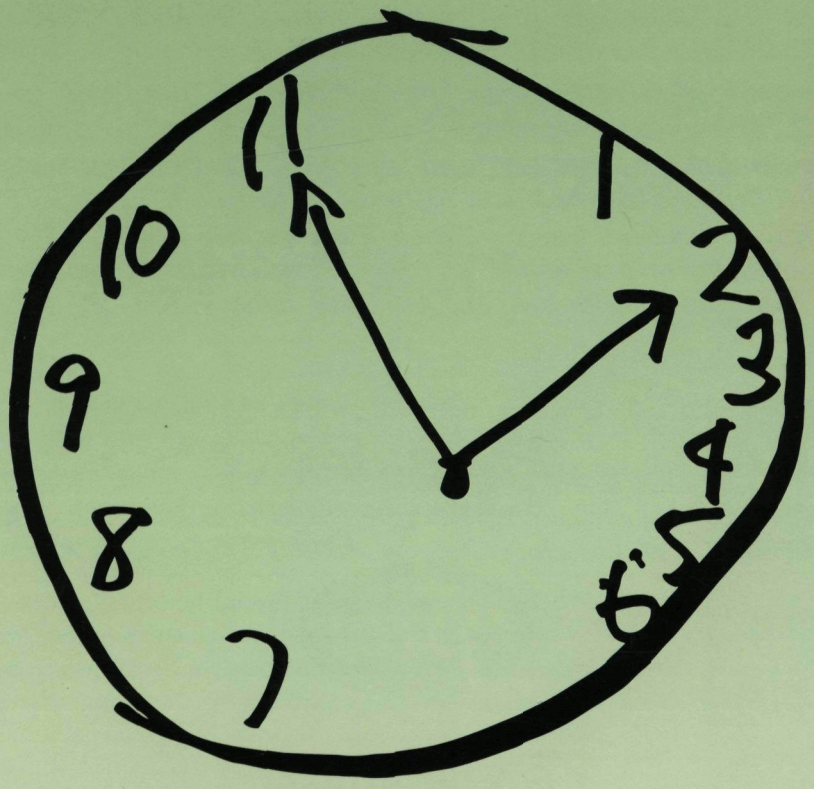

Once-a-Day
REMINYL ER

# Take the Time to Look at REMINYL* ER.

## Consider once-a-day REMINYL* ER as initial treatment in AD.[1]

PrREMINYL and PrREMINYL ER (galantamine hydrobromide) are indicated for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. REMINYL ER has not been studied in controlled clinical trials for longer than 6 months.

The most common side effects for REMINYL ER (vs. placebo) in a clinical trial were nausea (17% vs. 5%), dizziness (10% vs. 4%), injury (8% vs. 6%) and headache (8% vs. 6%). For patients who experienced adverse events, the majority occurred during the dose-escalation phase.

There is no evidence that galantamine alters the course of the underlying dementing process.

† Data does not support an indication for either vascular dementia (VaD) or Alzheimer's disease (AD) and concomitant cerebrovascular disease (AD+CVD).

In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), based on pharmacokinetic modelling, dosing with REMINYL should begin with 4 mg once daily for at least 1 week. For REMINYL ER, based on pharmacokinetic modelling, dosing should begin with 8 mg every other day for at least 1 week. Then the dosage should be increased to 4 mg twice a day for REMINYL or 8 mg once daily for REMINYL ER for at least 4 weeks. In these patients, daily doses should not exceed 16 mg/day. REMINYL and REMINYL ER are not recommended in patients with severe hepatic impairment (Child-Pugh score of 10-15).

In patients with renal impairment (creatinine clearance of 9-60 mL/min), dose escalation should proceed cautiously and the maintenance dose should generally not exceed 16 mg/day. REMINYL and REMINYL ER are not recommended in patients with creatinine clearance of less than 9 mL/min.

Dose reductions can be considered in patients treated with potent CYP2D6 or CYP3A4 inhibitors.[1]

REFERENCE: 1. REMINYL* (galantamine hydrobromide tablets), REMINYL* ER (galantamine hydrobromide extended-release capsules) Product Monograph, JANSSEN-ORTHO Inc., September 29, 2005.



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**AD with Cerebrovascular Disease and VaD data for REMINYL now included in Product Monograph.†**

PrReminyl* Galantamine hydrobromide tablets

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For brief prescribing information see page A-21