PRODUCT MONOGRAPH

Pr MYL-PREGABALIN

Pregabalin capsules

25 mg, 50 mg, 75 mg, 150 mg, 225 mg, 300 mg

Analgesic Agent

Mylan Pharmaceuticals ULC
85 Advance Road
Etobicoke, Ontario
M8Z 2S6

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Pregabalin capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Capsules, 25 mg, 50 mg, 75 mg, 150 mg, 225 mg, 300 mg	Lactose monohydrate, maize starch, and talc. Capsule shells contain gelatin and titanium dioxide. In addition, orange capsule shells contain red iron oxide. White capsule shells contain sodium lauryl sulphate and colloidal silicon dioxide.

INDICATIONS AND CLINICAL USE

Adults

MYL-PREGABALIN (pregabalin) is indicated for the management of neuropathic pain associated with:

- Diabetic peripheral neuropathy and
- Postherpetic neuralgia

MYL-PREGABALIN is indicated for the management of neuropathic pain associated with spinal cord injury.

MYL-PREGABALIN is indicated for the management of pain associated with fibromyalgia.

The efficacy of pregabalin 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 pregabalin during a 6-week open-label phase.

Geriatrics (>65 years of age): Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related

compromised renal function (see **WARNINGS AND PRECAUTIONS**, *Geriatrics (>65 years of age)*).

Pediatrics (<18 years of age): The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established and its use in this patient population is not indicated (see **WARNINGS AND PRECAUTIONS**, *Pediatrics (<18 years of age)).*

CONTRAINDICATIONS

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

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 pregabalin. 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. MYL-PREGABALIN 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 **ADVERSE REACTIONS**, Less Common Clinical Trial Adverse Reactions and Post-Marketing Adverse Drug Reactions).

Caution should be exercised when prescribing MYL-PREGABALIN 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 postmarketing reports of hypersensitivity reactions (eg, skin redness, blisters, hives, rash, dyspnea, and wheezing). Pregabalin should be discontinued immediately if such symptoms occur (see 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 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 (see Preclinical Toxicology). The clinical significance of this finding is uncertain. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in 8666 patients ranging in age from 12 to 100 years, new or worsening-preexisting tumors were reported in 57 patients. The most common malignant tumor diagnosed was skin carcinoma (17 patients) followed by breast carcinoma (8 patients), prostatic carcinoma (6 patients), carcinoma not otherwise specified (6 patients), and bladder carcinoma (4 patients). Without knowledge of the background incidence and recurrence in similar populations not treated with pregabalin, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

Ophthalmological Effects
In controlled studies, pregabalin treatment was associated with vision-related adverse events such as blurred vision (amblyopia) [6% pregabalin and 2% placebo] and diplopia (2% pregabalin and 0.5% placebo). Approximately 1% of pregabalin-treated patients discontinued treatment due to vision-related adverse events (primarily blurred vision). Of the patients who did not withdraw, the blurred vision resolved with continued dosing in approximately half of the cases (see Post-Marketing Adverse Drug Reactions).

Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated and 2% of placebo-treated patients. At this time, clinical significance of the ophthalmologic findings is unknown.

Patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment, including discontinuation of pregabalin, should be considered. More frequent assessments should be considered for patients who are already routinely monitored for ocular conditions.

Peripheral Edema
MYL-PREGABALIN 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 **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 pregabalin and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with pregabalin only, and 19% (23/120) of patients who were on both pregabalin and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on pregabalin only; and 7.5% (9/120) of patients on both drugs.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering MYL-PREGABALIN 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 **ADVERSE REACTIONS**, Less Common Clinical Trial Adverse Reactions).

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin (see 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.

Serious Skin Reactions

There have been very rare post-marketing reports of serious cutaneous reactions, including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), dermatitis exfoliative, bullous skin reactions, and erythema multiforme in patients treated with pregabalin (see Post-Market Adverse Drug Reactions). Post-market reporting rate is generally accepted to be an underestimate due to under-reporting. Most of the reports were in patients taking concomitant medications also associated with the potential development of these serious skin reactions. Therefore, in most cases, causality in relation to pregabalin could not be clearly established. Patients should be advised that if they experience a skin rash, they should discontinue MYL-PREGABALIN treatment and contact their physician for assessment and advice.

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 pregabalin, 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 MYL-PREGABALIN 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 ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions).

Weight Gain

MYL-PREGABALIN 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 **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 **WARNINGS AND PRECAUTIONS**, Peripheral Edema).

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

Among diabetic patients, pregabalin-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg.

In the controlled fibromyalgia clinical trials, 10.7% of pregabalin-treated patients experienced weight gain of 7% or greater compared to 4.9% of placebo-treated patients. Pregabalin-treated patients gained an average of 1.7 Kg compared to an average of 0.7 Kg weight gain in placebo patients.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1C}).

Dizziness and Somnolence

MYL-PREGABALIN may cause dizziness and somnolence. In controlled peripheral neuropathic pain and fibromyalgia 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 **ADVERSE REACTIONS**, Tables 2, 4, and 11, and Post-Marketing Adverse Drug Reactions).

Accordingly, patients should be advised not to drive or operate complex machinery or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental and/or motor performance adversely (see **Part III: CONSUMER INFORMATION**).

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 **ADVERSE REACTIONS**, *Adverse Events Following Abrupt or Rapid Discontinuation*).

Convulsions, including status epilepticus and grand mal convulsions, have occurred in non-epileptic patients during treatment with pregabalin or after abrupt discontinuation (see **ADVERSE REACTIONS**, Post-Marketing Adverse Drug Reactions).

Encephalopathy

There have been serious post-marketing reports of encephalopathy, mostly in patients with underlying conditions that may precipitate encephalopathy. Some cases were reported in patients with a history of kidney or liver disease. Since there have been rare reports of renal failure with pregabalin, specific caution should be exercised when prescribing MYL-PREGABALIN to the elderly with age-related compromised renal function and patients with kidney disease or risk factors for renal failure (see **WARNINGS AND PRECAUTIONS,** Renal Failure and **ADVERSE REACTIONS**, Post-Marketing Adverse Drug Reactions).

Suicidal Behaviour and Ideation

There have been post-marketing reports of suicide-related events, including completed suicide, suicide attempt, and suicidal ideation in patients treated with pregabalin for a variety of indications such as neuropathic pain, fibromyalgia, etc. In some of these reports, underlying psychiatric disorders may have contributed to the event. The mechanism of this risk is not known. Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients should be encouraged to report any distressing thoughts or feelings at anytime to their healthcare professional (see **ADVERSE REACTIONS**, Post-Marketing Adverse Drug Reactions).

Sexual Function/Reproduction

Impairment of Male Fertility

Preclinical Data

In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3-4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

In addition, adverse effects on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of 4 weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD.

In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established. The clinical significance of female fertility findings in animals is unknown.

Human Data

In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin 600 mg/day for 3 months (one complete sperm cycle). Pregabalin did not exhibit significant detrimental effects on the reproductive function of healthy male subjects, as measured by semen analysis, when compared with placebo (n = 16). However, due to the small sample size and short-term exposure to pregabalin (only one complete sperm cycle), no conclusions can be made regarding possible reproductive effects of pregabalin during long-term exposure. Effects on other male reproductive parameters in humans have not been adequately studied.

Special Populations

Renal

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 **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 **ACTION AND CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Adjustment of Dose in Renally-Impaired Patients
In patients with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Table 13 in **DOSAGE AND ADMINISTRATION**, Dosing Considerations).

