

# INFORMATION FOR AUTHORS SUBMISSION PROCESS

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### *Journals*

1. Rose ME, Huerbin MB, Melick J, 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*

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

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### PRESCRIBING SUMMARY



### PATIENT SELECTION CRITERIA

#### THERAPEUTIC CLASSIFICATION

Analgesic Agent

#### INDICATIONS AND CLINICAL USE

LYRICA (pregabalin) is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia and spinal cord injury. LYRICA is indicated for the management of pain associated with fibromyalgia. The efficacy of LYRICA in the management of pain associated with fibromyalgia for up to 6 months was demonstrated in a placebo-controlled trial in patients who had initially responded to LYRICA during a 6-week open-label phase.

#### Use in Special Populations

**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.

**Renal:** There have been reports of patients, with or without previous history, experiencing renal failure while receiving pregabalin alone or in combination with other medications. Discontinuation of pregabalin showed reversibility of this event in some cases (see Product Monograph, **WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions**; and **DOSAGE AND ADMINISTRATION**). Because pregabalin is eliminated primarily by renal excretion, the dose of pregabalin should be adjusted as noted for elderly patients or those with renal impairment (see Product Monograph, **ACTION AND CLINICAL PHARMACOLOGY AND DOSAGE AND ADMINISTRATION**).

**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.

**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.

#### CONTRAINDICATIONS

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



### SAFETY INFORMATION

#### WARNINGS AND PRECAUTIONS

**Angioedema:** There have been post-marketing reports of angioedema in patients, some without reported previous history/episode(s), during initial/acute and chronic treatment with LYRICA. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), neck, throat, and larynx/upper airway. There have been reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Some of these patients did not have reported previous history/episode(s) of angioedema. LYRICA should be immediately discontinued in patients with these symptoms. During the pre-marketing assessment of pregabalin in clinical trials, angioedema was reported as a rare reaction (see Product Monograph, **ADVERSE REACTIONS, Less Common Clinical Trial Adverse Reactions and Post-Marketing Adverse Drug Reactions**).

Caution should be exercised when prescribing LYRICA to patients with previous history/episode(s) of angioedema and related events. In addition, patients who are taking other drugs associated with angioedema (eg, ACE-inhibitors) may be at increased risk of developing this condition.

**Hypersensitivity:** There have been post-marketing reports of hypersensitivity reactions (e.g. skin redness, blisters, hives, rash, dyspnea, and wheezing). Pregabalin should be discontinued immediately if such symptoms occur (see Product Monograph, **Post-Marketing Adverse Drug Reactions**).

**Renal Failure:** In both clinical trials of various indications and post-marketing database, there are reports of patients, with or without previous history, experiencing renal failure while receiving pregabalin alone or in combination with other medications. Discontinuation of pregabalin should be considered as it has shown reversibility of this event in some cases. Caution is advised when prescribing pregabalin to the elderly or those with any degree of renal impairment (see Product Monograph, **Special Populations, Renal**; **Abrupt or Rapid Discontinuation**; **ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions**; and **DOSAGE AND ADMINISTRATION**).

**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. 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.

**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 Product Monograph, **Post-Marketing Adverse Drug Reactions**).

Patients should be informed that if changes in vision occur, they should notify their physician.

**Peripheral Edema:** LYRICA may cause peripheral edema. In controlled peripheral neuropathic pain and fibromyalgia clinical trials, pregabalin treatment caused peripheral edema in 9% of patients compared with 3% of patients in the placebo group. In these studies, 0.7% of pregabalin patients and 0.3% of placebo patients withdrew due to peripheral edema (see Product Monograph, **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 and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. 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.

**Congestive Heart Failure:** In controlled clinical studies, events of congestive heart failure were reported at an infrequent rate (between 0.1% and 1%; see Product Monograph, **ADVERSE REACTIONS, Less Common Clinical Trial Adverse Reactions**).

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin (see Product Monograph, **ADVERSE REACTIONS, Post-marketing Adverse Drug Reactions**). Although this adverse reaction has mostly been observed in elderly cardiovascular-compromised patients during pregabalin treatment for a neuropathic pain indication, some cases have occurred in patients without reported edema or previous history of cardiovascular disease. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

**Gastrointestinal:** There have been post-marketing reports of events related to reduced lower gastrointestinal tract function (eg, intestinal obstruction, paralytic ileus, and constipation) in patients, some without reported previous history/episode(s), during initial/acute and chronic treatment with LYRICA, primarily in combination with other

medications that have the potential to produce constipation. Some of these events were considered serious and required hospitalization. In a number of instances, patients were taking opioid analgesics including tramadol.

Caution should be exercised when LYRICA and opioid analgesics are used in combination, and measures to prevent constipation may be considered, especially in female patients and elderly as they may be at increased risk of experiencing lower gastrointestinal-related events (see Product Monograph, **ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions**).

**Weight Gain:** LYRICA may cause weight gain. In pregabalin-controlled peripheral neuropathic pain and fibromyalgia clinical trials with durations of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin-treated patients and 3% of placebo-treated patients. Few patients treated with pregabalin (0.6%) withdrew from controlled trials due to weight gain (see Product Monograph, **ADVERSE REACTIONS, Weight Gain**).

Pregabalin-associated weight gain was related to dose and duration of exposure. Pregabalin-associated weight gain did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema and was not necessarily due to edema-related events (see Product Monograph, **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.

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<sub>1c</sub>).

**Dizziness and Somnolence:** LYRICA may cause dizziness and somnolence. In controlled studies, pregabalin caused dizziness in 32% of patients compared to 8% in placebo. Somnolence was experienced by 17% and 4% 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 5% (placebo: 0.5%) and 3% (placebo: 0.1%) of the pregabalin-treated patients, respectively. For the remaining patients who experienced these events, dizziness and somnolence persisted until the last dose of pregabalin in 35% and 49% of the patients, respectively (see Product Monograph, **ADVERSE REACTIONS, Tables 2, 4, and 11, and Post-Marketing Adverse Drug Reactions**).

**Abrupt or Rapid Discontinuation:** Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis and diarrhea. Pregabalin should be tapered gradually over a minimum of one week rather than discontinued abruptly (see Product Monograph, **ADVERSE REACTIONS, Adverse Events Following Abrupt or Rapid Discontinuation**).

#### ADVERSE REACTIONS

*Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in clinical trials may not reflect the rates observed in practice and should not be compared to the rates in clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

#### Clinical Trial Adverse Drug Reactions

**Most Common Adverse Events in All Pre-marketing Controlled Clinical Studies of Neuropathic Pain:** The most commonly observed adverse events ( $\geq 5\%$  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.

**Adverse Events from a Controlled Clinical Study in Neuropathic Pain Associated with Spinal Cord Injury:** The most commonly observed treatment-related adverse events ( $\geq 5\%$  and twice the rate of that seen in placebo) in pregabalin-treated patients were: somnolence, dizziness, asthenia, dry mouth, edema, myasthenia, constipation, thinking abnormal, amblyopia, and amnesia. Adverse events were usually mild to moderate in intensity.

**Most Common Adverse Events in Controlled Clinical Studies in Fibromyalgia:** The most commonly observed treatment-related adverse events ( $\geq 5\%$  and twice the rate of that seen in placebo) in pregabalin-treated patients were: dizziness (37.5%), somnolence (18.6%), weight gain (10.6%), dry mouth (7.9%), blurred vision (6.7%), peripheral edema (6.1%), constipation (5.8%), and disturbance in attention (5.3%). Adverse events were usually mild to moderate in intensity.

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect a patient has had a serious or unexpected reaction to this drug, you may notify Health Canada by telephone: 1-866-234-2345.



## ADMINISTRATION

### DOSING CONSIDERATIONS

#### Patients with Impaired Renal Function

Pregabalin is primarily eliminated from the systemic circulation by renal excretion as unchanged drug. In some elderly patients and those with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Table in Supplemental Product Information).

#### Adults

**Neuropathic pain associated with diabetic peripheral neuropathy and 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 (see Product Monograph, **ADVERSE REACTIONS**, Tables 1 and 5). Doses above 600 mg/day have not been studied and are not recommended.

**Neuropathic pain associated with spinal cord injury:** The recommended starting dose for LYRICA is 150 mg/day, given in two divided doses (75 mg BID), 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, a maximum daily dose of 600 mg (300 mg twice a day, BID) may be considered. Doses above 600 mg/day have not been studied and are not recommended.

**Pain associated with fibromyalgia:** The recommended dosage is 300 to 450 mg/day, given in two divided doses. The recommended starting dose for LYRICA is 150 mg/day, given in two divided doses (75 mg BID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Based on individual response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg BID (450 mg/day). In some patients, efficacy of LYRICA has been demonstrated within the first 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 of fibromyalgia, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced significantly higher rates of adverse events and discontinued the trial more frequently (see Product Monograph, **ADVERSE REACTIONS**, Tables 7 and 10). In view of the dose-related adverse events, the decision to treat patients with doses above 450 mg/day should be based on clinical judgment of the treating physician. Doses above 600 mg/day have not been studied and are not recommended.

## ADMINISTRATION

LYRICA is given orally with or without food.



## TEXT REFERENCES

### References:

- LYRICA Product Monograph, Pfizer Canada Inc., June 21, 2010.
- Moulin DE *et al*. Pharmacological management of chronic neuropathic pain – consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage* 2007;12:13-21.
- Arnold LM *et al*. A 14-week, randomized, double-blind, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *J Pain* 2008;9:792-805.
- 14-week, randomized, double-blind, multiple-dose, placebo-controlled, multicentre study. 745 patients who had moderate-to-severe pain, i.e. mean baseline score (mean of the last 7 daily diary pain scores prior to study medication) of  $\geq 4$ , and a diagnosis of fibromyalgia based on the ACR criteria. This study used an enriched population as placebo responders ( $\geq 30\%$  reduction in mean pain scores) during the one-week run-in phase were discontinued and did not enter the double-blind phase. 1.6% of patients screened ( $n=19/1,195$ ) were reported to be placebo responders. Patients were randomized to LYRICA 300 mg/day ( $n=183$ ), 450 mg/day ( $n=190$ ), 600 mg/day ( $n=188$ ), or placebo ( $n=184$ ). Patients were allowed to take acetaminophen up to 4 g/day as needed for pain relief. The number of completers was: LYRICA 300 mg/day ( $n=123$ ), 450 mg/day ( $n=125$ ), 600 mg/day ( $n=113$ ), or placebo ( $n=125$ ). The primary endpoint was the reduction in endpoint mean pain scores. Pain scores rated on 11-point numerical scale from 0 (no pain) to 10 (worst possible pain) during the past 24 hours. Mean baseline pain scores were 6.7 for LYRICA 300 mg/day, 6.7 for 450 mg/day, 6.8 for 600 mg/day, and 6.6 for placebo.
- Crofford LJ *et al*. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. *Pain* 2008;136:419-31.
- 26-week, long-term relapse observation study. Patients who met the ACR criteria for fibromyalgia and who had a score of  $\geq 4$  on the pain Visual Analog Scale (VAS) were eligible to enter a 6-week, open-label, dose-optimization phase. During this phase, patients were titrated up to a total daily dose of 300 mg, 450 mg, or 600 mg. 566 LYRICA responders were randomized in the double-blind phase to either their optimized LYRICA dose ( $n=279$ ) or to placebo ( $n=287$ ). 38% of LYRICA responders completed 26 weeks of treatment vs 19% on placebo. The primary endpoint was time to loss of therapeutic response. Loss of therapeutic response was defined as having either a  $<30\%$  reduction in pain VAS score, or worsening of symptoms necessitating alternate treatment. Responders were defined as having a  $\geq 50\%$  reduction in pain on the VAS and self-rating on the Patient Global Impression of Change scale of "much improved" or "very much improved".
- Freyenhagen 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.
- In a 12-week, multicentre, randomized, double-blind, placebo-controlled study, 338 patients with either DPN ( $n=249$ ) or PHN ( $n=89$ ) were randomized to receive BID flexible-dose pregabalin (150-600 mg/day), fixed-dose pregabalin (600 mg/day) or placebo. In the flexible-dose arm, dose could be adjusted up or down over the first four weeks based on patients' individual response and tolerability. The primary efficacy measurement was mean pain score at endpoint, derived from ratings recorded by patients in a daily diary on an 11-point numerical pain rating scale (0=no pain, 10=worst possible pain). A significant difference in pain scores versus placebo was seen in the flexible dose range 150-600 mg/day ( $p \leq 0.05$ , weeks 2-3 and  $p \leq 0.01$ , weeks 4-12), and the fixed dose of 600 mg/day ( $p \leq 0.05$ , week 1 and  $p \leq 0.01$ , weeks 2-12).
- Mease PJ *et al*. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *J Rheumatol* 2008;35:502-14.
- Multicentre, double-blind, 13-week, randomized trial. 748 patients who met the ACR criteria for fibromyalgia and who had an average mean pain score of  $\geq 4$  on an 11-point numeric rating scale (NRS) during the baseline assessment were randomized to LYRICA 300 mg/day ( $n=185$ ), 450 mg/day ( $n=183$ ), 600 mg/day ( $n=190$ ), or placebo ( $n=190$ ). Patients were allowed to take acetaminophen up to 4 g/day as needed for pain relief. The number of completers was: LYRICA 300 mg/day ( $n=123$ ), 450 mg/day ( $n=121$ ), 600 mg/day ( $n=111$ ), or placebo ( $n=130$ ). The primary endpoint was the reduction in endpoint mean pain scores (mean of the last 7 daily pain scores while on study medication). Pain-related sleep difficulties were assessed using the Medical Outcomes Study-Sleep Scale (MOS-SS), a scale that runs from 0-100. Mean baseline MOS-SS score for overall sleep problem index was 65.0.

## SUPPLEMENTAL PRODUCT INFORMATION

### Warnings and Precaution

See the Product Monograph for further information on the following: tumorigenic potential, ophthalmological effects, peripheral edema, congestive heart failure, weight gain, dizziness and somnolence, sexual function/reproduction, and special populations.

### Drug Interactions

**Overview:** Since pregabalin is predominately excreted unchanged in the urine, undergoes negligible metabolism in humans ( $\approx 2\%$  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.

**Drug Abuse and Dependence/Liability:** 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).

### ADMINISTRATION

**Dosage Adjustment Based on Renal Function:** Dosing adjustment should be based on creatinine clearance (CL<sub>r</sub>), as indicated in Table 1. 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 below).

Table 1. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CL <sub>r</sub> ) (mL/min)	Total Pregabalin Daily Dose (mg/day)* Recommended Dose Escalation*				Dose Regimen
	Starting dose	up to		Maximum daily dose	
$\geq 60$	150	300	450	600	BID or TID
30-60	75	150	225	300	BID or TID
15-30	25-50	75	100-150	150	QD or BID
$< 15$	25	25-50	50-75	75	QD

**Supplementary dosage following hemodialysis (mg)<sup>†</sup>**

Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg

Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg

Patients on the 50-75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg

Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.  
<sup>\*</sup> Based on individual patient response and tolerability.  
<sup>†</sup> Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.  
<sup>‡</sup> Supplementary dose is a single additional dose.

### Overdosage

For management of a suspected drug overdose, contact your regional Poison Control Centre.

**Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans:** The highest known dose of pregabalin received in the clinical development program in which there was no fatal outcome 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. In post-marketing experience, fatal outcomes in cases in which pregabalin has been taken in combination with other medications have been reported with a pregabalin overdose as low as 800 mg in a day. In none of these cases has pregabalin been established as the cause of death or in pregabalin monotherapy. The lowest fatal dose with pregabalin alone has not yet been identified.

The most commonly reported adverse events observed when pregabalin was taken in overdose (dose range from 800 mg/day up to 11,500 mg as a single dose) included affective disorder, somnolence, confusional state, depression, agitation, and restlessness.

**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.

### Availability of Dosage Forms

LYRICA is available in dosage strengths of 25 mg, 50 mg, 75 mg, 100 mg\*, 150 mg, 200 mg\*, 225 mg, and 300 mg capsules.

\* Not commercially available in Canada

For a copy of the Product Monograph or full Prescribing Information, please contact: Pfizer Canada Medical Information at 1-800-463-6001 or visit [www.pfizer.ca](http://www.pfizer.ca).



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See our AD on A-6, A-7



## Safety Information



## Prescribing Summary



## Patient Selection Criteria

### Analgesic

#### INDICATIONS

CYMBALTA<sup>®</sup> (duloxetine hydrochloride) is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN).

CYMBALTA<sup>®</sup> is indicated for the management of pain associated with fibromyalgia (FM).

CYMBALTA<sup>®</sup> is indicated for the management of chronic low back pain (CLBP).

The efficacy of CYMBALTA<sup>®</sup> has been demonstrated in controlled clinical trials for up to 12 weeks in DPN and FM and up to 13 weeks in patients with CLBP. The physician who elects to use CYMBALTA<sup>®</sup> for extended periods in DPN, FM or CLBP, should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

#### CONTRAINDICATIONS

CYMBALTA<sup>®</sup> is contraindicated in patients with a known hypersensitivity to the drug or the other components of the product.

#### Monoamine Oxidase Inhibitors (MAOIs)

CYMBALTA<sup>®</sup> should not be used concomitantly with a monoamine oxidase inhibitor (MAOI), including the antibiotic linezolid and the thiazine dye methylnium chloride (methylene blue) which are less well-known examples of MAOIs or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping CYMBALTA<sup>®</sup> before starting an MAOI.

#### Hepatic Impairment

CYMBALTA<sup>®</sup> is contraindicated in patients with any liver disease resulting in hepatic impairment.

#### Uncontrolled Narrow-angle Glaucoma

In clinical trials, CYMBALTA<sup>®</sup> was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma.

#### Severe Renal Impairment

CYMBALTA<sup>®</sup> is contraindicated in patients with severe renal impairment (i.e., creatinine clearance <30 mL/min) or end-stage renal disease.

#### Thioridazine

Concomitant use of CYMBALTA<sup>®</sup> and thioridazine is contraindicated.

#### CYP1A2 Inhibitors

CYMBALTA<sup>®</sup> should not be used concomitantly with potent CYP1A2 inhibitors (e.g., fluvoxamine) and some quinolone antibiotics (e.g., ciprofloxacin or enoxacin).

#### USE IN SPECIAL POPULATIONS

##### Use in Pregnant Women:

Safe use of CYMBALTA<sup>®</sup> during pregnancy has not been established. Therefore, CYMBALTA<sup>®</sup> should not be administered to pregnant women or those intending to become pregnant, unless, in the opinion of the treating physician, the expected benefits to the patient markedly outweigh the possible hazards to the fetus.

Post-marketing reports indicate that some neonates exposed to SSRIs or newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery (see Product Monograph for complete details). When treating a pregnant woman with CYMBALTA<sup>®</sup> during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. There are no adequate and well-controlled studies in pregnant women. In animal reproductive studies, duloxetine has been shown to have adverse effects on embryo/fetal and post-natal development. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

The effect of duloxetine on labour and delivery in humans is unknown. However, because duloxetine and/or its metabolites cross the placenta in rats and because of the possibility that duloxetine and/or its metabolites may have adverse effects on the newborn, duloxetine should be used during labour and delivery only if the potential benefit justifies the potential risk to the fetus.

##### Use in Nursing Women:

Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on CYMBALTA<sup>®</sup> is not recommended. Patients should be advised to notify their physician if they are breastfeeding.

##### Use in Pediatrics (<18 years of age):

The safety and efficacy of CYMBALTA<sup>®</sup> in pediatric patients (<18 years of age) have not been established and its use in this patient population is not indicated.

##### Use in Geriatrics (≥65 years of age):

Of the 1429 CYMBALTA<sup>®</sup>-treated patients in the DPN studies, 31.9% (456) were 65 years of age or over. Of the 1226 CYMBALTA<sup>®</sup>-treated patients in FM studies, 7.9% (97) were 65 years of age or over. Of the 600 CYMBALTA<sup>®</sup>-treated patients in CLBP placebo-controlled clinical studies, 22.3% (134) were 65 years of age or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and although other reported clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

##### Use in Patients with Substantial Alcohol Use:

Use of CYMBALTA<sup>®</sup> in patients who consume substantial amounts of alcohol may be associated with severe liver

#### WARNINGS AND PRECAUTIONS

##### Potential Association with Behavioural and Emotional Changes, Including Self-Harm

Recent analyses of pediatric placebo-controlled clinical trial safety databases from selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo. The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.

There are clinical trial and post-marketing reports with SSRIs and other newer antidepressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, and depersonalization. In some cases, the events occurred within several weeks of starting treatment.

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

##### Discontinuation Symptoms

Patients currently taking SSRIs or newer antidepressants should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer antidepressant drug, a gradual reduction in the dose rather than an abrupt cessation is recommended.

##### Monoamine Oxidase Inhibitors (MAOI):

The effects of combined use of CYMBALTA<sup>®</sup> and MAOIs have not been evaluated in humans or animals. Because CYMBALTA<sup>®</sup> is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that CYMBALTA<sup>®</sup> not be used in combination with an MAOI, including the antibiotic linezolid and the thiazine dye methylnium chloride (methylene blue) which are less well-known examples of MAOIs, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping CYMBALTA<sup>®</sup> before starting an MAOI.

##### Hepatic Impairment:

Patients with clinically evident hepatic impairment have decreased duloxetine metabolism and elimination. CYMBALTA<sup>®</sup> is contraindicated in patients with any liver disease resulting in hepatic impairment.

##### Hepatotoxicity

CYMBALTA<sup>®</sup> increases the risk of elevation of serum aminotransferase levels. In clinical trials, the median time to detection of the aminotransferase elevation was about two months. In most patients, these were usually transient and self-limiting with continued use, or resolved upon discontinuation of CYMBALTA<sup>®</sup>. (SEE POST-MARKET ADVERSE DRUG REACTIONS)

CYMBALTA<sup>®</sup> should be used with caution in patients treated with other drugs associated with hepatic injury. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, CYMBALTA<sup>®</sup> should not ordinarily be prescribed to patients with substantial alcohol use.

Physicians should be aware of the signs and symptoms of liver damage (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms) and should investigate such symptoms promptly. CYMBALTA<sup>®</sup> should be discontinued and should not be restarted in patients with jaundice.

##### Controlled Narrow-angle Glaucoma:

In clinical trials, CYMBALTA<sup>®</sup> was associated with an increased risk of mydriasis; therefore it should be used cautiously in patients with controlled narrow-angle glaucoma.

##### Thioridazine:

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This effect appears to be dose-related. CYMBALTA<sup>®</sup> is a moderate inhibitor of CYP2D6 and increases the AUC and C<sub>max</sub> of drugs metabolized by CYP2D6. CYMBALTA<sup>®</sup> should not be used in combination with thioridazine.

##### Inhibitors of CYP1A2:

Because CYP1A2 is involved in duloxetine metabolism, the potential exists for increased concentrations of duloxetine when co-administered with a CYP1A2 inhibitor. CYMBALTA<sup>®</sup> should not be used concomitantly with potent CYP1A2 inhibitors (e.g., fluvoxamine) and some quinolone antibiotics (e.g., ciprofloxacin or enoxacin).

##### Sucrose:

CYMBALTA<sup>®</sup> capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

##### Cardiovascular:

##### Blood Pressure and Heart Rate

CYMBALTA<sup>®</sup> has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. (SEE POST-MARKET ADVERSE DRUG REACTIONS IN SUPPLEMENTAL PRODUCT INFORMATION)

Cases of hypertensive crisis have been reported very rarely with CYMBALTA<sup>®</sup>, especially in patients with pre-existing hypertension. CYMBALTA<sup>®</sup> should be used with caution in patients with uncontrolled hypertension as it may expose them to hypertensive crisis.

Blood pressure and heart rate should be evaluated prior to initiating treatment and periodically measured throughout treatment, especially in patients with known hypertension and/or other cardiac disease. CYMBALTA<sup>®</sup> should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when CYMBALTA<sup>®</sup> is used with drugs that may impair its metabolism. For patients who experience a sustained increase in blood pressure while receiving CYMBALTA<sup>®</sup> either dose reduction or gradual discontinuation should be considered.

##### Electrocardiogram Changes

CYMBALTA<sup>®</sup> has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's pre-marketing testing.

In MDD placebo-controlled clinical trials and DPN placebo-controlled trials, CYMBALTA®-treated patients did not develop abnormal ECGs at a rate different from that in placebo-treated patients.

#### Concomitant Illness:

Clinical experience with CYMBALTA® in patients with concomitant systemic illnesses is limited. Caution is advisable when using CYMBALTA® in patients with diseases or conditions that produce altered metabolism or hemodynamic responses (e.g., caution should be exercised in using CYMBALTA® in patients with conditions that slow gastric emptying).

#### Dependence:

##### Dependence Liability

In animal studies, duloxetine did not demonstrate stimulant or barbiturate-like (depressant) abuse potential.

While CYMBALTA® has not been systematically studied in humans for its potential for abuse there was no indication of drug-seeking behaviour in the clinical trials. However, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of CYMBALTA® (e.g., development of tolerance, incrementation of dose, drug-seeking behaviour).

#### Discontinuation of Treatment:

Discontinuation symptoms have been systematically evaluated in patients taking CYMBALTA®. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in CYMBALTA®-treated patients compared with those discontinuing from placebo: dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, insomnia, diarrhea, anxiety, and hyperhidrosis. Vertigo and nightmare have also been reported (0.9%).

Patients should be monitored for these symptoms when discontinuing treatment with CYMBALTA®. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response.

#### Endocrine:

##### Glucose Regulation

In DPN trials, CYMBALTA® treatment worsened glycemic control in some diabetic patients. In three clinical trials of CYMBALTA® for the management of pain associated with DPN, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 9.8 mmol/L (176 mg/dL), and the mean baseline hemoglobin A1c (HbA1c) was 7.8%. In the 12-week acute treatment phase of these studies, CYMBALTA® was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 0.67 mmol/L (12 mg/dL) in the CYMBALTA® group and decreased by 0.64 mmol/L (11.5 mg/dL) in the routine care group, which was statistically significantly different. HbA1c increased by 0.5% in the CYMBALTA® group and by 0.2% in the routine care groups.

#### Hematologic:

##### Abnormal Bleeding

There have been reports of bleeding abnormalities with selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs), including very rare cases of ecchymoses and gastrointestinal bleeding reported with CYMBALTA®. While a causal relationship to CYMBALTA® has not been established, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences. Skin and other mucous membrane bleedings have been reported following treatment with CYMBALTA®. Caution is advised in patients taking anticoagulants (e.g., warfarin) and/or medicinal products known to affect platelet function (e.g., nonsteroidal anti-inflammatory drugs and ASA), and in patients with known tendency for bleeding or those with predisposing conditions.

#### Hyponatremia:

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including CYMBALTA®. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when CYMBALTA® was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk. Discontinuation of CYMBALTA® should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

#### Neurologic:

##### Seizures

CYMBALTA® has not been systematically evaluated in patients with a seizure disorder. As with other CNS active drugs, CYMBALTA® should be used with caution in patients with a history of a seizure disorder.

#### Serotonin Syndrome/Neuroleptic Malignant Syndrome:

On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occurred in association with treatment with SSRIs, particularly when given in combination with other serotonergic and/or neuroleptic drugs. Serotonin syndrome symptoms may include mental status changes (e.g., confusion, irritability, extreme agitation progressing to delirium and coma), autonomic instability with rapid fluctuations of vital signs (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., rigidity, myoclonus, hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). As these syndromes may result in potentially life-threatening conditions, treatment with CYMBALTA® should be discontinued if such events occur and supportive symptomatic treatment should be initiated. CYMBALTA® should not be used in combination with MAOIs, including the antibiotic linezolid and the thiazine dye methylnium chloride (methylene blue) which are less well-known examples of MAOIs or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (e.g., triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome.

#### Triptans (5HT<sub>1</sub> Agonists)

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. If concomitant treatment with CYMBALTA® and a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

#### Effects on the Ability to Drive and Use Machines:

CYMBALTA® may be associated with undesirable effects such as sedation and dizziness. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that CYMBALTA® therapy does not affect their ability to engage in such activities.

#### Psychiatric:

##### Suicide

As with other drugs with similar pharmacological action (e.g., SSRIs or SNRIs), isolated cases of suicidal ideation and suicidal behaviours have been reported during CYMBALTA® therapy or early after treatment discontinuation. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose. Physicians should encourage patients to report any distressing thoughts or feelings at any time.

#### Activation of Mania/Hypomania

No activation of mania or hypomania was reported in DPN, FM, or CLBP placebo-controlled trials. As with similar CNS active drugs, CYMBALTA® should be used cautiously in patients with a history of mania.

The decision to initiate symptomatic treatment of depression should be made only after patients have been adequately assessed to determine if they are at risk for bipolar disorder.

#### Renal:

Increased plasma concentration of duloxetine occurs in patients with end-stage renal disease (requiring dialysis). Thus, CYMBALTA® is not recommended for patients with end-stage renal disease or severe renal impairment.

#### Adverse Reactions (see full listing in the Supplemental Product Information section)

CYMBALTA® has also been evaluated for safety in 1429 patients with neuropathic pain associated with DPN representing 894.13 patient-years of exposure. Among these 1429 CYMBALTA®-treated patients, 800 patients participated in three 12- to 13-week, placebo-controlled trials at doses ranging from 20 to 120 mg/day. An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration of 6 months (87 patients continued on to an open-label extension phase for an additional 24 weeks). Another 57 patients, originally treated with placebo, were exposed to CYMBALTA® for up to 12 months at 60 mg twice daily in an extension phase. Among these 1429 patients, 881 had  $\geq 6$  months of exposure to CYMBALTA®, and 515 had greater than 12 months of exposure.

CYMBALTA® has also been evaluated for safety in 1236 patients with fibromyalgia. In placebo-controlled trials, 369 patients received CYMBALTA® 60 mg QD (120.08 patient-years), 221 patients received CYMBALTA® 120 mg QD (102.18 patient-years), and 220 patients received CYMBALTA® 60 mg BID (36.49 patient-years) as a maximum dose.