Pregnancy

Preclinical Data
Pregabalin was not teratogenic in mice, rats, or rabbits. Pregabalin induced fetal toxicity in rats and rabbits at ≥ 39 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day [$AUC_{(0-24)}$ of 123 μg·hr/mL]. In the prenatal-postnatal toxicity study, pregabalin induced offspring developmental toxicity in rats at ≥5 times the maximum recommended human exposure. No developmental effects occurred at 2 times the maximum recommended human exposure (see **TOXICOLOGY**).

Human Data

Pregnant Women
There are no adequate and well-controlled studies in pregnant women. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of anticonvulsant medications that can be taken by women during pregnancy to treat disorders such as epilepsy, mood disorder, and chronic pain. The primary goal is to determine the frequency of major malformations, such as heart defects, spina bifida and cleft lip, in the infants exposed during pregnancy to anticonvulsant drugs. To enroll, patients can call the toll-free number, 1-888-233-2334. Information on the registry can be also found at the website http://www.massgeneral.org/aed/ (see **WARNINGS AND PRECAUTIONS**, Patient Counselling Information).

Labour and Delivery
The effects of pregabalin on labour and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥47 times the mean human exposure [$AUC_{(0-24)}$ of 123 μg·hr/mL] at the maximum recommended clinical dose of 600 mg/day (see **TOXICOLOGY**).

Nursing Women
Pregabalin is excreted in the milk of lactating women. As the safety of pregabalin in infants is not known, breast-feeding is not recommended during treatment with pregabalin. A decision must be made whether to discontinue breast-feeding or to discontinue from pregabalin therapy taking into

account the benefit of breast feeding for the child and the benefit of therapy for the women (see **TOXICOLOGY**). Patients should be advised to notify their physician if they are breast-feeding. The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Pregabalin was excreted into breast milk with average peak and steady-state concentrations approximately 53 and 76% of those in maternal plasma, respectively. The estimated average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 0.31 mg/kg/day, which on a mg/kg basis would be approximately 7% of the total maternal daily dose.

Pediatrics (<18 years of age)
The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established.

Geriatrics (>65 years of age)
Of the 1831 patients who received pregabalin in neuropathic pain studies, 528 were 65 to 74 years of age, and 452 were 75 years of age or older. No significant differences in efficacy were observed between these patients and younger patients. Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age- related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function. In general, the incidence of adverse events did not increase with age.

Creatine Kinase Elevations
Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin-treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Laboratory Changes, Decreased Platelet Count
Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of 20 x 10^3/μL, compared to 11 x 10^3/μL in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and < 150 x 10^3/μL.

In randomized controlled trials, pregabalin was not associated with an increase in bleeding related adverse events.

ECG Changes, PR Interval Prolongation

Pregabalin treatment was associated with mild PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3-6 msec at pregabalin doses ≥ 300 mg/day. This mean change difference was not associated with an increased risk of PR increase ≥ 25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse events of second or third degree AV block.

Patient Counselling Information

Patients receiving MYL-PREGABALIN should be given the following instructions by the physician:

1. **Angioedema:** Patients should be advised that MYL-PREGABLAIN may cause angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Instruct patients to discontinue MYL-PREGABALIN and immediately seek medical care if they experience these symptoms.

2. **Hypersensitivity:** Patients should be advised that pregabalin has been associated with hypersensitivity reactions such as wheezing, dyspnea, rash, hives, and blisters. Instruct patients to discontinue MYL-PREGABALIN and immediately seek medical care if they experience these symptoms.

3. **Suicidal Behaviour and Ideation:** Patients, their caregivers, and families should be counselled to monitor for signs of suicidal ideation and behaviours and should be encouraged to report any distressing thoughts or feelings at anytime to their healthcare professional.

4. **Dizziness and Somnolence:** Patients should be counseled that MYL-PREGABALIN may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental, visual, and/or motor performance adversely.

5. **Edema and Weight Gain:** Patients should be counseled that MYL-PREGABALIN may cause edema and weight gain. Patients should be advised that concomitant treatment with MYL-PREGABALIN and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure.

6. **Abrupt or Rapid Discontinuation:** Patients should be advised to take MYL-PREGABALIN as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, anxiety, hyperhidrosis, or diarrhea.

7. **Visual Disturbances:** Patients should be counseled that MYL-PREGABALIN may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician (see **WARNINGS AND PRECAUTIONS**, Ophthalmologic Effects).

8. **Muscle Pain, Tenderness or Weakness:** Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

9. **Concomitant Treatment with CNS Depressants, Alcohol:** Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence.

   In post-marketing experience, there are reports of respiratory failure and coma in patients taking pregabalin alone or in combination with other CNS depressants.

   Patients should be told to avoid consuming alcohol while taking MYL-PREGABALIN, as MYL-PREGABALIN may potentiate the impairment of motor skills and sedation of alcohol.

10. **Pregnant Women:** Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during their therapy, and to notify their physician if they are breast-feeding or intend to breast-feed during therapy.

    Patients should be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry (NAAED) if they become pregnant. This registry is collecting information about the safety of anticonvulsant medications that can be taken by women during pregnancy to treat disorders such as epilepsy, mood disorder, and chronic pain. To enroll, patients can call the toll free number 1-888-233-2334. Information on the registry can also be found at the website http://www.massgeneral.org/aed/ (see **WARNINGS AND PRECAUTIONS**; **Special Populations**, *Pregnant Women*).

11. **Animal Studies in Male Reproduction:** Men being treated with MYL-PREGABALIN who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity (see **WARNINGS AND PRECAUTIONS**, Sexual Function/Reproduction). The clinical significance of this finding is uncertain.

12. **Skin:** Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with MYL-PREGABALIN. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with pregabalin was observed in clinical trials (see **WARNINGS AND PRECAUTIONS**, Preclinical Toxicology).

Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking MYL-PREGABALIN.

Preclinical Toxicology

Carcinogenesis

Dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. In an investigative study in female B6C3F1 mice, chronic treatment (24 months) with pregabalin at 1000 mg/kg caused an increased incidence of hemangiosarcoma, consistent with previous studies, but not at 50 or 200 mg/kg. Discontinuation of treatment after 12 months at 1000 mg/kg did not significantly reduce the incidence of hemangiosarcoma at 24 months. Evidence of carcinogenicity was not seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD. The clinical significance in humans of this finding in mice is unknown.

Mutagenesis
Pregabalin is not genotoxic based on results of a battery of in vitro and in vivo tests. Pregabalin was not mutagenic in bacteria or in mammalian cells in vitro, was not clastogenic in mammalian systems in vitro and in vivo, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Dermatopathy
Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies.

Ocular Lesions
Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) ≥2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year. The clinical significance of this finding in rats is unknown.

Monitoring and Laboratory Tests
Routine therapeutic drug monitoring or clinical laboratory testing is not required for patients treated with MYL-PREGABALIN (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug 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.

In all controlled and uncontrolled trials during the pre-marketing development of pregabalin, more than 8666 patients have received pregabalin, with 83% of exposure at dosages of 300 mg/day or above and 32% at dosages of 600 mg/day or higher. Approximately 4010 patients had at least 6 months of exposure, 2415 had at least 1 year of exposure, and 939 had at least 2 years of exposure to pregabalin. In controlled trials, 1831 patients with neuropathic pain received pregabalin. In all controlled and uncontrolled studies in fibromyalgia, 3446 patients have received pregabalin doses of 150-600 mg/day. A total of 969 patients had at least 6 months of exposure and 440 patients had at least 1 year exposure to pregabalin. Doses above 600 mg/day have not been studied.

In a controlled study of neuropathic pain due to spinal cord injury, 137 patients were randomized to receive placebo (N=67) or escalating doses (150-600 mg/day) of pregabalin, (N=70). The controlled study was followed by an open-label trial in which 103 patients received pregabalin (150-600 mg/day). The median duration of therapy across the double-blind and open-label studies for those subjects treated in the open-label extension was 608 days (range 14-1248). Sixty-nine (67%) subjects received at least 1 year of open-label pregabalin and 31 (30.1%) received at least 2 years of open-label pregabalin.

Most Common Adverse Events in All Pre-marketing Controlled Clinical Studies of Neuropathic Pain

The most commonly observed adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients in pre-marketing studies were: dizziness, somnolence, peripheral edema, and dry mouth. Adverse events were usually mild to moderate in intensity.

Discontinuation Due to Adverse Events in Pre-marketing Controlled Clinical Studies

In all pre-marketing controlled studies, the discontinuation rate due to adverse events was 14% for patients receiving pregabalin and 7% for patients receiving placebo. The most common reasons for discontinuation due to adverse events (≥2%) in the pregabalin treatment groups were dizziness and somnolence. Other adverse events that led to withdrawal more frequently in the pregabalin group than the placebo group were ataxia (1%), and asthenia, confusion, headache and nausea (<1% each).

In pre-marketing controlled neuropathic pain studies, the discontinuation rate due to adverse events was 11% for pregabalin and 5% for placebo. The most common reasons for

discontinuation due to adverse events (≥2%) in the pregabalin treatment groups were dizziness and somnolence. Other adverse events that led to withdrawal more frequently in the pregabalin group than the placebo group were confusion (1%) and asthenia, peripheral edema and ataxia (<1% each).

Incidence of Adverse Events in Pre-marketing Controlled Clinical Studies of Neuropathic Pain

In summaries of adverse events, investigator's terms for individual adverse events have been grouped into a smaller number of standardized categories using the COSTART IV dictionary. The prescriber should be aware that the percentages in Table 1 through Table 8 cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

Adverse Events From Pre-marketing Controlled Clinical Studies of Neuropathic Pain

Diabetic Peripheral Neuropathy

Table 1 lists all adverse events, regardless of causality, occurring in ≥ 2% of patients with neuropathic pain associated with diabetic peripheral neuropathy receiving pregabalin for at least one of the pregabalin groups, and for which the incidence was greater than in the placebo group. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of mild or moderate. In these studies, 979 patients received pregabalin and 459 patients received placebo for up to 13 weeks.

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

Body System Preferred Term	Placebo (N = 459) %	Pregabalin (mg/day)			
		75 (N =77) %	150 (N = 212) %	300 (N = 321) %	600 (N = 369) %
Body as a whole					
Infection	6.1	3.9	7.5	8.4	4.6
Asthenia	2.4	3.9	1.9	4.4	7.3
Pain	3.9	5.2	4.2	2.5	4.9
Accidental injury	2.8	5.2	2.4	2.2	5.7
Back pain	0.4	0.0	2.4	1.2	1.9
Chest pain	1.1	3.9	1.4	1.2	1.6
Face edema	0.4	0.0	0.9	0.9	2.2
Digestive system					
Dry mouth	1.1	2.6	1.9	4.7	6.5
Constipation	1.5	0.0	2.4	3.7	6.0

Body System Preferred Term	Placebo (N = 459) %	Pregabalin (mg/day)			
		75 (N =77) %	150 (N = 212) %	300 (N = 321) %	600 (N = 369) %
Diarrhea	4.8	5.2	2.8	1.9	3.0
Flatulence	1.3	2.6	0	2.2	2.7
Vomiting	1.5	1.3	0.9	2.2	1.1
Hemic and lymphatic system					
Ecchymosis	0.2	2.6	0.5	0.6	0.3
Metabolic and nutritional disorders					
Peripheral edema	2.4	3.9	6.1	9.3	12.5
Weight gain	0.4	0.0	4.2	3.7	6.2
Edema	0.0	0.0	1.9	4.0	1.9
Hypoglycemia	1.1	1.3	3.3	1.6	1.1
Nervous system					
Dizziness	4.6	7.8	9.0	23.1	29.0
Somnolence	2.6	3.9	6.1	13.1	16.3
Neuropathy	3.5	9.1	1.9	2.2	5.4
Ataxia	1.3	6.5	0.9	2.2	4.3
Vertigo	1.1	1.3	1.9	2.5	3.5
Confusion	0.7	0.0	1.4	2.2	3.3
Euphoria	0.0	0.0	0.5	3.4	1.6
Thinking abnormal[a]	0.0	1.3	0.0	0.9	3.0
Abnormal gait	0.0	1.3	0.0	0.6	2.7
Reflexes decreased	1.7	3.9	0.5	1.2	1.4
Amnesia	0.2	2.6	0.9	0.0	2.2
Hypesthesia	0.7	2.6	0.0	0.0	0.8
Hyperalgesia	0.2	2.6	0.0	0.0	0.3
Respiratory system					
Dyspnea	0.7	2.6	0.0	1.9	1.9
Skin and appendages					
Pruritus	13	2.6	0.0	0.9	0.0
Special senses					
Blurred vision[b]	1.5	2.6	1.4	2.8	5.7
Conjunctivitis	0.2	2.6	1.4	0.6	0.3

a Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slow thinking.
b Investigator term; summary level term is amblyopia.

Discontinuation in Controlled Clinical Studies of Diabetic Peripheral Neuropathy

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

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

Number (%) of Patients

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

Postherpetic Neuralgia

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

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

Body System Preferred Term	Placebo (N = 398) %	Pregabalin (mg/day)			
		75 (N =84) %	150 (N = 302) %	300 (N = 312) %	600 (N = 154) %
Body as a whole					
Infection	3.5	14.3	8.3	6.4	2.6
Headache	5.3	4.8	8.9	4.5	8.4
Pain	3.8	4.8	4.3	5.4	4.5
Asthenia	4.0	3.6	5.0	2.6	5.2
Accidental injury	1.5	3.6	2.6	3.2	5.2
Flu syndrome	1.3	1.2	1.7	2.2	1.3
Face edema	0.8	0.0	1.7	1.3	3.2
Malaise	1.0	2.4	0.3	0.6	0.0
Cardiovascular system					
Vasodilatation	1.3	2.4	1.0	0.6	0.0
Digestive system					
Dry mouth	2.8	7.1	7.0	6.1	14.9
Constipation	2.3	3.6	4.6	5.4	5.2
Diarrhea	4.0	2.4	4.3	3.5	4.5
Flatulence	1.0	2.4	1.3	1.6	3.2
Vomiting	0.8	1.2	0.7	2.9	2.6
Metabolic and nutritional disorders					
Peripheral edema	3.5	0.0	7.9	15.7	16.2
Weight gain	0.3	1.2	1.7	5.4	6.5
Edema	1.3	0.0	1.0	2.2	5.8
Hyperglycemia	0.8	2.4	0.3	0.0	0.0
Nervous system					
Dizziness	9.3	10.7	17.9	31.4	37.0
Somnolence	5.3	8.3	12.3	17.9	24.7
Ataxia	0.5	1.2	2.0	5.4	9.1
Abnormal gait	0.5	0.0	2.0	3.8	7.8
Confusion	0.3	1.2	2.3	2.9	6.5

Body System Preferred Term	Placebo (N = 398) %	Pregabalin (mg/day)			
		75 (N =84) %	150 (N = 302) %	300 (N = 312) %	600 (N = 154) %
Thinking abnormal[a]	1.5	0.0	1.7	1.3	5.8
Incoordination	0.0	2.4	1.7	1.3	2.6
Amnesia	0.0	0.0	1.0	1.3	3.9
Speech disorder	0.0	0.0	0.3	1.3	3.2
Insomnia	1.8	0.0	0.7	2.2	0.0
Euphoria	0.0	2.4	0.0	1.3	1.3
Nervousness	0.5	0.0	1.0	0.3	2.6
Tremor	1.5	1.2	0.0	1.0	2.6
Hallucinations	0.0	0.0	0.3	0.3	3.2
Hyperesthesia	0.3	2.4	0.3	0.0	1.3
Respiratory system					
Bronchitis	0.8	0.0	1.3	1.0	2.6
Pharyngitis	0.8	0.0	2.6	0.6	0.6
Rhinitis	1.8	1.2	0.7	0.6	3.2
Skin and appendages					
Rash	3.0	2.4	2.0	2.9	5.2
Special senses					
Blurred vision[b]	2.5	1.2	5.0	5.1	9.1
Diplopia	0.0	0.0	1.7	1.9	3.9
Abnormal vision	0.3	0.0	1.0	1.6	5.2
Urogenital system					
Urinary tract infection	1.5	0.0	2.3	1.6	3.2

a Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slow thinking.
b Investigator term; summary level term is amblyopia.