CYMBALTA® has been evaluated for safety in 698 patients with CLBP (representing 237.99 patient-years exposure to duloxetine). In 12- to 13-weeks placebo-controlled studies, the majority of the CYMBALTA®-treated patients (428, 71.3%) received CYMBALTA® 60 mg QD. Approximately a quarter of CYMBALTA®-treated patients (139, 23.2%) received duloxetine 120 mg QD at some point during the acute phase.

Approximately 12% of the 800 patients who received CYMBALTA® in acute placebo-controlled trials for neuropathic pain associated with DPN discontinued treatment due to an adverse event, compared with 5% of the 339 patients receiving placebo. Nausea (CYMBALTA® 3.0%, placebo 0.3%), dizziness (CYMBALTA® 1.1%, placebo 0.3%), and somnolence (CYMBALTA® 1.2%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (defined as discontinuation occurring in at least 1% of the CYMBALTA®-treated patients and at a rate of at least twice that of placebo).

Approximately 19% of the 876 patients who received CYMBALTA® in placebo-controlled trials for FM discontinued treatment due to an adverse event, compared with 11.8% of the 535 patients receiving placebo. Nausea (CYMBALTA® 1.9%, placebo 0.7%), fatigue (CYMBALTA® 1.3%, placebo 0.2%) and somnolence (CYMBALTA® 1.5%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (as defined in the paragraph above).

Approximately 17% of the 600 patients who received CYMBALTA® in 13-week placebo-controlled trials for CLBP discontinued treatment due to an adverse reaction, compared with 6.3% of the 441 patients receiving placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (CYMBALTA® 3.0%, placebo 0.7%) and somnolence (CYMBALTA® 1.0%, placebo 0.0%).

The most commonly observed adverse events in CYMBALTA®-treated DPN patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea, constipation, dry mouth, vomiting, fatigue, decreased appetite, somnolence, erectile dysfunction, and hyperhidrosis.

The most commonly reported adverse events in CYMBALTA®-treated FM patients with an incidence in the CYMBALTA® treatment group  $\geq 5.0\%$  and that were significantly more frequent compared to placebo were: nausea, headache, dry mouth, insomnia, fatigue, constipation, diarrhea, dizziness, somnolence, hyperhidrosis, and decreased appetite.

The most commonly observed adverse events in CYMBALTA®-treated CLBP patients (incidence 5% or greater and at least twice the incidence in placebo patients) included nausea, insomnia, somnolence, constipation, dry mouth, fatigue, and dizziness.

#### Post-market Adverse Drug Reactions:

Post-marketing surveillance has identified reports of hepatic injury, including hepatocellular, pure cholestatic and mixed injury ranging from mild elevations in laboratory values to more severe clinical signs and symptoms of liver injury. Isolated cases of liver failure, including fatal cases, have been reported. Most of these cases have been reported in patients with past or current medical and other risk factors for liver injury, including alcohol abuse, hepatitis, or exposure to drugs with known adverse effects on the liver and it is unclear to what extent duloxetine may have played a contributing role.

Adverse events reported rarely (<0.1% and  $\geq 0.01\%$ ), across all indications, include: hematochezia, hallucinations, urinary retention, and rash. A causal relationship between CYMBALTA® and the emergence of these events has not been clearly established. (SEE SUPPLEMENTAL PRODUCT INFORMATION)

#### Drug Interactions:

##### Serious Drug Interactions

Monooxidase Inhibitors: See CONTRAINDICATIONS  
Thioridazine: See CONTRAINDICATIONS

### Potential for Other Drugs to Affect Duloxetine

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism. CYMBALTA® is a moderate inhibitor of CYP2D6.

### Inhibitors of CYP1A2:

CYMBALTA® should not be used concomitantly with potent CYP1A2 inhibitors (e.g., fluvoxamine) and some quinolone antibiotics (e.g., ciprofloxacin and enoxacin).

### Inhibitors of CYP2D6:

Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average 60%) of duloxetine. Caution is advised if administering CYMBALTA® with inhibitors of CYP2D6 (e.g., SSRIs).

### Potential for Duloxetine to Affect Other Drugs

#### Drugs Metabolized by CYP2D6:

Caution should be used if duloxetine is co-administered with medications that are predominately metabolized by the CYP2D6 system and which have a narrow therapeutic index such as antiarrhythmics (e.g., flecainide and encainide).

#### Drugs Metabolized by CYP1A2:

Duloxetine has been shown to be a potential inhibitor of the CYP1A2 isoform in *in vitro* studies. CYMBALTA® is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

#### Drugs Highly Bound to Plasma Protein:

Duloxetine is highly bound to plasma proteins (>90%). Therefore, administration of CYMBALTA® to a patient taking another drug that is highly protein bound may cause increased free concentrations of either drug.

#### CNS Drugs:

Caution is advised when CYMBALTA® is taken in combination with other centrally acting drugs and substances, especially those with a similar mechanism of action, including alcohol. Concomitant use of other drugs with serotonergic activity (e.g., SNRIs, SSRIs, triptans, or tramadol) may result in serotonin syndrome.

#### Serotonergic Drugs:

Based on the mechanism of action of duloxetine and the potential for serotonin syndrome, caution is advised when CYMBALTA® is co-administered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, lithium, tramadol, or St. John's Wort.

#### Triptans (5HT<sub>1</sub> agonists):

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. If concomitant treatment with CYMBALTA® and a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

#### Tricyclic Antidepressants (TCA):

Caution is advised in the co-administration of tricyclic antidepressants (TCAs) (e.g., amitriptyline, desipramine, nortriptyline) with duloxetine, because duloxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with duloxetine.

#### Warfarin:

Increases in INR have been reported when duloxetine was co-administered to patients treated with warfarin.

#### Drugs that Affect Gastric Acidity:

CYMBALTA® has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. Caution is advised in using CYMBALTA® in patients with conditions that may slow gastric emptying (e.g. some patients with diabetic gastroparesis). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine.

To report an adverse effect, please call 1 866-364-4043.



## Administration

CYMBALTA® may be administered with or without food; however, **food may help reduce the incidence of initial nausea**. Results from a well-controlled dose comparison study (N=647) have demonstrated that patients taking CYMBALTA® 60 mg/day with food experienced similar rates of nausea as patients treated with CYMBALTA® 30 mg/day with or without food.

CYMBALTA® should be swallowed whole and should not be chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating.

**CYMBALTA® is not indicated for use in children less than 18 years of age.**

#### Neuropathic Pain Associated with Diabetic Peripheral Neuropathy:

The recommended dose is 60 mg once daily. A lower starting dose of 30 mg may be considered for tolerability reasons in some patients, with a target dose of 60 mg/day within 1–2 weeks. Efficacy of CYMBALTA® has been demonstrated within the first week. Some patients may benefit from dosages above the recommended 60 mg once daily up to a maximum dose of 120 mg per day. While a 120 mg/day dose was shown to be safe and effective, there is no evidence that doses higher than 60 mg confer additional significant benefit, and the higher dose is less well tolerated. Doses above 120 mg have not been evaluated and are not recommended.

#### Fibromyalgia:

The recommended dose is 60 mg once daily. A lower starting dose of 30 mg may be considered for tolerability reasons in some patients, with a target dose of 60 mg/day within 1–2 weeks. Some patients may respond within the first week. There is no evidence that doses greater than 60 mg/day (e.g., 120 mg/day) confer additional benefit. Additionally, patients who do not respond to 60 mg/day may not respond to 120 mg/day. Furthermore, doses higher than 60 mg/day are associated with more severe and frequent rate of adverse reactions. The safety of doses above 120 mg once daily has not been evaluated.

#### Chronic Low Back Pain:

The recommended dose is 60 mg once daily. A lower starting dose of 30 mg may be considered for tolerability reasons in some patients, with a target dose of 60 mg/day within 1–2 weeks. Some patients may respond within the first week. There is no evidence that higher doses confer additional benefit, even in patients who do not respond to a 60 mg dose, and higher doses are associated with a higher rate of adverse reactions. The safety of doses above 120 mg once daily has not been evaluated.

### Patients with Renal Impairment:

CYMBALTA® is not recommended for patients with end-stage renal disease (requiring dialysis) or in severe renal impairment (estimated creatinine clearance <30 mL/min).

### Patients with Hepatic Impairment:

CYMBALTA® should not be used in patients with any liver disease resulting in hepatic impairment.

### Elderly Patients:

No dose adjustment is recommended for elderly patients on the basis of age. Caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

### Treatment of Pregnant Women During the Third Trimester:

When treating pregnant women with CYMBALTA® during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering CYMBALTA® in the third trimester.

### Discontinuation of Treatment:

When discontinuing CYMBALTA® after more than 1 week of therapy, it is recommended that the dose be tapered to minimize the risk of discontinuation symptoms. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

### Switching Patients to or from a Monoamine Oxidase Inhibitor:

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with CYMBALTA®. In addition, at least 5 days should be allowed after stopping CYMBALTA® before starting an MAOI.



## Study References

1. CYMBALTA® Product Monograph. Eli Lilly Canada Inc., April 8, 2011.

### Supplemental Product Information

#### Adverse Reactions:

Treatment-emergent Adverse Events Incidence in the Acute Phase of Neuropathic Pain Associated with DPN Placebo-controlled Trials<sup>1</sup>

System Organ Class/ Adverse Event	Percentage of Patients Reporting Event			
	CYMBALTA® 60 mg QD (N=344)	CYMBALTA® 60 mg BID (N=341)	CYMBALTA® Total* (N=800)	Placebo (N=339)
<b>Gastrointestinal Disorders</b>				
Nausea	24	27	24	9
Diarrhea	11	7	10	7
Constipation	8	12	9	2
Dry mouth	6	10	8	3
Vomiting	5	6	6	3
Dyspepsia <sup>2</sup>	4	4	4	2
<b>General Disorders and Administration Site Conditions</b>				
Fatigue <sup>2</sup>	12	16	12	6
Abdominal pain <sup>4</sup>	5	2	4	2
<b>Infections and Infestations</b>				
Nasopharyngitis	5	7	6	5
Influenza <sup>3</sup>	3	2	3	3
<b>Metabolism and Nutrition Disorders</b>				
Decreased appetite <sup>6</sup>	7	14	10	1
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Back pain	5	2	4	3
Muscle spasm	3	3	3	2
<b>Nervous System Disorder</b>				
Somnolence <sup>7</sup>	17	21	17	5
Headache	12	11	12	9
Dizziness	11	13	11	6
Parosmia <sup>8</sup>	2	2	2	1
<b>Psychiatric Disorders</b>				
Insomnia <sup>9</sup>	8	10	9	5
Agitation <sup>10</sup>	3	3	3	1
<b>Renal and Urinary Disorders</b>				
Pollakiuria	1	3	2	1
<b>Reproductive System and Breast Disorder</b>				
Erectile dysfunction <sup>11</sup>	2	8	5	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Cough <sup>12</sup>	3	4	4	4
Pharyngolaryngeal pain	1	4	3	2
<b>Skin and Subcutaneous Tissue Disorders</b>				
Hyperhidrosis	8	10	9	2

\* Includes all doses used in DPN studies (i.e., 20 mg QD, 60 mg QD and 60 mg BID)

<sup>1</sup> Events reported by at least 2% of patients treated with CYMBALTA® and more often than placebo. The following events were reported by at least 2% of patients treated with CYMBALTA® for DPNP and had an incidence equal to or less than placebo: pain in extremity, upper respiratory tract infection, arthralgia, cough, influenza, pruritus, musculoskeletal pain (includes myalgia and neck pain), and edema peripheral.

<sup>2</sup> Includes stomach discomfort.

- <sup>1</sup> Also includes asthenia.  
<sup>2</sup> Includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain.  
<sup>3</sup> 2.8% of patients treated with CYMBALTA<sup>®</sup>, 2.7% of patients who received placebo.  
<sup>4</sup> Includes anorexia.  
<sup>5</sup> Includes hypersomnia, sedation.  
<sup>6</sup> Includes hypoesthesia, hypoaesthesia facial, and paraesthesia oral.  
<sup>7</sup> Also includes middle insomnia, early morning awakening, and initial insomnia.  
<sup>8</sup> Also includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation.  
<sup>9</sup> Male patients only (CYMBALTA<sup>®</sup> 60 mg QD, N=201; CYMBALTA<sup>®</sup> 60 mg BID, N=190; all CYMBALTA<sup>®</sup>, N=466; placebo, N=181).  
<sup>10</sup> 3.9% of patients treated with CYMBALTA<sup>®</sup>, 3.8% of patients who received placebo.

**Treatment-emergent Adverse Events Incidence in the FM Placebo-controlled Trials\***

System Organ Class/ Adverse Event	Percentage of Patients Reporting Event	
	Placebo (N=535)	CYMBALTA <sup>®</sup> (N=876)
<b>Cardiac Disorders</b>		
Palpitations	2	2
<b>Eye Disorders</b>		
Vision blurred	1	2
<b>Gastrointestinal Disorders</b>		
Nausea	11	29
Dry mouth	5	18
Constipation	4	15
Diarrhea	8	12
Dyspepsia	3	5
<b>General Disorders and Administration Site Conditions</b>		
Fatigue <sup>6</sup>	8	15
<b>Immune System Disorders</b>		
Seasonal allergy	2	3
<b>Infections and Infestations</b>		
Upper respiratory tract infection	6	7
Urinary tract infection	3	3
Influenza	2	2
Gastroenteritis viral	2	2
<b>Investigations</b>		
Weight increased	1	2
<b>Metabolism and Nutrition Disorders</b>		
Decreased appetite <sup>6</sup>	2	11
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Musculoskeletal pain	4	5
Muscle spasms	3	4
<b>Nervous System Disorders</b>		
Headache	12	20
Dizziness	7	11
Somnolence <sup>5</sup>	3	11
Tremor	1	4
Paraesthesia	4	4
Migraine	3	3
Dysgeusia	1	3
<b>Psychiatric Disorders</b>		
Insomniad	10	16
Agitation	2	6
Sleep disorder	2	3
Abnormal dreams <sup>7</sup>	1	3
Orgasm abnormal <sup>8</sup>	<1	3
Libido decreased <sup>9</sup>	<1	2
<b>Reproductive System and Breast Disorders</b>		
Ejaculation disorder <sup>10</sup>	0	4
Penis disorder <sup>1</sup>	0	2
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Cough	3	4
Pharyngolaryngeal pain	3	3
<b>Skin and Subcutaneous Tissue Disorders</b>		
Hyperhidrosis	1	7
Rash	2	4
Pruritis	2	3
<b>Vascular Disorders</b>		
Hot flush	2	3

- \* Events reported by at least 2% of patients treated with CYMBALTA<sup>®</sup> and more often than with placebo. The following events were reported by at least 2% of patients treated with CYMBALTA<sup>®</sup> for FM and had an incidence equal to or less than placebo: nasopharyngitis, back pain, sinusitis, anxiety, arthralgia, depression, pain in extremity, vomiting, pain, abdominal pain, bronchitis, abdominal pain upper.  
<sup>1</sup> Male patients only (N=46 duloxetine-treated patients versus 26 placebo patients)  
<sup>2</sup> Also includes asthenia  
<sup>3</sup> Also includes anorexia  
<sup>4</sup> Also includes hypersomnia and sedation  
<sup>5</sup> Also includes middle insomnia, early morning awakening, and initial insomnia  
<sup>6</sup> Also includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation  
<sup>7</sup> Also includes nightmare  
<sup>8</sup> Also includes anorgasmia  
<sup>9</sup> Also includes loss of libido  
<sup>10</sup> Also includes ejaculation failure and ejaculation dysfunction