Discontinuation in Controlled Clinical Studies of Postherpetic Neuralgia

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

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

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

Incidence of Most Common Dose-Related Treatment-Emergent Adverse Events

Most common dose-related treatment-emergent adverse events are presented in Table 5 (diabetic peripheral neuropathy), Table 6 (postherpetic neuralgia), and Table 7 (fibromyalgia).

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

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

a Investigator term; summary level term is amblyopia.

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

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

a Investigator term; summary level term is amblyopia.

Table 7. Incidence (%) of Most Common Dose-Related Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Pain Associated with Fibromyalgia

System Organ Class and Preferred Term (MedDRA version 10.1)	Placebo (N = 689) %	Pregabalin (mg/day)			
		150 (N = 132) %	300 (N = 685) %	450 (N = 687) %	600 (N = 564) %
Dizziness	10.4	22.7	32.6	42.5	46.5
Somnolence	4.6	12.9	18.5	19.9	20.7
Weight increased	2.5	7.6	11.1	10.0	13.7
Peripheral edema	2.5	5.3	6.7	6.4	10.8
Dry mouth	1.7	6.8	6.7	9.2	9.4
Constipation	2.8	3.8	5.8	6.8	9.2
Fatigue	5.4	4.5	7.2	8.4	8.2
Balance disorder	0.1	1.5	3.2	4.9	6.9
Disturbance in attention	1.3	3.8	4.4	6.4	6.9
Increased appetite	1.3	3.8	3.4	4.5	5.5
Euphoria	0.9	1.5	4.1	4.8	5.1

Adverse Events From a Controlled Clinical Study in Neuropathic Pain Associated With Spinal Cord Injury

The most commonly observed treatment-related adverse events (≥ 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.

Table 8 lists all adverse events, regardless of causality, occurring in ≥ 2% of patients receiving pregabalin and for which the incidence was greater than in the placebo group. A majority of pregabalin-treated patients had adverse events with a maximum intensity of mild or moderate. In this study, 70 patients received pregabalin and 67 patients received placebo for up to 12 weeks.

Table 8. Incidence (%) of Treatment-Emergent Adverse Events in a Placebo-Controlled Study in Neuropathic Pain Associated With Spinal Cord Injury (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

Body System Preferred Term	Placebo N = 67 %	Pregabalin (150 - 600 mg/day) N = 70 %
Body as a whole		
Asthenia	6.0	15.7
Infection	6.0	8.6
Abdomen enlarged	0.0	4.3
Pain	1.5	4.3
Back pain	1.5	2.9
Cellulitis	0.0	2.9
Flu syndrome	1.5	2.9
Neck pain	1.5	2.9

Body System Preferred Term	Placebo N = 67 %	Pregabalin (150 - 600 mg/day) N = 70 %
Cardiovascular system		
Hypotension	0.0	2.9
Digestive system		
Dry mouth	3.0	15.7
Constipation	6.0	12.9
Gastroenteritis	0.0	2.9
Increased appetite	0.0	2.9
Metabolic and nutritional disorders		
Edema	0.0	12.9
Peripheral edema	6.0	10.0
Weight gain	0.0	4.3
Musculoskeletal system		
Myasthenia	4.5	8.6
Joint disorder	0.0	2.9
Nervous system		
Somnolence	9.0	41.4
Dizziness	9.0	24.3
Amnesia	3.0	10.0
Thinking abnormal[a]	1.5	8.6
Paresthesia	1.5	5.7
Euphoria	0.0	4.3
Speech disorder	1.5	4.3
Twitching	0.0	4.3
Withdrawal syndrome	0.0	4.3
Skin and appendages		
Skin ulcer	1.5	4.3
Alopecia	0.0	2.9
Vesiculobullous rash	0.0	2.9
Special senses		
Blurred vision[b]	3.0	8.6
Diplopia	1.5	2.9
Tinnitus	0.0	2.9
Urogenital system		
Urinary incontinence	3.0	5.7

[a] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slow thinking.
[b] Investigator term; summary level term is amblyopia.

Discontinuation in a Controlled Clinical Study in Neuropathic Pain Associated With Spinal Cord Injury

Approximately 21% of patients receiving pregabalin and 13% receiving placebo discontinued due to adverse events. The adverse events most commonly leading to discontinuation are presented in Table 9.

Table 9. Adverse Events Most Frequently (≥2% of patients) Leading to Discontinuation in a Placebo-Controlled Study in Patients With Neuropathic Pain Associated with Spinal Cord Injury

Number (%) of Patients		
COSTART Preferred Term	**Placebo (N = 67)**	**Pregabalin (N = 70) 150 – 600 mg/day**
Somnolence	0 (0.0)	4 (5.7)
Edema	0 (0.0)	4 (5.7)
Asthenia	0 (0.0)	3 (4.3)

Overall, the most frequent treatment-related adverse events in the open-label study were related to the nervous system and included: somnolence (18.4%), dizziness (16.5%), and insomnia (10.7%). Other frequent treatment-related adverse events included: asthenia (12.6%), nausea (11.7%), and constipation (10.7%).

Most Common Adverse Events in Controlled Clinical Studies in Fibromyalgia

The most commonly observed treatment-related adverse events (≥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.

Adverse Events from Controlled Clinical Studies in Fibromyalgia

Table 10 lists all adverse events occurring in ≥2% of patients receiving pregabalin and for which the incidence was greater than in the placebo group. A majority of pregabalin-treated patients in these studies had adverse events with mild or moderate intensity. There was a dose-related increase in the incidence of adverse events (see Table 7). Severe adverse events occurred at roughly the same rate in low versus high doses of pregabalin.

Table 10. Incidence (%) of Treatment-Emergent Adverse Events in Controlled Fibromyalgia Studies (in at Least 2% of Pregabalin-Treated Patients and More Frequent Than in Placebo-Treated Patients)

System Organ Class and Preferred Term (MedDRA version 10.1)	**Placebo (N = 689) %**	**Pregabalin (mg/day)**			
		150 (N = 132) %	**300 (N = 685) %**	**450 (N = 687) %**	**600 (N = 564) %**
Ear and labyrinth disorders					
Vertigo	0.9	1.5	3.1	3.2	3.5
Eye disorders					
Blurred vision[a]	1.0	8.3	5.8	6.4	10.1
Gastrointestinal disorders					
Dry mouth	1.7	6.8	6.7	9.2	9.4
Constipation	2.8	3.8	5.8	6.8	9.2
Abdominal distention	1.5	2.3	2.2	1.9	2.0
Flatulence	1.0	0.8	0.9	2.0	2.3
General disorders and administration site conditions					
Fatigue	5.4	4.5	7.2	8.4	8.2
Peripheral edema	2.5	5.3	6.7	6.4	10.8
Feeling abnormal	0.3	0.8	1.9	1.9	2.0
Feeling drunk	0	0.8	2.3	1.5	2.1
Infections and infestations					

System Organ Class and Preferred Term (MedDRA version 10.1)	Placebo (N = 689) %	Pregabalin (mg/day)			
		150 (N = 132) %	300 (N = 685) %	450 (N = 687) %	600 (N = 564) %
Sinusitis	3.0	3.8	3.6	5.2	4.1
Investigations					
Weight increased	2.5	7.6	11.1	10.9	13.7
Metabolism and nutritional disorders					
Increased appetite	1.3	3.8	3.4	4.5	5.5
Fluid retention	0.7	1.5	2.2	2.0	2.0
Musculoskeletal and connective tissue disorders					
Arthralgia	2.5	3.8	3.6	3.2	4.6
Muscle spasm	1.9	2.3	3.4	3.3	3.2
Nervous system disorders					
Dizziness	10.4	22.7	32.6	42.5	46.5
Somnolence	4.6	12.9	18.5	19.9	20.7
Disturbance in attention	1.3	3.8	4.4	6.4	6.9
Balance Disorder	0.1	1.5	3.2	4.9	6.9
Memory Impairment	0.6	0.8	2.6	3.5	3.5
Hypoesthesia	0.6	1.5	2.0	2.8	2.3
Temor	0.6	0	0.6	2.9	3.0
Lethargy	0.4	2.3	1.3	0.7	1.4
Psychiatric disorders					
Euphoria	0.9	1.5	4.1	4.8	5.1
Anxiety	0.9	1.5	1.9	2.5	1.8
Confusion	0.1	0	2.0	1.9	2.7

[a]Investigator term; summary level term is amblyopia.

Discontinuation Due to Adverse Events in Controlled Clinical Studies in Fibromyalgia

Approximately 20% of patients receiving pregabalin and 11% receiving placebo discontinued due to adverse events. The adverse events most commonly leading to discontinuation were dizziness (6.1%) and somnolence (3.3%) as presented in Table 11. Other events leading to discontinuation in clinical trials of fibromyalgia included weight gain (1.1%), vision blurred (0.8%) and peripheral edema (0.6%). There was a dose-dependent increase in rate of discontinuation due to adverse events.

Table 11. Adverse Events Most Frequently (≥2% of patients) Leading to Discontinuation in Placebo-Controlled Studies in Patients With Pain Associated with Fibromyalgia

Number (%) of Patients					
System Organ Class and Preferred Term (MedDRA version 10.1)	Placebo (N=689)	Pregabalin (mg/day)			
		150 (N =132)	300 (N = 675)	450 (N = 687)	600 (N = 564)
Dizziness	0.4%	1.5%	4.1%	6.6%	9.2%
Somnolence	0.1%	0.8%	2.9%	3.2%	4.6%

Adverse Events Following 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 **WARNINGS AND PRECAUTIONS**, Abrupt or Rapid Discontinuation].

Other Events Observed During the Premarketing Evaluation of Pregabalin
Following is a list of treatment-emergent adverse events reported during premarketing assessment of pregabalin in clinical trials (over 8600 adult subjects) except those already listed in the previous tables or elsewhere in labeling. In the tabulations that follow, a COSTART-based dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 8600 adult individuals exposed to multiple doses of pregabalin who experienced an event of the type cited on at least 1 occasion while receiving pregabalin. It is important to emphasize that although the events reported occurred during treatment with pregabalin, they were not necessarily caused by it.

Less Common Clinical Trial Adverse Drug Reactions (<2%)

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body System	**Adverse Events**
Body as a whole	
Frequent	Flu syndrome, back pain, allergic reaction, fever, generalized edema
Infrequent	Neck pain, neoplasm, cellulitis, cyst, chills, malaise, overdose, moniliasis, hernia, viral infection, photosensitivity reaction, pelvic pain, abdomen enlarged, abscess, neck rigidity, lab test abnormal, drug level increased, carcinoma, sepsis, suicide attempt, reaction unevaluable
Rare	Infection fungal, unexpected benefit, chills and fever, body odor, drug level decreased, halitosis, hangover effect, injection site reaction, hormone level altered, hypothermia, infection bacterial, injection site hemorrhage, intentional overdose, mucous membrane disorder, accidental overdose, adenoma, anaphylactoid reaction, ascites, chest pain substernal, death, sarcoidosis, sudden death, immune system disorder, increased drug effect, injection site pain, Lupus Erythematosus syndrome, medication error, sarcoma, shock, tolerance decreased
Cardiovascular	
Frequent	Hypertension, vasodilatation
Infrequent	Palpitation, migraine, tachycardia, peripheral vascular disorder, electrocardiogram abnormal, cardiovascular disorder, angina pectoris, congestive heart failure, hemorrhage, myocardial infarct, hypotension, postural hypotension, ventricular extrasystoles, atrial fibrillation, coronary artery disorder, bradycardia, cerebrovascular accident, arrhythmia, cerebral ischemia, vascular disorder, sinus bradycardia, myocardial ischemia, bundle branch block, AV block first degree, arteriosclerosis, deep thrombophlebitis, phlebitis, arterial anomaly, heart failure, pulmonary embolus, retinal vascular disorder, varicose vein
Rare	Heart arrest, vascular anomaly, occlusion, supraventricular tachycardia, atrial arrhythmia, atrial flutter,

Body System	Adverse Events
	cerebral infarct, coronary occlusion, thrombophlebitis, thrombosis, cardiomegaly, extrasystoles, pallor, AV block, AV block second degree, cardiomyopathy, peripheral gangrene, QT interval prolonged, retinal artery occlusion, supraventricular extrasystoles, cerebral hemorrhage, digitalis intoxication, ventricular arrhythmia, aortic stenosis, bigeminy, cerebrovascular disorder, left heart failure, ventricular tachycardia, AV block complete, carotid occlusion, carotid thrombosis, cor pulmonale, embolus lower extremity, endocarditis, heart block, increased capillary fragility, intracranial aneurysm, nodal tachycardia, QT interval shortened, retinal vein thrombosis, ST elevated, T inverted, vascular headache, vasculitis
Digestive system	
Frequent	Nausea, diarrhea, anorexia, gastrointestinal disorder
Infrequent	Gastroenteritis, tooth disorder, periodontal abscess, colitis, gastritis, liver function tests abnormal, increased salivation, thirst, nausea and vomiting, rectal disorder, gingivitis, dysphagia, stomatitis, mouth ulceration, cholelithiasis, rectal hemorrhage, gastrointestinal hemorrhage, glossitis, tooth caries, abnormal stools, cholecystitis, melena, oral moniliasis, esophagitis, tongue disorder, cheilitis, tongue edema
Rare	Eructation, pancreatitis, stomach ulcer, ulcerative stomatitis, esophageal stenosis, fecal incontinence, gum hemorrhage, intestinal obstruction, enteritis, peptic ulcer, enterocolitis, gum hyperplasia, hepatomegaly, liver fatty deposit, tenesmus, biliary pain, fecal impaction, jaundice, periodontitis, ulcerative colitis, aphthous stomatitis, cholestatic jaundice, gastrointestinal carcinoma, hemorrhagic gastritis, hepatitis, liver tenderness, nausea, vomiting and diarrhea, salivary gland enlargement, stomach atony, bloody diarrhea, cardiospasm, duodenal ulcer, gamma glutamyl transpeptidase increased, hematemesis, hepatoma, intestinal perforation, intestinal stenosis, intestinal ulcer, leukoplakia of mouth, necrotizing pancreatitis, pancreas disorder, pseudomembranous colitis, sialadenitis, stomach ulcer hemorrhage, tongue discoloration
Endocrine system	
Infrequent	Diabetes mellitus, hypothyroidism
Rare	Goiter, prolactin increased, thyroid disorder, gonadotropic follicle stim hormone increase, hyperthyroidism, thyroiditis, adrenal insufficiency, parathyroid disorder, thyroid carcinoma, thyroid neoplasia, virilism
Hemic and lymphatic	
Infrequent	Anemia, leukopenia, thrombocytopenia, lymphadenopathy, hypochromic anemia, leukocytosis, eosinophilia
Rare	Lymphocytosis, petechia, iron deficiency anemia, cyanosis, lymphedema, polycythemia, lymphoma like reaction, megaloblastic anemia, splenomegaly, purpura, thrombocythemia, thrombocytopenic purpura, chronic leukemia, coagulation disorder, erythrocytes abnormal, leukemoid reaction, lymphangitis, macrocytic anemia, neutropenia, pancytopenia, prothrombin decreased, rupture of spleen, sedimentation rate increased
Metabolic and nutritional	
Infrequent	Hyperglycemia, SGPT increased, hypoglycemia, hypokalemia, hypercholesteremia, SGOT increased, weight loss, hyperlipemia, amylase increased, hyperuricemia, alkaline phosphatase increased, creatinine increased, hyponatremia, gout, dehydration, BUN increased, healing abnormal
Rare	Hypercalcemia, hyperkalemia, hypocalcemia, bilirubinemia, alcohol intolerance, hypoglycemic reaction, ketosis, calcium disorder, hypochloremia, hypomagnesemia, hypoproteinemia, NPN increased, uremia, acidosis, avitaminosis, enzymatic abnormality, gamma globulins increased, hypernatremia, hypophosphatemia, lactic acidosis, obesity
Musculoskeletal system	
Frequent	Arthralgia, myalgia, arthritis, leg cramps, myasthenia
Infrequent	Tendon disorder, arthrosis, joint disorder, bone disorder, tenosynovitis, bursitis, tendinous