**Treatment-emergent Adverse Events Incidence in the CLBP Placebo-controlled Trials\***

System Organ Class/ Adverse Event	Percentage of Patients Reporting Reaction	
	Placebo (N=441)	CYMBALTA <sup>®</sup> (N=600)
<b>Gastrointestinal Disorders</b>		
Nausea	3	16
Dry mouth	2	9
Constipation	2	7
Diarrhea	4	6
Abdominal pain <sup>1</sup>	2	3
Flatulence	-	-
<b>General Disorders and Administration Site Conditions</b>		
Fatigue (including asthenia)	1	6
<b>Infections and Infestations</b>		
Influenza	3	4
<b>Metabolism and Nutritional Disorders</b>		
Decreased appetite (including anorexia)	<1	4
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Musculoskeletal pain (including myalgia and neck pain)	2	3
<b>Nervous System Disorders</b>		
Somnolence (including hypersomnia and sedation)	1	8
Dizziness	2	6
Headache	-	-
<b>Psychiatric Disorders</b>		
Insomnia <sup>2</sup>	4	8
Libido decreased (including loss of libido)	1	3
<b>Skin and Subcutaneous Tissue Disorders</b>		
Hyperhidrosis	1	3

- \* Events reported by at least 2% of patients treated with CYMBALTA<sup>®</sup> and more often than placebo. The following events were reported by at least 2% of patients treated with CYMBALTA<sup>®</sup> and CLBP and had an incidence equal to or less than placebo: arthralgia, and nasopharyngitis.  
<sup>1</sup> Also includes abdominal pain upper, abdominal discomfort, and gastrointestinal pain  
<sup>2</sup> Also includes initial insomnia, middle insomnia, terminal insomnia

**Other Adverse Events**

**Weight Changes**

In DPN, FM, and CLBP studies, patients treated with CYMBALTA<sup>®</sup> (N=2271) for up to 26-weeks experienced a mean weight loss of approximately 0.59 kg compared with a mean weight gain of approximately 0.18 kg in placebo-treated patients.  
 In 3 placebo-controlled DPN clinical trials, patients treated with CYMBALTA<sup>®</sup> for up to 13 weeks experienced a mean weight loss of 0.92 kg, compared with a mean weight gain of 0.16 kg in placebo-treated patients. In long-term trials of up to 52 weeks in duration, the mean decrease in weight was 0.35 kg for CYMBALTA<sup>®</sup>-treated patients.  
 In FM studies, patients treated with CYMBALTA<sup>®</sup> for up to 26-weeks experienced a mean weight loss of approximately 0.4 kg compared with a mean weight gain of approximately 0.3 kg in placebo-treated patients. In one long-term FM 60-week uncontrolled study, (195 patients completed the study) CYMBALTA<sup>®</sup> patients had a mean weight increase of 0.7 kg.  
 In one long-term CLBP 54-week study (13-week, placebo-controlled acute phase and 41-week uncontrolled extension phase), CYMBALTA<sup>®</sup>-treated patients (N=109) experienced a mean weight decrease of 0.6 kg compared with a mean weight increase of 0.1 kg in placebo-treated patients (N=116) during the acute phase of the study. In the open-label phase, all patients treated with CYMBALTA<sup>®</sup> (N=178) had a mean weight increase of 0.4 kg.

**Post-market Adverse Drug Reactions**

Other adverse reactions reported very rarely (<0.01%) from post-marketing experience include: thrombocytopenia, supraventricular arrhythmia, tinnitus upon treatment discontinuation, syndrome of inappropriate antidiuretic hormone (SIADH), glaucoma, gastrointestinal bleeding, hepatitis, jaundice, anaphylactic reaction, hypersensitivity, alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, bilirubin increased, hyponatremia, hyperglycemia (reported especially in diabetic patients), muscle spasm, trismus, extrapyramidal disorder, restless leg syndrome, serotonin syndrome, seizures, seizure upon treatment discontinuation, mania, aggression and anger (particularly early in treatment or after treatment discontinuation), gynecological bleeding, angioedematous edema, confusion, ecchymosis, erythema multiforme, Stevens-Johnson Syndrome, urticaria, orthostatic hypotension (especially at the initiation of treatment), syncope (especially at initiation of treatment), and hypertensive crisis. A causal relationship between CYMBALTA<sup>®</sup> and the emergence of these events has not been clearly established.

**Management of Overdose**

No specific antidote is known, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, hemoperfusion, and exchange perfusion are unlikely to be beneficial. In managing overdose, consider the possibility of multiple drug involvement. A specific caution involves patients who are taking or have recently taken duloxetine and might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation.

For management of a suspected overdose, contact your regional Poison Control Centre.

**Storage and Stability**

Store between 15° and 30°C.

**Availability**

CYMBALTA<sup>®</sup> (duloxetine hydrochloride) delayed-release capsules are available in 30 mg and 60 mg strengths.  
 30 mg: The 30 mg capsule has an opaque white body and opaque blue cap, and is imprinted with "30 mg" on the body and "9543" on the cap. It is available in blister cartons of 28 capsules.  
 60 mg: The 60 mg capsule has an opaque green body and opaque blue cap, and is imprinted with "60 mg" on the body and "9542" on the cap. It is available in blister cartons of 28 capsules.

Complete product monograph available on request:



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 Toronto, Ontario  
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or visit [www.lillyinteractive.ca](http://www.lillyinteractive.ca)



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 CACYM00068





**Maxalt**<sup>®</sup>  
rizatriptan benzoate tablets

**Maxalt RPD**<sup>®</sup>  
rizatriptan benzoate wafers

## **i** Prescribing Summary

## **G** Patient Selection Criteria

**THERAPEUTIC CLASSIFICATION:** 5-HT<sub>1</sub> Receptor Agonist  
**INDICATIONS AND CLINICAL USE**

### **Adults**

MAXALT<sup>®</sup> is indicated for acute treatment of migraine attacks with or without aura in adults. MAXALT<sup>®</sup> is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, ophthalmoplegic or basilar migraine (see CONTRAINDICATIONS in the Supplemental Product Information section). Safety and effectiveness of MAXALT<sup>®</sup> have not been established for cluster headache, which is present in an older, predominantly male population.

### **Pediatrics (<18 years of age)**

The safety and efficacy of MAXALT<sup>®</sup> has not been established in patients under 18 years of age and its use in this age group is not recommended (see WARNINGS AND PRECAUTIONS).

### **Geriatrics (>65 years of age)**

The safety and effectiveness of MAXALT<sup>®</sup> has not been adequately studied in individuals over 65 years of age. Its use in this age group is, therefore, not recommended (see WARNINGS AND PRECAUTIONS).

### **Special Populations and Conditions**

For use in special populations (see Supplemental Product Information, WARNINGS AND PRECAUTIONS, Special Populations and Conditions).

### **CONTRAINDICATIONS**

MAXALT<sup>®</sup> is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). In addition, patients with other significant underlying cardiovascular diseases (e.g., atherosclerotic disease, congenital heart disease) should not receive MAXALT<sup>®</sup>. Ischemic cardiac syndromes include, but are not restricted to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs).

Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see WARNINGS AND PRECAUTIONS).

Because MAXALT<sup>®</sup> may increase blood pressure, it is contraindicated in patients with uncontrolled or severe hypertension (see WARNINGS AND PRECAUTIONS).

MAXALT<sup>®</sup> is contraindicated within 24 hours of treatment with another 5-HT<sub>1</sub> agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

MAXALT<sup>®</sup> is contraindicated in patients with hemiplegic, ophthalmoplegic or basilar migraine.

Concurrent administration of MAO inhibitors or use of rizatriptan within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see Drug Interactions).

Because there are no data available, MAXALT<sup>®</sup> is contraindicated in patients with severe hepatic impairment.

MAXALT<sup>®</sup> is contraindicated in patients who are hypersensitive to rizatriptan or any component of the formulation.



## **Safety Information**

### **WARNINGS AND PRECAUTIONS**

#### **General**

MAXALT<sup>®</sup> should only be used where a clear diagnosis of migraine has been established.

For a given attack, if a patient has no response to the first dose of rizatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

#### **Psychomotor Effect**

Dizziness, somnolence and asthenia/fatigue were experienced by some patients in clinical trials with MAXALT<sup>®</sup> (see ADVERSE EVENTS). Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that MAXALT<sup>®</sup> does not adversely affect them.

#### **Cardiovascular**

##### **Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events**

MAXALT<sup>®</sup> has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. Following the use of other 5-HT<sub>1</sub> agonists, in rare cases these symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of other 5-HT<sub>1</sub> agonists, and may therefore also occur with MAXALT<sup>®</sup>. Because of the potential of this class of compounds (5-HT<sub>1B/1D</sub> agonists) to cause coronary vasospasm, MAXALT<sup>®</sup> should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that MAXALT<sup>®</sup> not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is unknown. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, MAXALT<sup>®</sup> should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are considered to have a satisfactory cardiovascular evaluation, the first dose of rizatriptan should be administered in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following MAXALT<sup>®</sup>, in these patients with risk factors. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.

Intermittent long-term users of MAXALT<sup>®</sup> who have or acquire risk factors predictive of CAD, as described above, should receive periodic interval cardiovascular evaluation as they continue to use MAXALT<sup>®</sup>.

If symptoms consistent with angina occur after the use of MAXALT<sup>®</sup>, ECG evaluation should be carried out to look for ischemic changes.

*The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to MAXALT<sup>®</sup>.*

Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness and tightness) has been reported after administration of rizatriptan. Because drugs in this class may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following MAXALT<sup>®</sup> administration should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS).

##### **Cardiac Events and Fatalities Associated with 5-HT<sub>1</sub> Agonists**

MAXALT<sup>®</sup> may cause coronary artery vasospasm. Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT<sub>1</sub> agonists. Considering the extent of use of 5-HT<sub>1</sub> agonists in patients with migraine, the incidence of these events is extremely low.

##### **Premarketing Experience with MAXALT<sup>®</sup>**

Among the approximately 4200 patients who were treated with at least a single oral dose of either 5 or 10 mg rizatriptan in premarketing clinical trials of MAXALT<sup>®</sup>, electrocardiac adverse experiences were observed in 33 patients. One patient was reported to have chest pain with possible ischemic ECG changes following a single dose of 10 mg.

##### **Postmarketing Experience with MAXALT<sup>®</sup>**

Serious cardiovascular events have been reported in association with the use of MAXALT<sup>®</sup>. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of reported cases that were actually caused by MAXALT<sup>®</sup> or to reliably assess causation in individual cases.

##### **Cerebrovascular Events and Fatalities Associated with 5-HT<sub>1</sub> Agonists**

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT<sub>1</sub> agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. Before treating migraine headaches with MAXALT<sup>®</sup> in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. If a patient does not respond to the first dose, the opportunity should be taken to review the diagnosis before a second dose is given. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

##### **Special Cardiovascular Pharmacology Studies with Another 5-HT<sub>1</sub> Agonist**

In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT<sub>1</sub> agonist at a subcutaneous dose of 1.5 mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and one had insignificant coronary artery disease.

In an additional study with this same drug, migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5 mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increased coronary resistance (~20%), and decreased hyperemic myocardial blood flow

<sup>®</sup>Registered Trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Used under license.

(~10%) were noted. The relevance of these findings to the use of the recommended oral dose of this 5-HT<sub>1</sub> agonist is not known.

Similar studies have not been done with MAXALT®. However, owing to the common pharmacodynamic actions of 5-HT<sub>1</sub> agonists, the possibility of cardiovascular effects of the nature described above should be considered for any agent of this pharmacological class.

#### Other Vasospasm-Related Events

5-HT<sub>1</sub> agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive postmarket experience has shown the use of another 5-HT<sub>1</sub> agonist to be associated with rare occurrences of peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea.

#### Increase in Blood Pressure

Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT<sub>1</sub> agonists with and without a history of hypertension. In healthy young male and female subjects who received maximal doses of MAXALT® (10 mg every 2 hours for 3 doses), slight increases in blood pressure (approximately 2–3 mmHg) were observed. Rizatriptan is contraindicated in patients with uncontrolled or severe hypertension (see CONTRAINDICATIONS). In patients with controlled hypertension, MAXALT® should be administered with caution, as transient increases in blood pressure and peripheral vascular resistance have been observed in a small portion of patients.

#### Endocrine and Metabolism

##### Phenylketonurics

Phenylketonuric patients should be informed that MAXALT RPD® Wafers contain phenylalanine (a component of aspartame). Each 5 mg wafer contains 1.05 mg phenylalanine, and each 10 mg wafer contains 2.10 mg phenylalanine.

##### Hepatic/Biliary/Pancreatic

Rizatriptan should be used with caution in patients with moderate hepatic insufficiency due to an increase in plasma concentrations of approximately 30% (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the Product Monograph and DOSAGE AND ADMINISTRATION). Since there are no data in patients with severe hepatic impairment, rizatriptan is contraindicated in this population (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

##### Immune

Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT<sub>1</sub> agonists such as MAXALT®. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. Owing to the possibility of cross-reactive hypersensitivity reactions, MAXALT® should not be used in patients having a history of hypersensitivity to chemically-related 5-HT<sub>1</sub> receptor agonists.

##### Neurologic

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT<sub>1</sub> agonists for severe headache that were subsequently shown to have been secondary to an evolving neurological lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the first dose of MAXALT®.

##### Seizures

Caution should be observed if MAXALT® is to be used in patients with a history of epilepsy or structural brain lesions which lower the convulsion threshold. There have been very rare reports of seizures following administration of MAXALT® in patients with or without risk factors or previous history of seizures (see ADVERSE REACTIONS, Post-Marketing Adverse Reactions, Nervous System in the Supplemental Product Information).

#### Ophthalmologic

##### Binding to Melanin-Containing Tissues

The propensity for rizatriptan to bind melanin has not been investigated. Based on its chemical properties, rizatriptan may bind to melanin and accumulate in melanin-rich tissue (e.g., eye) over time. This raises the possibility that rizatriptan could cause toxicity in these tissues after extended use. There were, however, no adverse ophthalmologic changes related to treatment with rizatriptan in the one-year dog toxicity study. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

##### Renal

Rizatriptan should be used with caution in dialysis patients due to a decrease in the clearance of rizatriptan, resulting in approximately 44% increase in plasma concentrations (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the Product Monograph, and DOSAGE AND ADMINISTRATION).

##### Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. If concomitant treatment with MAXALT® and SSRIs (e.g., sertraline, escitalopram oxalate, and fluoxetine) or SNRIs (e.g., venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) (see DRUG INTERACTIONS).

##### Special Populations and Conditions

For use in special populations (see Supplemental Product Information, WARNINGS AND PRECAUTIONS, Special Populations and Conditions).