Body System	Adverse Events
	contracture, osteoporosis, tendon rupture, bone pain
Rare	Rheumatoid arthritis, osteomyelitis, rhabdomyolysis, myopathy, muscle atrophy, myositis, pyogenic arthritis, bone neoplasm, musculoskeletal congenital anomaly, pathological fracture
Nervous system	
Frequent	Insomnia, anxiety, libido decreased, depersonalization, hypertonia, neuropathy
Infrequent	Reflexes decreased, sleep disorder, abnormal dreams, hostility, hallucinations, hyperkinesia, personality disorder, dysarthria, hyperesthesia, hypokinesia, circumoral paresthesia, libido increased, neuralgia, vestibular disorder, aphasia, movement disorder, hyperalgesia, apathy, hypotonia, convulsion, facial paralysis, psychosis
Rare	Drug dependence, neuritis, paranoid reaction, CNS depression, CNS neoplasia, manic reaction, neurosis, extrapyramidal syndrome, meningitis, hemiplegia, reflexes increased, akathisia, delirium, paralysis, withdrawal syndrome, brain edema, CNS stimulation, dyskinesia, encephalopathy, foot drop, grand mal convulsion, hypalgesia, peripheral neuritis, psychotic depression, addiction, arachnoiditis, cerebellar syndrome, cogwheel rigidity, dementia, dystonia, Guillain-Barre syndrome, intracranial hemorrhage, multiple sclerosis, myelitis, schizophrenic reaction, subarachnoid hemorrhage, torticollis
Respiratory system	
Frequent	Sinusitis, rhinitis, dyspnea, cough increased, pneumonia, lung disorder
Infrequent	Asthma, epistaxis, laryngitis, voice alteration, respiratory disorder, sputum increased
Rare	Apnea, emphysema, aspiration pneumonia, hyperventilation, lung edema, pleural disorder, atelectasis, hemoptysis, hiccup, hypoxia, laryngismus, lung fibrosis, pleural effusion, lung function decreased, pulmonary hypertension, yawn, bronchiectasis, bronchiolitis, carcinoma of lung, hypoventilation, laryngeal neoplasia, nasal septum disorder, pneumothorax
Skin and appendages	
Infrequent	Pruritus, sweating, skin disorder, acne, dry skin, alopecia, skin ulcer, herpes simplex, urticaria, nail disorder, eczema, herpes zoster, skin benign neoplasm, fungal dermatitis, maculopapular rash, vesiculobullous rash, skin carcinoma, furunculosis, skin discoloration, skin hypertrophy, psoriasis, seborrhea, hirsutism
Rare	Skin nodule, angioedema, cutaneous moniliasis, skin atrophy, exfoliative dermatitis, pustular rash, ichthyosis, skin melanoma, subcutaneous nodule, sweating decreased, hair disorder, lichenoid dermatitis, melanosis, miliaria, purpuric rash, skin necrosis, Stevens Johnson Syndrome
Special sense	
Frequent	Eye disorder, conjunctivitis, otitis media
Infrequent	Retinal disorder, tinnitus, eye pain, cataract specified, dry eyes, taste perversion, ear pain, lacrimation disorder, ear disorder, deafness, eye hemorrhage, photophobia, glaucoma, vitreous disorder, corneal lesion, otitis externa, refraction disorder, blepharitis, retinal edema, taste loss, abnormality of accommodation
Rare	Hyperacusis, keratitis, mydriasis, parosmia, ptosis, retinal hemorrhage, color blindness, retinal depigmentation, retinal detachment, corneal opacity, corneal ulcer, iritis, night blindness, optic atrophy, retinal degeneration, cataract NOS, scleritis, strabismus, anisocoria, blindness, exophthalmos, keratoconjunctivitis, ophthalmoplegia, papilledema
Urogenital system	
Frequent	Anorgasmia
Infrequent	Urinary frequency, urinary incontinence, cystitis, abnormal ejaculation, urination impaired, dysuria, metrorrhagia,

Body System	Adverse Events
	hematuria, vaginal moniliasis, prostatic disorder, vaginitis, dysmenorrhea, urinary urgency, kidney calculus, breast pain, menstrual disorder, amenorrhea, menorrhagia, kidney function abnormal, nephritis, urine abnormality, vaginal hemorrhage, urinary retention, urinary tract disorder, leukorrhea, breast neoplasm, menopause, oliguria, polyuria, albuminuria, pyuria,
Rare	Breast carcinoma, penis disorder, papanicolau smear suspicious, fibrocystic breast, prostatic carcinoma, uterine fibroids enlarged, acute kidney failure, creatinine clearance decreased, nephrosis, nocturia, polycystic kidney, bladder carcinoma, breast enlargement, cervicitis, cervix disorder, female lactation, glycosuria, gynecomastia, hypomenorrhea, kidney pain, mastitis, pyelonephritis, kidney failure, breast abscess, epididymitis, orchitis, prostate neoplasia, prostatic specific antigen increase, salpingitis, urogenital disorder, urolithiasis, uterine disorder, vulvovaginal disorder, balanitis, bladder calculus, calcium crystalluria, cervix neoplasm,dyspareunia, endometrial carcinoma, endometrial disorder, glomerulitis, hydronephrosis, ovarian cancer, unintended pregnancy, urethral pain, urethritis, urogenital anomaly, urogenital neoplasia, uterine hemorrhage

Comparison of Gender and Race

The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

Peripheral Edema

Incidence of peripheral edema in pre-marketing controlled peripheral neuropathic pain studies was 10.4% in the pregabalin group compared with 2.9% in the placebo group. The incidence in the controlled fibromyalgia studies was 7.6% in the pregabalin group compared with 2.5% in the placebo group. In clinical trials, these events of peripheral edema were dose-related, mostly mild to moderate in intensity and rarely led to withdrawal. Peripheral edema was not associated with cardiovascular complications such as hypertension or congestive heart failure and there was no evidence of hemodilution or changes in any laboratory parameters indicative of underlying organ dysfunction (see **WARNINGS AND PRECAUTIONS**, Peripheral Edema).

Weight Gain

In the pre-marketing controlled peripheral neuropathic pain studies, patients on pregabalin had a higher incidence (5.9%) of weight gain as defined by a ≥7% increase from baseline weight as compared with the placebo group (1.6%). The mean change in the pregabalin group was an increase of 1.5 kg compared with 0.2 kg in the placebo group; few patients (0.1%) withdrew due to weight gain.

The incidence in the controlled fibromyalgia studies was 11.5% in the pregabalin group compared with 2.5% in the placebo group; approximately 1% of pregabalin-treated patients withdrew due to weight gain.

This weight gain was dose-related, and not associated with clinically important changes in blood pressure or cardiovascular adverse events. There was no relationship between baseline body mass index and the incidence of ≥7% weight gain in the controlled trials.

Based on the results of a controlled study of reproductive function in healthy male volunteers, the ≥ 7% weight gain on pregabalin appeared to be reversible. In this study, there were no reports of peripheral edema (see **WARNINGS AND PRECAUTIONS**, Weight Gain).

Abnormal Hematologic And Clinical Chemistry Findings

In all pre-marketing controlled trials, 1.0% of patients on pregabalin and 0.5% of placebo patients had an increase in creatine kinase of ≥ 3X upper limit of normal. Renal dysfunction was generally not associated with the elevated creatine kinase in these patients. Mean changes in creatine kinase ranged from 9.6 to 26.3 U/L for pregabalin-treated patients and 4.8 U/L for the placebo patients (see **DOSAGE AND ADMINISTRATION**, Patients With Renal Impairment). Routine therapeutic drug monitoring or clinical laboratory testing is not required for patients treated with MYL-PREGABALIN (see **WARNINGS AND PRECAUTIONS**, *Creatinine Kinase Elevations*).

Post-Marketing Adverse Drug Reactions

Since the first global approval of pregabalin on 06 July 2004 through 31 March 2012, there has been an estimated 15,951,859 million patient-years of exposure to pregabalin. Table 12 is based on post- market spontaneous adverse event reports. The percentages shown are calculated by dividing the number of adverse events reported to the company by the estimated number of patient years exposed to pregabalin. Because these adverse reactions are reported spontaneously from a population of uncertain size, it is not possible to reliably estimate their frequency. Furthermore, a causal relationship between pregabalin and the emergence of these events has not been clearly established.

Table 12. Post-market Spontaneous Adverse Event Reports

Adverse Event	Frequency			
	Common ≥1%	**Uncommon < 1% and ≥ 0.1%**	**Rare < 0.1% and ≥ 0.01%**	**Very rare < 0.01%**
Cardiovascular				
congestive heart failure[a]				X
Eye disorders[b]				
diplopia				X
vision blurred				X
visual disturbance				X
vision loss				X
Psychiatric disorders				
aggression				X
confusional state				X
depression				X
euphoric mood				X
insomnia				X
psychotic disorder[c]				X
Gastrointestinal disorders				
diarrhea				X
dry mouth				X
nausea				X
vomiting				X

Table 12. Post-market Spontaneous Adverse Event Reports				
Adverse Event	**Frequency**			
	Common ≥1%	**Uncommon < 1% and ≥ 0.1%**	**Rare < 0.1% and ≥ 0.01%**	**Very rare < 0.01%**
intestinal obstruction[d]				X
paralytic ileus[d]				X
General disorders and administration site conditions				
fatigue				X
feeling abnormal				X
pain				X
Immune system disorders				
angioedema[e]				X
hypersensitivity [f]				X
Nervous system disorders				
ataxia				X
coordination abnormal				X
dizziness[g]				X
dysarthria				X
headache				X
memory impairment				X
paresthesia				X
somnolence[g]				X
speech disorder				X
tremor				X
coma				X
loss of consciousness				X
mental impairment				X
Renal and urinary disorders				
urinary retention				X
Respiratory, thoracic and mediastinal disorders				
dyspnea				X
pulmonary edema				X
Skin and subcutaneous tissue disorders				
hyperhidrosis				X
pruritus				X

[a] These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic pain indication (see **WARNINGS AND PRECAUTIONS**, Congestive Heart Failure)
[b] There have also been rare reports of accommodation disorder, eyelid edema and eye redness (see **WARNINGS AND PRECAUTIONS**, Opthalmological Effects)
[c] There have been rare reports of psychotic disorders in patients receiving pregabalin
[d] See below and **WARNINGS AND PRECAUTIONS**, Gastrointestinal
[e] see **WARNINGS AND PRECAUTIONS**, Angioedema
[f] see **WARNINGS AND PRECAUTIONS**, Hypersensitivity
[g] see **WARNINGS AND PRECAUTIONS**, Dizziness and Somnolence

Gastrointestinal: There have been post-marketing events related to reduced lower gastrointestinal tract function (eg. intestinal obstruction, paralytic ileus, and constipation) primarily reported when pregabalin was given in combination with other medications that have the potential to produce constipation, such as opioid analgesics (see **WARNINGS AND PRECAUTIONS**, Gastrointestinal).

Urinary and Renal Disorder: renal failure. There have been rare post-marketing 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. Caution is advised when prescribing pregabalin to the elderly or those with impaired renal function (see Special Populations, *Renal;* **WARNINGS and PRECAUTIONS**, Renal Failure, and **DOSAGE AND ADMINISTRATION**).

Cardiovascular: congestive heart failure. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic pain indication (see **WARNINGS AND PRECAUTIONS**, Congestive Heart Failure).

Respiratory, Thoracic and Mediastinal Disorder: pulmonary edema. There have been post-marketing reports of pulmonary edema in patients receiving pregabalin. Although this adverse reaction has mostly been observed in elderly patients with predisposing factors, some cases have occurred in patients with no known previous history or predisposing conditions.

Eye disorders: diplopia, vision blurred, visual disturbance and vision loss. There have also been rare reports of accommodation disorder, eyelid edema and eye redness (see **WARNINGS AND PRECAUTIONS**, Opthalmological Effects).

Encephalopathy: There have been serious post-marketing reports of encephalopathy, mostly in patients with underlying conditions that may precipitate encephalopathy. Some cases were reported in patients with a history of kidney or liver disease. Since there have been rare reports of renal failure with pregabalin, specific caution should be exercised when prescribing MYL-PREGABALIN to the elderly with age-related compromised renal function and patients with kidney disease or risk factors for renal failure (see **WARNINGS AND PRECAUTIONS**, Renal Failure and **WARNINGS AND PRECAUTIONS**, Encephalopathy).

Convulsions: convulsions, including status epilepticus and grand mal convulsions, have been reported in non-epileptic patients during treatment with pregabalin or following abrupt discontinuation (see **WARNINGS AND PRECAUTIONS**, Abrupt Discontinuation).

Suicidal Behaviour and Ideation: There have been post-marketing reports of suicide-related events, including completed suicide, suicide attempt, and suicidal ideation in patients treated with pregabalin for a variety of indications such as neuropathic pain, fibromyalgia, etc. In some of these reports, underlying psychiatric disorders may have contributed to the event. The mechanism of this risk is not known. Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients should be encouraged to report any distressing thoughts or feelings at anytime to their healthcare professional (see **WARNINGS AND PRECAUTIONS**, Suicidal Behaviour and Ideation).