#### ADVERSE REACTIONS

(see Supplemental Product Information for full listing)

##### Adverse Drug Reaction Overview

**Serious cardiac events, including some that have been fatal, have occurred following use of 5-HT<sub>1</sub> agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS).**

##### Long-Term Safety

In long-term extension studies, a total of 1854 patients treated 16,150 migraine attacks with MAXALT® 5 mg Tablets and 24,043 attacks with MAXALT® 10 mg Tablets over a period of up to 1 year. In general, the types of clinical adverse experiences observed in the extension studies were similar to those observed in the acute studies. However, the incidences of most clinical adverse events were approximately 3-fold higher in extension, as expected, based on increased observation time. The most common adverse events per attack (defined as occurring at an incidence of at least 1%) for MAXALT® 5 mg and 10 mg, respectively, were as follows: nausea (3%, 4%), dizziness (2%, 2%), somnolence (2%, 4%), asthenia/fatigue (2%, 2%), headache (1%, 2%), vomiting (1%, <1%), chest pain (<1%, 1%) and paresthesia (<1%, 2%). Due to the lack of placebo controls in the extension studies, the role of MAXALT® in causation cannot be reliably determined.

To report a suspected adverse reaction, please contact Merck Frosst Canada Ltd. by:

Toll-free telephone: 1-800-567-2594

Toll-free fax: 1-877-428-8675

By regular mail: Merck Frosst Canada Ltd., P.O. Box 1005, Pointe-Claire – Dorval, QC H9R 4P8

#### DRUG INTERACTIONS

##### Ergot-Containing Drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and rizatriptan within 24 hours is contraindicated (see CONTRAINDICATIONS).

##### Monoamine Oxidase Inhibitors

Rizatriptan is principally metabolized via monoamine oxidase, 'A' subtype (MAO-A). In a drug interaction study, when MAXALT® 10 mg was administered to subjects (n=12) receiving concomitant therapy with the selective, reversible MAO-A inhibitor, moclobemide 150 mg t.i.d., there were mean increases in rizatriptan AUC and C<sub>max</sub> of 119% and 41%, respectively; and the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased more than 400%. The interaction would be expected to be greater with irreversible MAO inhibitors. Drug interaction studies were not conducted with selective MAO-B inhibitors.

The specificity of MAO-B inhibitors diminishes with higher doses and varies among patients. Therefore, co-administration of rizatriptan in patients taking MAO-A or MAO-B inhibitors is contraindicated (see CONTRAINDICATIONS).

##### Nadolol/Metoprolol

In a drug interactions study, effects of multiple doses of nadolol 80 mg or metoprolol 100 mg every 12 hours on the pharmacokinetics of a single dose of 10 mg rizatriptan were evaluated in healthy subjects (n=12). No pharmacokinetic interactions were observed.

##### Oral Contraceptives

In a study of concurrent administration of an oral contraceptive during 6 days of administration of MAXALT® (10–30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

##### Other 5-HT<sub>1</sub> Agonists

The administration of rizatriptan with other 5-HT<sub>1</sub> agonists has not been evaluated in migraine patients.

Because their vasospastic effects may be additive, co-administration of rizatriptan and other 5-HT<sub>1</sub> agonists within 24 hours of each other is contraindicated (see CONTRAINDICATIONS).

##### Propranolol

MAXALT® should be used with caution in patients receiving propranolol, since the pharmacokinetic behavior of rizatriptan during co-administration with propranolol may be unpredictable. In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects (n=11), mean plasma AUC and C<sub>max</sub> for rizatriptan were increased by 70% and 75%, respectively, during propranolol administration. In one subject, a 4-fold increase in AUC and 5-fold increase in C<sub>max</sub> was observed. This subject was not distinguishable from the others based on demographic characteristics. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol (see DOSAGE AND ADMINISTRATION).

##### Selective Serotonin Reuptake Inhibitors / Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of life-threatening serotonin syndrome have been reported in post-marketing experience during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans (see WARNINGS AND PRECAUTIONS).

In a pharmacokinetic study with paroxetine and rizatriptan, paroxetine had no influence on the plasma levels of rizatriptan.

##### Food

Interactions with food have not been studied. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, MAXALT® was administered without regard to food.

## Administration

### DOSAGE AND ADMINISTRATION

(see Product Monograph for complete information)

#### Dosing Considerations

MAXALT® is recommended only for the acute treatment of migraine attacks. MAXALT® should not be used prophylactically. Controlled trials have not established the effectiveness of a second dose if the initial dose is ineffective.

The safety of treating, on average, more than four headaches in a 30-day period has not been established.

#### Recommended Dose and Dosage Adjustment

##### ADULTS

##### MAXALT® Tablets and MAXALT RPD® Wafers

The recommended single adult dose is 5 mg. The maximum recommended single dose is 10 mg. There is evidence that the 10 mg dose may provide a greater effect than the 5 mg dose (see CLINICAL TRIALS in the Product Monograph). The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 10 mg dose with the potential risk for increased adverse events.

For MAXALT RPD® Wafers, administration with liquid is not necessary. The wafer is packaged in a blister within an outer aluminum pouch. Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the wafer placed on the tongue, where it will dissolve and be swallowed with the saliva.

#### Redosing

Doses should be separated by at least 2 hours; no more than a total of 20 mg (Tablets or Wafers) should be taken in any 24-hour period.

#### Patients receiving propranolol

A single 5 mg dose of MAXALT® should be used. In instances should the total daily dose exceed 10 mg per day, given in two doses, separated by at least two hours (see DRUG INTERACTIONS).

#### Renal Impairment

In hemodialysis patients with severe renal impairment (creatinine clearance <2 mL/min/1.73 m<sup>2</sup>), the AUC of rizatriptan was approximately 44% greater than in patients with normal renal function (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the Product Monograph). Consequently, if treatment is deemed advisable in these patients, the 5 mg MAXALT® Tablet or Wafer should be administered. No more than a total of 10 mg should be taken in any 24-hour period. Repeated dosing in renally impaired patients has not been evaluated.

#### Hepatic Impairment

MAXALT® is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) due to the absence of safety data. Plasma concentrations of rizatriptan were approximately 30% greater in patients with moderate hepatic insufficiency (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the Product Monograph). Consequently, if treatment is deemed advisable in the presence of moderate hepatic impairment, the 5 mg MAXALT® Tablet or Wafer should be administered. No more than a total of 10 mg should be taken in any 24-hour period. Repeated dosing in hepatically impaired patients has not been evaluated.

#### Patients with Hypertension

MAXALT® should not be used in patients with uncontrolled or severe hypertension. In patients with mild to moderate controlled hypertension, patients should be treated cautiously at the lowest effective dose.

#### OVERDOSAGE

No overdoses of MAXALT® were reported during clinical trials.

Rizatriptan 40 mg (administered as either a single dose or as two doses with a 2-hour interdose interval) was generally well tolerated in over 300 patients; dizziness and somnolence were the most common drug-related adverse effects.

In a clinical pharmacology study in which 12 subjects received rizatriptan, at total cumulative doses of 80 mg (given within four hours), two subjects experienced syncope and/or bradycardia. One subject, a female aged 29 years,

developed vomiting, bradycardia, and dizziness beginning three hours after receiving a total of 80 mg rizatriptan (administered over two hours); a third degree AV block, responsive to atropine, was observed an hour after the onset of the other symptoms. The second subject, a 25-year-old male, experienced transient dizziness, syncope, incontinence, and a 5-second systolic pause (on ECG monitor) immediately after a painful venipuncture. The venipuncture occurred two hours after the subject had received a total of 80 mg rizatriptan (administered over four hours).

In addition, based on the pharmacology of rizatriptan, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Gastrointestinal decontamination (i.e., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with MAXALT®. The elimination half-life of rizatriptan is 2 to 3 hours (see ACTION AND CLINICAL PHARMACOLOGY in the Product Monograph). Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

There is no specific antidote to rizatriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

The effects of hemo- or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

### Supplemental Product Information

#### WARNINGS AND PRECAUTIONS

##### Special Populations and Conditions

**Pregnant Women:** In a reproduction study in rats, birth weights and pre- and post-weaning weight gain were reduced in the offspring of females treated prior to and during mating and throughout gestation and lactation. These effects occurred in the absence of any apparent maternal toxicity (maternal plasma drug exposures were 22 and 337 times, respectively, the exposure in humans receiving the maximum recommended daily dose (MRDD) of 20 mg). The developmental no-effect dose was equivalent to 2.25 times human exposure at the MRDD.

In embryofetal development studies, no teratogenic effects were observed when pregnant rats and rabbits were administered doses at the equivalent of 337 times and 168 times, respectively, the human MRDD, during organogenesis. However, fetal weights were decreased in conjunction with decreased maternal weight gain at these same doses. The developmental no-effect dose in both rats and rabbits was 22 times the human MRDD. Toxicokinetic studies demonstrated placental transfer of drug in both species.

There are no adequate and well-controlled studies in pregnant women; therefore, rizatriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

##### Impairment of Fertility

In a fertility study in rats, altered estrus cyclicity and delays in time to mating were observed in females treated orally with an equivalent of 337 times the maximum recommended daily dose (MRDD) of 20 mg in humans. The no-effect dose was 22 times the MRDD. There was no impairment of fertility or reproductive performance in male rats treated with up to 825 times the MRDD.

**Nursing Women:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MAXALT® is administered to women who are breast-feeding. Rizatriptan is extensively excreted in rat milk, at a level of 5-fold or greater than maternal plasma levels.

**Pediatrics (< 18 years of age):** MAXALT® is not recommended for use in patients under 18 years of age. In a randomized placebo-controlled trial of 291 adolescent migraineurs, aged 12-17 years, the efficacy of MAXALT® Tablets (5 mg) was not different from that of placebo (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the product monograph).

**Geriatrics (> 65 years of age):** The safety and effectiveness of MAXALT® has not been adequately studied in individuals over 65 years of age. The risk of adverse reactions to this drug may be greater in elderly patients, as they are more likely to have decreased hepatic function, be at higher risk for CAD, and experience blood pressure increases that may be more pronounced. Clinical studies with MAXALT® did not include a substantial number of patients over 65 years of age (n=17). Its use in this age group is, therefore, not recommended.

##### Special Disease Conditions:

MAXALT® should be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the product monograph).

##### Monitoring and Laboratory Tests

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with MAXALT®.

#### ADVERSE REACTIONS

##### Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

##### Experience in Controlled Clinical Trials with MAXALT®

##### Typical 5-HT<sub>1</sub> Agonist Adverse Reactions

As with other 5-HT<sub>1</sub> agonists, MAXALT® has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limb.

##### Acute Safety

Adverse experiences to rizatriptan were assessed in controlled clinical trials that included over 3700 patients who received single or multiple doses of MAXALT® Tablets. The most common adverse events during treatment with MAXALT® were asthenia/fatigue, somnolence, pain/pressure sensation and dizziness. These events appeared to be dose-related. In long-term extension studies

where patients were allowed to treat multiple attacks for up to 1 year, 4% (59 out of 1525 patients) withdrew because of adverse experiences.

Tables 1 and 2 list the adverse events regardless of drug relationship (incidence  $\geq 1\%$  and greater than placebo) after a single dose of MAXALT® Tablets and MAXALT RPD® Wafers, respectively. Most of the adverse events appear to be dose-related. 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 behavior, and the kinds of patients treated may differ.

**Table 1**  
Incidence ( $\geq 1\%$  and Greater than Placebo) of Adverse Experiences After a Single Dose of MAXALT® Tablets or Placebo (Prior to Subsequent Dose) in Phase III Controlled Clinical Trials\*

Number of Patients	% of Patients		
	Placebo	MAXALT® 5 mg	MAXALT® 10 mg
<b>Symptoms of Potentially Cardiac Origin</b>			
Upper Limb Sensations*	1.3	1.7	1.8
Chest Sensations*	1.0	1.6	3.1
Neck/Throat/Jaw Sensations*	0.6	1.4	2.5
Palpitations	0.2	0.9	1.0
<b>Body as a Whole</b>			
Asthenia/Fatigue	2.1	4.2	6.9
Abdominal Pain	1.0	1.7	2.2
<b>Digestive System</b>			
Nausea	3.5	4.1	5.7
Dry Mouth	1.3	2.6	3.0
Vomiting	2.1	1.6	2.3
<b>Nervous System</b>			
Dizziness	4.5	4.2	8.9
Somnolence	3.5	4.2	8.4
Headache	0.8	1.8	2.1
Paresthesia	1.0	1.5	2.9
Tremor	1.0	1.3	0.3
Insomnia	0.3	1.0	0.3
<b>Skin and Skin Appendage</b>			
Flushing	1.0	0.6	1.1

\*The term "sensations" encompasses adverse events described as pain, discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, weakness and strange sensations.

\*Data from Studies 022, 025, 029 and 030.

**Table 2**  
Incidence ( $\geq 1\%$  and Greater than Placebo) of Adverse Experiences After a Single Dose of MAXALT RPD® Wafers or Placebo (Prior to Subsequent Dose) in Phase III Controlled Clinical Trials\*

Number of Patients	% of Patients		
	Placebo	MAXALT RPD® 5 mg	MAXALT RPD® 10 mg
<b>Symptoms of Potentially Cardiac Origin</b>			
Chest Sensations*	0.4	1.4	1.7
Neck/Throat/Jaw Sensations*	0.4	1.4	2.0
Tachycardia	1.1	1.4	0.3
Upper Limb Sensations*	0.4	0.7	2.0
Palpitations	0.4	0.4	1.0
<b>Body as a Whole</b>			
Asthenia/Fatigue	0.4	2.1	3.6
<b>Digestive System</b>			
Dry Mouth	2.1	6.4	6.0
Nausea	5.7	6.4	7.0
Dyspepsia	0.7	1.1	2.0
Acid Regurgitation	0	1.1	0.7
Salivation Increase	0	0	1.3
<b>Musculoskeletal System</b>			
Regional Heaviness	0	0	1.0
<b>Nervous System</b>			
Dizziness	3.9	6.4	8.6
Somnolence	2.8	4.3	5.3
Headache	0.7	1.8	2.0
Insomnia	0	1.4	0.7
Paresthesia	0.4	1.4	3.0
Hypesthesia	0	1.4	0.7
Mental Acuity Decreased	0	1.1	0.3
Tremor	0.7	1.1	0
Nervousness	0.4	1.1	0.7
<b>Respiratory System</b>			
Pharyngeal Discomfort	0	1.1	0.7
<b>Skin and Skin Appendage</b>			
Sweating	0.7	1.1	1.0
<b>Special Senses</b>			
Taste Perversion	1.1	1.4	2.3
Blurred Vision	0	0.4	1.3

\*The term "sensations" encompasses adverse events described as pain, discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, weakness and strange sensations.

\*Data from Studies 039 and 049.

MAXALT® was generally well-tolerated. Adverse experiences were typically mild in intensity and were transient. The frequencies of adverse experiences in clinical trials did not increase when up to three doses were taken within 24 hours. The incidences of adverse experiences were not affected by age, gender or use of prophylactic medications. There were insufficient data to assess the impact of race on the incidence of adverse events.

#### Other Events Observed in Association with the Administration of MAXALT®

In the section that follows, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open studies, the role of MAXALT® in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc. limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used MAXALT® 5 mg and 10 mg tablets in Phase II and III studies (n=3716) and reported an event divided by the total number of patients exposed to MAXALT®. All reported events are included, except those

already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those defined as those occurring in at least 1/100 patients; infrequent adverse experiences are those occurring in 1/100 to 1/1000 patients; and rare adverse experiences are those occurring in fewer than 1/1000 patients.

#### **Body as a Whole**

Frequent were warm sensations, chest pain and chills/cold sensations. Infrequent were heat sensitivity, facial edema, hangover effect, abdominal distention, edema/swelling and malaise. Rare were fever, orthostatic effects, and syncope.

#### **Cardiovascular**

Frequent was palpitation. Infrequent were tachycardia, cold extremities, hypertension, arrhythmia, and bradycardia. Rare were angina pectoris and blood pressure increased.

#### **Digestive**

Frequent was diarrhea. Infrequent were dyspepsia, thirst, acid regurgitation, dysphagia, constipation, flatulence, and tongue edema. Rare were anorexia, appetite increase, gastritis, paralysis (tongue), eructation and glosodynia.

#### **Metabolic**

Infrequent was dehydration.

#### **Musculoskeletal**

Infrequent were muscle weakness, stiffness, myalgia, muscle cramp, musculoskeletal pain, and arthralgia.

#### **Neurological/Psychiatric**

Frequent were hypesthesia and mental acuity decreased. Infrequent were nervousness, vertigo, insomnia, anxiety, depression, euphoria, disorientation, ataxia, dysarthria, confusion, dream abnormality, gait abnormality, irritability, memory impairment, agitation, hyperesthesia, sleep disorder, speech disorder, migraine and spasm. Rare were dysesthesia, depersonalization, akinesia/bradykinesia, apprehension, hyperkinesia, hypersomnia, and hyporeflexia.

#### **Respiratory**

Frequent were dyspnea and pharyngeal discomfort. Infrequent were pharyngitis, irritation (nasal), congestion (nasal), dry throat, upper respiratory infection, yawning, respiratory congestion, dry nose, epistaxis, and sinus disorder. Rare were cough, hiccups, hoarseness, rhinorrhea, sneezing, tachypnea, and pharyngeal edema.

#### **Special Senses**

Frequent was taste perversion. Infrequent were blurred vision, tinnitus, dry eyes, burning eye, eye pain, eye irritation, ear pain, and tearing. Rare were hyperacusis, smell perversion, photophobia, photopsia, itching eye, and eye swelling.

#### **Skin and Skin Appendage**

Infrequent were sweating, pruritus, rash, and urticaria. Rare were erythema, acne, and photosensitivity.

#### **Urogenital System**

Frequent was hot flashes. Infrequent were urinary frequency, polyuria, and menstruation disorder. Rare was dysuria.

The adverse experience profile seen with MAXALT RPD® Wafers was similar to that seen with MAXALT® Tablets.

#### **Post-Market Adverse Drug Reactions**

The following additional adverse reactions have been reported very rarely and most have been reported in patients with risk factors predictive of CAD: Myocardial ischemia or infarction, cerebrovascular accident.

The following adverse reactions have also been reported:

**Hypersensitivity:** Hypersensitivity reaction, anaphylaxis/anaphylactoid reaction, angioedema (e.g., facial edema, tongue swelling, pharyngeal edema), wheezing, urticaria, rash, toxic epidermal necrolysis.

**Nervous System:** serotonin syndrome.

**Seizures:** There have been very rare reports of seizures following administration of MAXALT® in patients with or without risk factors or previous history of seizures (see WARNINGS AND PRECAUTIONS).

**Musculoskeletal:** facial pain.

**Special Senses:** Dysgeusia.

**Vascular disorders:** Peripheral vascular ischemia

#### **Drug Abuse and Dependence**

Although the abuse potential of MAXALT® has not been specifically assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received MAXALT® in clinical trials or their extensions. The 5-HT<sub>1B/1D</sub> agonists, as a class, have not been associated with drug abuse.

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Product Monograph available at  
[www.merckfrosst.com](http://www.merckfrosst.com)  
or upon request at 1-800-567-2594



Merck Frosst Canada Ltd., Kirkland, Quebec, H9H 3L1

### Lifetime Achievement Award of the Canadian Neurological Society Given to Dr. Henry J.M. Barnett

The Canadian Neurological Society awarded its inaugural Lifetime Achievement Award to Dr. Henry J.M. Barnett at the home of his daughter and son-in-law, Jane and James Drake, on the evening of June 27, 2011. Family and friends, including several colleagues and faculty members who served under Dr. Barnett's leadership, were in attendance. Drs. Michael D. Hill [Past-chair of the *Scientific Program Committee, CNSF*] and G. Bryan Young [Editor-in-Chief of the *CJNS*] presented Dr. Barnett with the award and a gift of a leather-bound volume of his memoirs, most of which were published in the *Canadian Journal of Neurological Sciences*.



The award and gift were tributes to a great man, now approaching 90, with a remarkable career. Dr. Barnett (Barney to his friends and colleagues) was born in 1922 in Newcastle-upon-Tyne in England, the son of a church minister. He moved to Canada with his family as a child and was raised and educated in Toronto, graduating in Medicine in the war-accelerated class of 1944. His neurological education was later obtained in Toronto, Queen Square in London, England and Oxford. After obtaining his FRCPC in neurology in 1952 he was a neurologist at the Toronto General Hospital and then was Chief of Neurology at Sunnybrook Hospital in Toronto. His close association with Dr. Charles Drake, one of Canada's most prestigious neurosurgeons, led to his move to London, Ontario in 1969. Indeed, Barney regaled us with a story of how he had written a manifesto in Toronto about how Neurosurgery, Neurology, Neuropathology and Neuroradiology should be combined into one department that had been thoroughly rejected in Toronto. It was only when Dr. Drake came to visit him and was forced to stay longer than expected due to an ice storm that the idea was shared and the seed of the Department of Clinical Neurological Sciences at UWO was first sown. Dr. Barnett served as Professor and Chair of the Department of Clinical Neurological Sciences at the University of Western Ontario from 1974 to 1984 and became Scientific Director of the Robarts Research Institute from 1984 until his retirement. This concept of a combined clinical neuroscience department was unique but has now been copied in Calgary. Barney regards this as one of, if not his single, most important contributions.

Dr. Barnett made many landmark contributions to our understanding of syringomyelia and later in cerebrovascular disease: the ASA-sulfinpyrazone study, the EC-IC bypass study, NASCET study, and the ACE study were milestone randomized trials in clinical stroke. He was successful in getting large research grants, headed large, multicentred studies and published numerous books and articles, as well as serving as Editor-in-Chief of *Stroke*.

Dr. Barnett is also a prominent ornithologist and naturalist. One catches a glimpse of these strong interests in reading his memoirs. He assigned some of his property north of King City to the Nature Conservancy of Canada to protect this natural area in perpetuity.

Despite some recent health challenges, Barney is remarkably robust, full of anecdotes and keen to see the continuing positive developments of Canadian neuroscience. We are proud of this outstanding Canadian, who continues to write and entertain with his keen mind and dry wit. Congratulations, Barney!

*G. Bryan Young and Michael D. Hill*

### CORRECTION

PMID: 21672700 [PubMed - in process] ISSN: 0317-1671 (Print)  
Can J Neurol Sci. 2011 Jul;38(4):600-11.

#### **ARAC - The Montreal Jewish General Hospital Alzheimer Risk Assessment Clinic**

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This article is listed as a REVIEW ARTICLE. It should be listed as an ORIGINAL ARTICLE.

# COPAXONE<sup>®</sup> (glatiramer acetate injection)

Treat from the start. Treat for the long run.



## Prescribing Summary



## Patient Selection Criteria

**THERAPEUTIC CLASSIFICATION:** Immunomodulator

### INDICATIONS AND CLINICAL USE

COPAXONE<sup>®</sup> is indicated for: the treatment of ambulatory patients with Relapsing Remitting Multiple Sclerosis (RRMS), to decrease the frequency of clinical exacerbations, to reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans; for the treatment of patients who have experienced a single demyelinating event, accompanied by abnormal MRI scans and are considered to be at risk of developing Clinically Definite MS (CDMS), after alternative diagnoses are excluded, to delay the onset of definite MS, to decrease the number and volume of active brain lesions and overall disease burden (as identified by MRI scans).

The safety and efficacy of COPAXONE<sup>®</sup> in chronic progressive MS have not been established.

### CONTRAINDICATIONS

COPAXONE<sup>®</sup> (glatiramer acetate) is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.



## Safety Information

### WARNINGS AND PRECAUTIONS

The only recommended route of administration of COPAXONE<sup>®</sup> (glatiramer acetate) injection is the subcutaneous route. COPAXONE<sup>®</sup> should not be administered by the intravenous route.

**Cardiovascular; Symptoms of Potentially Cardiac Origin:** Approximately 13% of COPAXONE<sup>®</sup> patients in the multicenter controlled trials (compared to 5% of placebo patients) experienced at least one episode of what was described as transient chest pain (see ADVERSE REACTIONS: Chest Pain). While some of these episodes occurred in the context of the Immediate Post-Injection Reaction (see ADVERSE REACTIONS: Immediate Post-Injection Reaction), many did not. The pathogenesis of this symptom is unknown. Patients in controlled clinical trials were free of significant cardiovascular problems (New York Heart Association Class I and II) and thus the risks associated with COPAXONE<sup>®</sup> treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown. COPAXONE<sup>®</sup> has been associated with an Immediate Post-Injection Reaction consisting of a constellation of symptoms appearing immediately after injection that could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (see ADVERSE REACTIONS: Immediate Post-Injection Reaction). COPAXONE<sup>®</sup> has not been studied in patients with a history of severe anaphylactoid reactions, obstructive pulmonary disease or asthma, nor in patients under treatment for either of these two latter conditions. Particular caution is therefore advised regarding the use of COPAXONE<sup>®</sup> in such patients.

Anaphylactoid reactions associated with the use of COPAXONE<sup>®</sup> have been reported in rare instances (<1/1000) during the post-marketing period. Some cases required treatment with epinephrine and other appropriate medical treatment.

**General:** Patients should be instructed in aseptic reconstitution and self-injection techniques to assure the safe administration of COPAXONE<sup>®</sup> (glatiramer acetate), including a careful review of the Part III – Consumer Information. The first injection should be performed under the supervision of an appropriately qualified health care professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically re-evaluated. Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. A puncture-resistant container for disposal of used needles and syringes should be used by the patient. Patients should be instructed on the safe disposal of full containers.

**Localized Adverse Reactions Associated with Subcutaneous Use:** At injection sites, localized lipoatrophy and, rarely, injection-site skin necrosis have been reported during clinical trials and post-marketing experience. Lipoatrophy may occur after treatment onset (sometimes as early as several months) and may be permanent. There is no known therapy for lipoatrophy. To assist in possibly minimizing these events, the patient should be advised to follow proper injection technique and to rotate injection areas and sites on a daily basis (see Part III – Consumer Information).

**Immune: Considerations Involving the Use of a Product Capable of Modifying Immune Responses:** COPAXONE<sup>®</sup> is an antigenic substance and thus it is possible that detrimental host responses can occur with its use. Whether COPAXONE<sup>®</sup> can alter normal human immune responses, such as the recognition of foreign antigens is unknown. It is therefore possible that treatment with COPAXONE<sup>®</sup> may undermine the body's defenses against infections and tumor surveillance. Systematic assessments of these risks have not been done. Continued alteration of cellular immunity due to chronic treatment with glatiramer acetate might result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in practically all patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled clinical trial of 125 RRMS patients given glatiramer acetate 20 mg for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype – and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested. Nevertheless, anaphylaxis can be associated with the administration of almost any foreign substance and, therefore, this risk cannot be excluded.

**Carcinogenesis and Mutagenesis:** Preclinical studies to assess the carcinogenic potential of glatiramer acetate in mice and rats do not suggest any evidence of carcinogenic potential related to glatiramer acetate administered subcutaneously at dose levels of up to 30 mg/kg/day in rats and 60 mg/kg/day in mice (see TOXICOLOGY: Carcinogenicity). The relevance of these findings for humans is unknown (see PRECAUTIONS – Considerations Involving the Use of a Product Capable of Modifying Immune Responses).

**Renal:** The pharmacokinetics of COPAXONE<sup>®</sup> in patients with impaired renal function have not been determined.

**Special Populations: Pregnant Women:** There are no adequate and well-controlled studies in pregnant women. No evidence of reproductive toxicity was observed in preclinical studies (see TOXICOLOGY: Reproduction and Teratology). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. During pre-marketing clinical trials with COPAXONE<sup>®</sup>, seven women conceived while being treated with the active drug. One case was lost to follow-up. Three of the patients electively discontinued pregnancy. Three patients stopped treatment 1, 1.5 and 2 months after learning they were pregnant; all delivered healthy babies.

**Nursing Women:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, treating a nursing woman with COPAXONE<sup>®</sup> should only be considered after careful risk/benefit assessment and be used with caution.

**Pediatrics (< 18 years of age):** The safety and effectiveness of COPAXONE<sup>®</sup> have not been established in individuals below 18 years of age.

**Geriatrics (> 65 years of age):** COPAXONE<sup>®</sup> has not been studied in the elderly (> 65 years old).

**Monitoring and Laboratory Tests:** Data collected pre- and post-market do not suggest the need for routine laboratory monitoring.

### ADVERSE REACTIONS

**Adverse Drug Reaction Overview:** In the 4 placebo-controlled clinical trials, the most commonly observed adverse events associated with the use of COPAXONE<sup>®</sup> occurring at an incidence of at least 10% and at least 1.5 times higher than in placebo-treated patients were: injection-site reactions, vasodilatation, rash, dyspnea and chest pain.

In the placebo-controlled clinical trials approximately 5% discontinued treatment due to an adverse event compared to 1% for placebo-treated patients. The adverse events most commonly associated with discontinuation were (in order of descending frequency): injection-site reactions, dyspnea, urticaria, vasodilatation and hypersensitivity. Treatment discontinuation due to a serious adverse event considered by investigators to be related to COPAXONE<sup>®</sup> treatment included a case of life-threatening serum sickness.

**Immediate Post-Injection Reaction:** Approximately 14% of Multiple Sclerosis patients exposed to COPAXONE<sup>®</sup> in the 4 placebo-controlled studies reported a post-injection reaction immediately following subcutaneous injection of COPAXONE<sup>®</sup> compared to 2% for placebo-treated patients. An immediate post-injection reaction is a constellation of symptoms occurring immediately after injection that includes at least two of the following: flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (individual symptoms are listed separately in Table 1). These symptoms were invariably transient, self-limited, did not require specific treatment and in general, arose several months after initiation of treatment, although they may occur earlier in the course of treatment. A given patient may experience one or several episodes of these symptoms during treatment with COPAXONE<sup>®</sup>. Whether these episodes are mediated by an immunologic or non immunologic mechanism, and whether several similar episodes seen in a given patient have identical mechanisms is unknown. In fact, whether or not this constellation of symptoms actually represents a specific syndrome is unknown. During the post-marketing period, there have been reports of patients with similar symptoms who received emergency medical care (see WARNINGS AND PRECAUTIONS: Symptoms of Potentially Cardiac Origin).

**Chest Pain:** Approximately 13% of glatiramer acetate patients in the 4 placebo-controlled studies (compared to 5% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of the chest pain to an injection of glatiramer acetate was not always known, although the pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown. Patients in clinical trials were free of significant cardiovascular disease

(New York Heart Association Class I or II); therefore, the risks associated with glatiramer acetate treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown (see WARNINGS AND PRECAUTIONS: Symptoms of Potentially Cardiac Origin). For adverse event reporting, please contact Health Canada by phone at: 1-866-234-2345, or Teva Canada Innovation at: 1-800-283-0034.

## ADMINISTRATION

### DOSAGE AND ADMINISTRATION

COPAXONE® should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Multiple Sclerosis. The only recommended route of administration of COPAXONE® (glatiramer acetate) injection is the subcutaneous route. COPAXONE® should not be administered by the intravenous route.

**Recommended Dose and Dosage Adjustment:** The recommended dose of COPAXONE® (glatiramer acetate) for injection or glatiramer acetate injection for the treatment of Clinically Isolated Syndrome and Relapsing Remitting MS is a daily injection of 20 mg given subcutaneously. For the pre-filled syringe of COPAXONE®, please see the Part III – Consumer Information – pre-filled syringe for instructions on the preparation and injection of COPAXONE®.

### SUPPLEMENTAL PRODUCT INFORMATION

#### ADVERSE REACTIONS

**Clinical Trial Adverse Drug Reactions:** Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates. The adverse reaction data in this section is derived from 4 pivotal, double-blind, placebo-controlled clinical trials which were conducted during pre-marketing and post-marketing periods in a total of 512 patients treated with glatiramer acetate and 509 patients treated with placebo for up to 36 months. Three trials were conducted in RRMS. The fourth trial was in patients presenting with a first clinical event and MRI features suggestive of MS and included 243 patients treated with glatiramer acetate and 238 patients treated with placebo. All adverse events were recorded by the clinical investigators, using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into standardized categories using MedDRA dictionary terminology. The following table lists treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with glatiramer acetate in the placebo-controlled trials. These signs and symptoms were numerically more common in patients treated with glatiramer acetate than in patients treated with placebo.

Table 1: Controlled Trials – Incidence of Glatiramer Acetate Adverse Reactions ≥2% and More Frequent than Placebo

MedDRA Version 10.0	GA 20 mg (n=512) % of Patients	Placebo (n=509) % of Patients
<b>Blood and Lymphatic System Disorders</b>		
Lymphadenopathy	7.2	2.9
<b>Cardiac Disorders</b>		
Palpitations	7.6	3.3
Tachycardia	4.7	1.6
<b>Eye Disorders</b>		
Eye Disorder	3.3	1.2
Diplopia	2.9	1.8
<b>Gastrointestinal Disorders</b>		
Nausea	14.5	10.4
Vomiting	7.4	4.3
Constipation	7.0	6.3
Dyspepsia	6.6	6.5
Dysphagia	2.3	1.2
Fecal Incontinence	2.3	2.0
<b>General Disorders and Administration Site Conditions</b>		
Injection-Site Erythema	46.1	10.6
Injection-Site Pain	36.3	17.1
Injection-Site Mass	25.8	5.9
Injection-Site Pruritus	24.4	2.8
Asthenia	23.8	23.2
Injection-Site Edema	20.9	4.5
Pain	18.9	16.7
Chest pain	12.5	4.9
Injection-Site Inflammation	8.2	1.6
Injection-Site Reaction	8.2	1.4
Pyrexia	6.4	5.7
Injection-Site Hypersensitivity	4.1	0.0
Local Reaction	3.7	1.4
Face Edema	3.3	0.6
Edema Peripheral	3.3	2.4
Chills	2.9	0.4
Injection-Site Atrophy*	2.0	0.0
Injection-Site Fibrosis	2.0	0.6
<b>Immune System Disorders</b>		
Hypersensitivity	3.3	1.8
<b>Infections and Infestations</b>		
Infection	31.8	30.8
Influenza	15.4	14.5
Rhinitis	7.4	5.9
Bronchitis	6.4	5.7
Gastroenteritis	6.3	4.3
Vaginal Candidiasis	4.9	2.6
Otitis Media	3.7	2.9
Herpes Simplex	2.5	1.8
Tooth Abscess	2.3	2.2
<b>Metabolism and Nutrition Disorders</b>		
Weight Increased	2.9	0.8
Anorexia	2.3	2.2
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Back Pain	13.5	11.2
Arthralgia	10.4	9.4
Neck Pain	4.5	3.9

\* "Injection-site atrophy" comprises terms relating to localized lipatrophy at injection site.

MedDRA Version 10.0	GA 20 mg (n=512) % of Patients	Placebo (n=509) % of Patients
<b>Nervous System Disorders</b>		
Headache	30.9	29.1
Hypertonia	7.8	7.3
Tremor	4.1	1.8
Migraine	3.7	2.4
Syncopal	3.1	1.8
<b>Psychiatric Disorders</b>		
Depression	13.1	12.0
Anxiety	11.1	8.8
Nervousness	2.3	1.0
<b>Renal and Urinary Disorders</b>		
Micturition Urgency	5.1	4.3
Polakiuria	4.7	4.5
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Dyspnea	13.3	2.8
Cough	6.6	5.3
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	13.7	9.0
Hyperhidrosis	6.6	4.7
Pruritus	5.1	4.3
Echymosis	3.5	3.3
Ulceration	3.1	1.6
Skin Disorder	2.9	0.8
<b>Vascular Disorders</b>		
Vasodilatation	18.0	4.7

Data on adverse events occurring in the controlled clinical trials were analyzed to evaluate gender-related differences. No clinically significant differences were identified. In these clinical trials 96% of patients were Caucasian. This percentage reflects the higher representation of Caucasian in the MS population, even though it does not reflect the exact world racial distribution among MS patients. In addition, the vast majority of patients treated with COPAXONE® were between the ages of 18 and 45. Consequently, inadequate data are available to perform an analysis of the incidence of adverse events related to clinically relevant age subgroups. Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE®. Clinically significant changes in laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE® and placebo groups in blinded clinical trials. No patient receiving COPAXONE® withdrew from any placebo-controlled trial due to abnormal laboratory findings which were assessed as possibly related to glatiramer acetate.

**Other Adverse Events Observed During All Clinical Trials:** In the pre-marketing clinical trials, approximately 900 individuals have received at least one dose of COPAXONE® (glatiramer acetate) in controlled and uncontrolled clinical trials. Total patient exposure to COPAXONE® in clinical trials ranged from 6 months (593 patients) to 2 years (306 patients), with a subset of patients continuing to 10 years (n=108) and some patients to an average of 13.6 years (n=100) in open-label extensions at a daily dose of 20 mg. During these trials, all adverse events were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using COSTART II dictionary terminology. All reported events that occurred at least twice and potentially important events occurring once, are included except those already listed in the previous table, those too general to be informative, trivial events, and other events which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: Frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients. **Body as a whole:** Frequent: Injection-site edema, injection-site atrophy, abscess and injection-site hypersensitivity. Infrequent: Injection-site hematoma, injection-site fibrosis, moon face, cellulitis, generalized edema, hemic, injection-site abscess, sunken sickness, suicide attempt, injection-site hypertrophy, injection-site melanosis, lipoma, and photosensitivity reaction. **Cardiovascular:** Frequent: Hypertension. Infrequent: Hypotension, myocardial infarction, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension and varicose veins. **Digestive:** Frequent: Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration and duodenal ulcer. **Endocrine:** Infrequent: Goiter, hyperthyroidism, and hypothyroidism. **Gastrointestinal:** Frequent: Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis. **Hemic and Lymphatic:** Infrequent: Leukopenia, anemia, cyanosis, eosinophilia, hematocrits, lymphedema, paronychia, and splenomegaly. **Metabolic and Nutritional:** Infrequent: Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma. **Musculoskeletal:** Frequent: Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis. **Nervous:** Abnormal dreams, emotional lability and shapov. Infrequent: Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, focal paralysis, decreased libido, moic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression and transient stupor. **Respiratory:** Frequent: Hyperinflation, hay fever. Infrequent: Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration. **Skin and Appendages:** Frequent: Eczema, herpes zoster, pustular rash, skin atrophy and warts. Infrequent: Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash. **Special Senses:** Frequent: Visual field defect. Infrequent: Dry eyes, orbits externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss. **Urogenital:** Frequent: Amenorrhea, hematuria, impotence, menorrhagia, suspicious Papinicolow smear, urinary frequency and vaginal hemorrhage. Infrequent: Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, breast pain, carcinoma cervix in situ, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

#### Post-Market Adverse Drug Reactions

**Adverse Events Reported Post-Marketing and Not Previously Noted in Clinical Trials:** Post-marketing experience has shown an adverse event profile similar to that presented above. Reports of adverse reactions occurring under treatment with COPAXONE® (glatiramer acetate) in either ongoing phases of clinical trials or from spontaneous reports, that have been received since market introduction and that may have or not have causal relationship to the drug include the following: **Body as a Whole:** Sepsis, SLE syndrome, hydrocephalus, enlarged abdomen, injection-site hypersensitivity, allergic reaction, anaphylactoid reaction, bacterial infection, fever, infection. **Cardiovascular:** Thrombosis, peripheral vascular disease, pericardial effusion, myocardial infarct, deep thrombophlebitis, coronary occlusion, congestive heart failure, cardiomyopathy, cardiomegaly, arrhythmia, angina pectoris, tachycardia. **Digestive:** Tongue edema, stomach ulcer hemorrhage, liver function abnormality, liver damage, hepatitis, encephalitis, cirrhosis of the liver, cholelithiasis, diarrhea, gastrointestinal disorder. **Hemic and Lymphatic:** Thrombocytopenia, lymphoma-like reaction, acute leukemia. **Metabolic and Nutritional:** Hypercholesterolemia. **Musculoskeletal:** Rheumatoid arthritis, generalized spasm. **Nervous:** Myelitis, meningitis, CNS neoplasm, cerebrovascular accident, brain edema, abnormal dreams, aphasia, convulsion, neuralgia, anxiety, foot drop, nervousness, speech disorder, vertigo. **Respiratory:** Pulmonary embolus, pleural effusion, carcinoma of lung, hay fever, laryngismus. **Skin and Appendages:** Herpes simplex, pruritus, rash, urticaria. **Special Senses:** Glaucoma, blindness, visual field defect. **Urogenital:** Urogenital neoplasm, urine abnormality, ovarian carcinoma, nephrosis, kidney failure, breast carcinoma, bladder carcinoma, urinary frequency. **Localized Adverse Reactions Associated with Subcutaneous Use:** At injection sites, localized lipatrophy and, rarely, injection-site skin necrosis have been reported during post-marketing experience. Lipatrophy may occur after treatment onset (sometimes as early as several months) and may be permanent. There is no known therapy for lipatrophy. To assist in possibly minimizing these events the patient should be advised to follow proper injection technique and to rotate injection areas and sites on a daily basis (see Part III – Consumer Information).

#### DRUG INTERACTIONS

Interactions between COPAXONE® and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE® with therapies commonly used in MS patients. This includes the concurrent use of corticosteroids for up to 28 days. COPAXONE® has not been formally evaluated in combination with Interferon beta. However, 246 patients who failed on or who did not tolerate therapy with Interferon beta and were later treated with COPAXONE® within the framework of an open clinical trial did not report any serious or unexpected adverse events thought to be related to treatment.

#### OVERDOSAGE

Overdose with COPAXONE® has been reported in three patients. One patient injected four doses (80 mg total) of COPAXONE® at once. No sequelae were noted. Two other patients, a 28-year old male and a 37-year old female, were given 3 injections of 20 mg of COPAXONE® at one half hour intervals by error. Neither patient evidenced any change in blood pressure, heart rate, or temperature. Telephone follow-up several hours later produced no report of adverse experiences from either patient. The maximum COPAXONE® dose reported in an overdose case is 80 mg glatiramer acetate injection.

Based on Product Monograph dated April 2, 2010. Product Monograph available on request.



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# Academic Pediatric and Congenital Neurosurgeon

Section of Neurosurgery, Department of Surgery

Located in the thriving, multicultural city of Winnipeg, the University of Manitoba offers students and faculty a vibrant learning community, exceptional facilities and the chance to explore ideas, challenge assumptions and turn theory into reality. Our researchers are among the best in the world, finding new ways to protect the environment, improve human health, advance technology and strengthen communities in Canada and beyond. With more than 30,000 students, faculty, and staff, and over 90 degree programs, the University of Manitoba plays a key role in the social, cultural, and economic well-being of our community and our world.



The Department of Surgery, Faculty of Medicine at the University of Manitoba and the Surgery Program of the Winnipeg Regional Health Authority, are seeking applications for a geographical full time Neurosurgeon with fellowship training in Pediatric Neurosurgery to further develop the program in Pediatric Neurosurgery at Winnipeg Children's Hospital. The successful applicant will join a well-established neurosurgery group with one Pediatric Neurosurgeon and 7 adult Neurosurgeons providing full sub-specialty coverage. **Position Number: 12697**

A focused interest in adult congenital neurosurgery and neuroendoscopy would be an asset. Protected research time and start up funding is available for suitable candidates.

This position will commence **January 1, 2012**. University rank will be commensurate with qualifications and experience.

Candidates must have specialty qualifications in Neurosurgery in the country of current practice, and must be eligible for registration with the College of Physicians and Surgeons of Manitoba. Certification in Neurosurgery by the Royal College of Physicians and Surgeons of Canada is preferred. Remuneration and academic rank will be commensurate with experience and qualifications.

The City of Winnipeg has a rich cultural environment with symphony, opera, dance, theatre and ethnic festivals. The region also provides ample opportunities for outdoor recreation in all seasons.

The University of Manitoba encourages applications from qualified women and men including members of visible minorities, Aboriginal peoples and persons with disabilities. All qualified candidates are encouraged to apply; however Canadians and permanent residents will be given priority. Applications, accompanied by a curriculum vitae, a list of publications, and the names of three referees, should be sent to: **Dr. R. Nason, Professor and Head, Department of Surgery, AE101- 820 Sherbrook Street, Winnipeg, Manitoba, Canada R3A 1R9**

Application materials, including cover letter, curriculum vitae, and letters of reference, will be handled in accordance with the protection of privacy provisions of "The Freedom of Information and Protection of Privacy Act" (Manitoba) and will be provided to participating members of the search process.

**CLOSING DATE:** November 1, 2011 (position will remain open until filled)

For more information on this opportunity, please visit [umanitoba.ca/employment](http://umanitoba.ca/employment)



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DEPARTMENT OF MEDICINE

### Join Dynamic Neuroscience Team In Ottawa Epileptologist needed to lead and grow established epilepsy program

The Division of Neurology at The Ottawa Hospital is seeking a neurologist with subspecialty training in the field of clinical epilepsy to build on its strong clinical epilepsy platform. This full time academic position is affiliated with the University of Ottawa and offers an excellent opportunity for career growth in a collaborative environment. The division has an established epilepsy clinic with EEG and video-monitoring facilities, wide neurology subspecialty expertise and a highly sought after residency program. We offer a thriving academic environment with extensive links and opportunities in teaching and research.

The city of Ottawa, with its 1.2 million inhabitants, has the highest average income and education of any city in Canada and provides a thriving multicultural and bilingual environment. Numerous cultural activities as well as readily accessible sporting and natural resources make it an ideal family and healthy living environment.

Canadian and foreign trained applicants with strong clinical and academic credentials in the field of epilepsy will be considered. Kindly forward a letter outlining your interest and a CV to:

Dr. Pierre Bourque, Chief, Division of Neurology  
Ottawa Hospital, Civic Campus,  
C2200, 1053 Carling Avenue,  
Ottawa, ON K1Y 4E9

For more information visit our website at:  
[www.thinkottawamedicine.ca](http://www.thinkottawamedicine.ca)



## Academic Neurosurgeons in the Fields of Functional, Oncology, Neurovascular and Spinal Neurosurgery



The Division of Neurosurgery at the Toronto Western Hospital, University Health Network and University of Toronto, is undergoing a major expansion. We therefore initially invite applications for three full-time academic positions at the level of Assistant Professor or higher by neurosurgeons having a clinical subspecialty interests in one of: Cerebrovascular and/or Endovascular, Oncology/Skull-base, Spinal, and Functional Neurosurgery as well as neuro-critical care.

Each successful applicant will also fulfill the mandate of a clinician-scientist, a clinician-investigator, or a clinician-educator. Each position offers an extraordinary opportunity to work in a leading Neurosciences centre and collaborate in excellent clinical and research programs at the Krembil Neurosciences Centre in a multidisciplinary clinical environment. Duties will include patient care, teaching, trainee supervision and research. Time for research will be protected.

The Division of Neurosurgery at the Krembil Neuroscience Centre, Toronto Western Hospital, University of Toronto, is one of the largest academic neurosurgical units in the world. Excellent facilities for clinical neuroscience supported by state-of-the-art clinical, ICU and experimental imaging facilities provide an environment conducive to leading-edge research. The anticipated expansion in the number of neurosurgical faculty will occur over the next three years, and parallels significant growth in research facilities, renovations of OR infrastructure, increased critical care resources and growth of the individual clinical programs, namely neurovascular therapeutics, complex spine, functional and epilepsy, and skull-base/oncology.

Qualifications include an MD, specialist certification in neurosurgery and eligibility for licensure in the province of Ontario. A postgraduate degree (MSc or PhD) in basic or clinical research, fellowship training in the specific subspecialty area and commitment to academic excellence as demonstrated by a portfolio of significant scholarly works are key considerations. Candidates must be eligible for certification with the Royal College of Physicians and Surgeons of Canada and licensure with the College of Physicians and Surgeons of Ontario. Salary support and start-up funding commensurate with the successful candidate's research commitments will be available.

All qualified candidates are encouraged to apply, however, Canadians and permanent residents will be given priority. The University Health Network and the University of Toronto are strongly committed to diversity within its community and especially welcomes applications from visible minority group members, women, Aboriginal persons, and persons with disabilities, members of sexual minority groups, and others who may contribute to the further diversification of ideas.

The position of Cerebrovascular and/or endovascular surgeon is available immediately, and applications will be accepted until this post is filled. For the remaining posts, please forward a curriculum vitae, statement of academic interests and the names of three referees by December 31, 2011 to:

Dr. Michael Tymianski, Interim Head, Division of Neurosurgery

Toronto Western Hospital, University Health Network, 399 Bathurst Street, WW 4-435, Toronto, Ontario, Canada, M5T 2S8

Email: [mike.tymianski@uhn.on.ca](mailto:mike.tymianski@uhn.on.ca)

## NEUROSURGERY DIVISION HEAD DEPARTMENT OF SURGERY UNIVERSITY HEALTH NETWORK



The Department of Surgery at the University Health Network is inviting applications for a new Head of its Division of Neurosurgery. The successful candidate must have an established record of scholarly achievement, with a primary interest in academic neurosurgery and be eligible for appointment at the rank of Associate or Full Professor at the University of Toronto. In addition to scholarly achievement, the preferred candidate should ideally possess a capacity for team-building, fostering multi-disciplinary collaboration, and entrepreneurship. This appointment is for a five-year term, renewal for a second five year term after review. Salary is commensurate with qualifications and experience. Candidates must be eligible for certification with the Royal College of Physicians and Surgeons of Canada, and licensure with the College of Physicians and Surgeons of Ontario. The effective date of this appointment is January 1st, 2012.

University Health Network is comprised of the Toronto General Hospital, Toronto Western Hospital and Princess Margaret Hospital and is one of Canada's largest and leading academic hospitals. The Division of Neurosurgery at University Health Network is one of the largest academic neurosurgical units in the world, and comprises advanced clinical and research programs in neuro-oncology, neurovascular, functional and spinal surgery. The Division of Neurosurgery currently comprises 12 full-time clinical faculty members and three scientists who collaborate in patient care, education, research and innovation in the context of a wide variety of multi-disciplinary programs including the Krembil Neuroscience Centre, The Toronto Western Hospital Research Institute, Surgical Programs & Critical Care, Neurology and the Joint Department of Medical Imaging to name a few.

The Division currently has active resident and fellowship programs. The Division Head is responsible for the overall clinical and academic program including teaching and research and plays a central coordinating role in promoting mentorship, clinical care and recruitment.

Please submit applications and curriculum vitae by September 30th, 2011 to: Shaf Keshavjee MD, Surgeon-in-Chief, Department of Surgery, University Health Network, Toronto General Hospital, RFE 1-408, 190 Elizabeth Street, Toronto, Ontario, Canada. M5G 2C4.

The University Health Network and the University of Toronto are strongly committed to diversity within its community and especially welcomes applications from visible minority group members, women, aboriginal persons, persons with disabilities, members of sexual minority groups, and others who may contribute to the further diversification of ideas. All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority.

# Board of Directors and Committee Chairs

## The Canadian Neurological Sciences Federation (CNSF) and The Neurological Sciences Foundation of Canada (NSFC)



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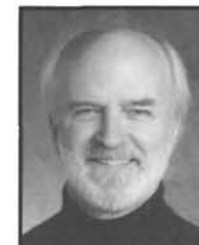
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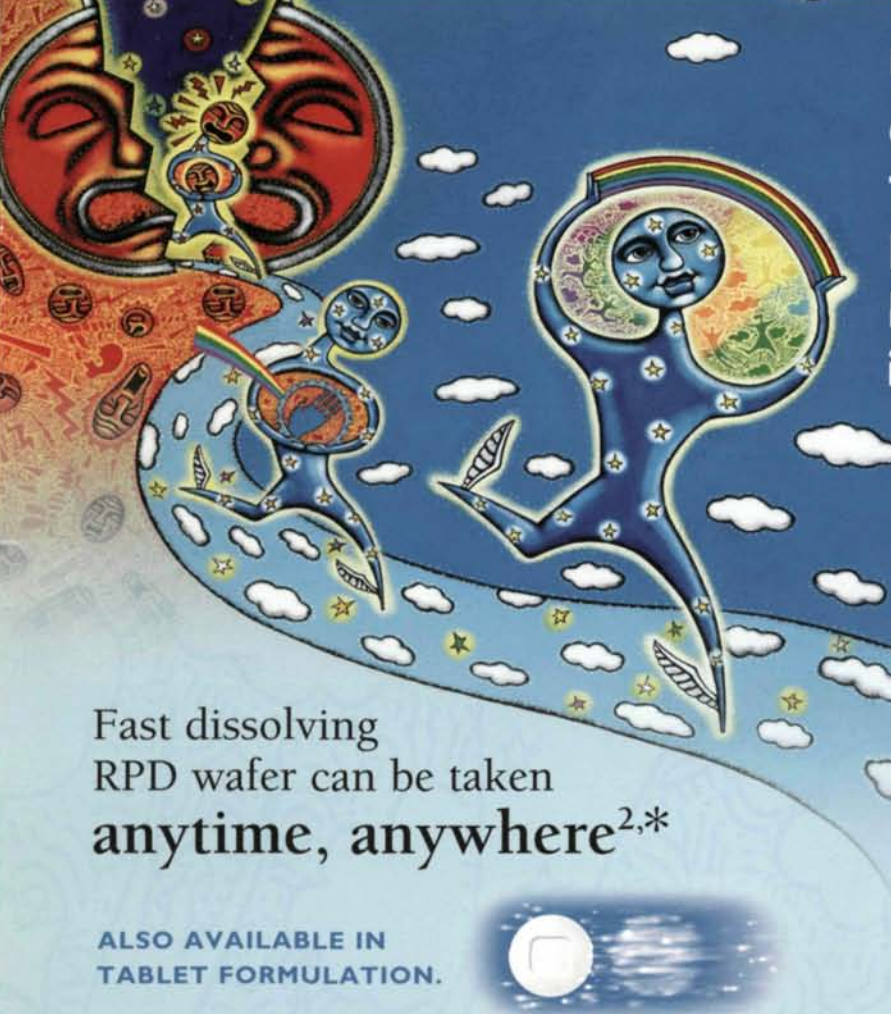
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# Pr MAXALT RPD® (rizatriptan benzoate): The Most Dispensed Non-tablet Formulation Migraine Drug in Canada<sup>1</sup>

Fast dissolving  
RPD wafer can be taken  
**anytime, anywhere<sup>2,\*</sup>**

ALSO AVAILABLE IN  
TABLET FORMULATION.



MAXALT® (rizatriptan benzoate) is indicated for the acute treatment of migraine attacks with or without aura in adults. MAXALT® is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, ophthalmoplegic or basilar migraine. Safety and effectiveness of MAXALT® have not been established for cluster headache, which is present in an older, predominantly male population.

MAXALT® is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). In addition, patients with other significant underlying cardiovascular diseases should not receive MAXALT®.

MAXALT® is also contraindicated in patients with uncontrolled or severe hypertension.

MAXALT® is contraindicated in co-administration with monoamine oxidase (MAO) inhibitors within 2 weeks after discontinuation of treatment, and within 24 hours of administration of 5-HT<sub>1</sub> agonists or ergot-type medications. For a complete list of contraindications, please consult the Product Monograph.

The recommended single adult dose is 5 mg. The maximum recommended single dose is 10 mg.

The most common adverse events during treatment with MAXALT® (rizatriptan benzoate) tablets 10 mg were dizziness (8.9%), somnolence (8.4%), asthenia/fatigue (6.9%), nausea (5.7%) and

pain/pressure sensation (chest, 3.1%; neck/throat/jaw, 2.5%; upper limb, 1.8%).

The most common adverse events during treatment with Pr MAXALT RPD® (rizatriptan benzoate) wafers 10 mg were dizziness (8.6%), nausea (7.0%), dry mouth (6.0%), somnolence (5.3%), asthenia/fatigue (3.6%), and pain/pressure sensation (chest, 1.7%; neck/throat/jaw, 2.0%; upper limb, 2.0%).

MAXALT RPD® wafers contain phenylalanine (a component of aspartame).

\*The wafer will dissolve rapidly and be swallowed with saliva. No liquid is needed to take the wafer.<sup>2</sup>

RPD = Rapidly dissolving

#### References:

1. Brogan Inc. Geographic Prescription Monitor (GPM®) September 2008 to August 2009.
2. Data on file, Merck Frosst Canada Ltd.: Product Monograph, MAXALT®, 2009.

BEFORE PRESCRIBING MAXALT®, PLEASE CONSULT THE ENCLOSED PRESCRIBING INFORMATION.

PRODUCT MONOGRAPH AVAILABLE FOR DOWNLOAD AT  
[www.merckfrosst.com](http://www.merckfrosst.com)

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Merck Frosst Canada Ltd., Kirkland, Quebec



MXT-08-CDN-34381016-JA

**Pr Maxalt®**  
(rizatriptan benzoate)

See prescribing summary on pages A-19 to A-22

FOR YOUR PATIENTS WITH CIS OR RRMS\*

CONSIDER

# COPAXONE®

## FOR YOUR PATIENTS FROM THE START AND FOR THE LONG RUN

### IN RRMS — DEMONSTRATED IMPACT ON DISABILITY AND REDUCTION IN RELAPSE RATES

- Greater reduction in mean change in EDSS scores vs. placebo over 2 years [COPAXONE® -0.05, placebo +0.21; n = 251; p = 0.023]<sup>††</sup>
- 29% mean reduction in relapse rates at 24 months [COPAXONE® 1.19, placebo 1.68; n = 251; p = 0.007]<sup>††</sup>

### IN CIS — DELAYED TIME TO CDMS<sup>‡§</sup>

- COPAXONE® prolonged the time to CDMS by 386 days<sup>§†</sup> (Placebo 336 days vs. COPAXONE® 722 days; n = 481; p = 0.0005)<sup>†</sup>

### ESTABLISHED SAFETY PROFILE

- Over 13 years of safety data in open-label extension trials<sup>†</sup>
- No recommended monitoring of liver and thyroid function or complete blood count<sup>†</sup>

COPAXONE® is indicated for the treatment of ambulatory patients with Relapsing Remitting Multiple Sclerosis (RRMS) to decrease the frequency of clinical exacerbations; to reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans.

COPAXONE® is indicated for the treatment of patients who have experienced a single demyelinating event, accompanied by abnormal MRI scans and are considered to be at risk of developing Clinically Definite MS (CDMS), after alternative diagnoses are excluded; to delay the onset of definite MS; to decrease the number and volume of active brain lesions and overall disease burden (as identified by MRI scans).

The safety and efficacy of COPAXONE® in chronic progressive MS have not been established. In placebo-controlled clinical trials, the most commonly observed adverse events associated with the use of COPAXONE® occurring at an incidence of at least 10% and at least 1.5 times higher than in placebo treated patients were: injection site reactions, vasodilatation, rash, dyspnea and chest pain.

**COPAXONE®**  
(glatiramer acetate injection)

Treat from the start. Treat for the long run.

\* CIS: Clinically Isolated Syndrome; RRMS: Relapsing Remitting Multiple Sclerosis

† Multicenter, double-blind, randomized, placebo-controlled trial in 251 patients with RRMS who were randomized to receive 20 mg/day glatiramer acetate (n = 125) or placebo (n = 126) subcutaneously. Patients were diagnosed with RRMS by standard criteria, and had at least 2 exacerbations during the 2 years immediately preceding enrollment. Primary outcome measure was the mean number of relapses during treatment.

‡ CDMS: Clinically Definite Multiple Sclerosis

§ Delay to CDMS is based on the 25<sup>th</sup> percentile; Kaplan-Meier estimates

†† Multicenter, randomized, double-blind, placebo-controlled, parallel group study in 481 patients for up to three years (glatiramer acetate 20 mg/day; n = 243; placebo: n = 238) was performed in patients with a well-defined, single, unifocal neurological presentation and MRI features suggestive of MS (at least two cerebral lesions on T2-weighted MRI). A total of 25% of glatiramer acetate patients, and 43% of placebo patients converted to CDMS in an average duration of treatment of 2.4 years.

Reference:

1. COPAXONE® (glatiramer acetate injection) Product Monograph, TEVA Canada Innovation, April 2010.



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