Serious Skin Reactions
There have been very rare post-marketing reports of serious cutaneous reactions, including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), dermatitis exfoliative,

bullous skin reactions, and erythema multiforme in patients treated with pregabalin (see **WARNINGS AND PRECAUTIONS**). Post-market reporting rate is generally accepted to be an underestimate due to under-reporting. Most of the reports were in patients taking concomitant medications also associated with the potential development of these serious skin reactions. Therefore, in most cases, causality in relation to pregabalin could not be clearly established. Patients should be advised that if they experience a skin rash, they should discontinue MYL-PREGABALIN treatment and contact their physician for assessment and advice.

Drug Abuse and Dependence/Liability

In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, a single dose of pregabalin 450 mg received subjective ratings of "good drug effect", "high", and "liking" to a degree that was similar to a single dose of diazepam 30 mg. In controlled clinical studies in over 5500 patients, 4% of pregabalin-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse event. However, in clinical trials of diabetic peripheral neuropathy, euphoria was reported as an adverse event by 1.8% of pregabalin-treated patients and 0 % of placebo-treated patients, and in clinical trials of postherpetic neuralgia, euphoria was reported as an adverse event by 0.9% of pregabalin-treated patients and 0% of placebo-treated patients. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, or diarrhea suggestive of physical dependence [see **WARNINGS AND PRECAUTIONS**, Abrupt or Rapid Discontinuation].

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of pregabalin misuse or abuse (eg, development of tolerance, dose escalation, drug-seeking behaviour).

DRUG INTERACTIONS

Overview

Since pregabalin is predominately excreted unchanged in the urine, undergoes negligible metabolism in humans (≤2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, MYL-PREGABALIN (pregabalin) is unlikely to produce, or be subject to, pharmacokinetic interactions.

Pharmacokinetic

In Vitro Studies: In vitro drug metabolism studies revealed that pregabalin at concentrations which were, in general, 10-fold greater than observed in Phase 2/3 clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems.

In Vivo Studies: The drug interaction data described in this section were obtained from studies involving healthy adults, patients with epilepsy, and patients with chronic pain disorders.

Carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate: In vitro and in vivo studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no clinically significant pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs.

Tiagabine: The results of a population pharmacokinetic analysis indicated that in patients with partial seizures tiagabine had no clinically significant effect on pregabalin clearance.

Gabapentin: The pharmacokinetics of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single dose administration of 100 mg pregabalin and 300 mg gabapentin, and in 18 healthy subjects following concomitant multiple dose administration of 200 mg pregabalin q8h and 400 mg gabapentin q8h. Gabapentin pharmacokinetics following single and multiple dose administration were unaltered by pregabalin coadministration. The rate of pregabalin absorption was reduced by approximately 26% (single dose administration) and 18% (multiple dose administration) based on lower C_{max} values; however, the extent of pregabalin absorption was unaffected by gabapentin coadministration.

Oral Contraceptives: Pregabalin coadministration (200 mg TID) had no effect on the steady state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 μg, respectively) in healthy subjects.

Lorazepam: Multiple dose administration of pregabalin (300 mg BID) in healthy subjects had no effect on the rate and extent of lorazepam single dose pharmacokinetics and single dose administration of lorazepam (1 mg) had no clinically significant effect on the steady state pharmacokinetics of pregabalin.

Oxycodone: Multiple dose administration of pregabalin (300 mg BID) in healthy subjects had no effect on the rate and extent of oxycodone single dose pharmacokinetics. Single dose administration of oxycodone (10 mg) had no clinically significant effect on the steady state pharmacokinetics of pregabalin.

Ethanol: Multiple dose administration of pregabalin (300 mg BID) in healthy subjects had no effect on the rate and extent of ethanol single dose pharmacokinetics and single dose administration of ethanol (0.7 g/kg) had no clinically significant effect on the steady state pharmacokinetics of pregabalin.

Diuretics, Oral Hypoglycemics, and Insulin: A population pharmacokinetic analysis in patients with chronic pain showed no clinically significant effect on pregabalin clearance with the concomitant use of diuretics, oral hypoglycemics, and insulin.

Pharmacodynamic

Oxycodone, lorazepam, ethanol: Multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. Pregabalin may potentiate the effects of ethanol and lorazepam. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

In post-marketing experience, there are reports of respiratory failure and coma in patients taking pregabalin alone or in combination with other CNS depressants.

Thiazolidinedione Antidiabetic Agents: Higher frequencies of weight gain and peripheral edema were observed in patients taking both pregabalin and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy.

As the thiazolidinedione class of antidiabetic drugs or MYL-PREGABALIN can cause weight gain and/or fluid retention alone or together, possibly exacerbating or leading to heart failure, caution should be exercised when co-administering MYL-PREGABALIN and these agents (see **WARNINGS AND PRECAUTIONS**, Peripheral Edema).

Drug-Food Interactions

The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total amount of pregabalin absorbed. Therefore, pregabalin can be taken with or without food.

Drug-Herb Interactions

MYL-PREGABALIN has no known drug-herb interactions.

Drug-Laboratory Interactions

MYL-PREGABALIN has no known drug-laboratory test interactions.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Patients with Impaired Renal Function

Pregabalin is primarily eliminated from the systemic circulation by renal excretion as unchanged drug. In some elderly patients and those with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Dosage Adjustment Based on Renal Function, below).

In accordance with current clinical practice, if MYL-PREGABALIN (pregabalin) has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week (see **WARNINGS AND PRECAUTIONS**, Abrupt or Rapid Discontinuation).

***Adults*:**

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

The recommended starting dose for MYL-PREGABALIN 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 pregabalin 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, pregabalin 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 **ADVERSE REACTIONS**, Tables 1 and 5). Doses above 600 mg/day have not been studied and are not recommended.

Neuropathic Pain Associated with Postherpetic Neuralgia

The recommended starting dose for MYL-PREGABALIN 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 pregabalin 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, pregabalin 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 **ADVERSE REACTIONS**, Tables 3 and 6). 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 MYL-PREGABALIN 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 pregabalin 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 MYL-PREGABALIN 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 pregabalin 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, pregabalin 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 **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.

Dosage Adjustment Based on Renal Function

MYL-PREGABALIN is primarily eliminated by renal excretion. Therefore, the dose should be adjusted for patients with reduced renal function. Pregabalin clearance is directly proportional to creatinine clearance. Therefore, dosing adjustment should be based on creatinine clearance (CL_{Cr}), as indicated in Table 13.

To use this dosing table, an estimate of the patient's creatinine clearance (CL_{Cr}) in mL/min is needed. CL_{Cr} in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

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

Pregabalin is effectively removed from plasma by hemodialysis. Over a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients receiving hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table 13).

Table 13. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a] Recommended Dose Escalation*				Dose Regimen
	Starting Dose	→ up to		Maximum daily dose	
≥ 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)[b]					
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg. Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg. Patients on the 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.
* Based on individual patient response and tolerability.
[a] Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.
[b] Supplementary dose is a single additional dose.

Geriatrics (> 65 years): Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function.

Pediatrics (<18 years of age): The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established and its use in this patient population is not recommended.

Administration

MYL-PREGABALIN (pregabalin) is given orally with or without food (see **DRUG INTERACTIONS**, Drug Food Interactions).

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

MYL-PREGABALIN (pregabalin) binds to the α_2-δ subunit of the voltage-gated calcium channels in central nervous system tissues. *In vitro*, pregabalin reduces calcium influx at nerve terminals, which may inhibit the release of excitatory neurotransmitters such as glutamate. Through this mechanism, MYL-PREGABALIN may modulate nerve impulses involved in the transmission of pain. . However, the clinical relevance of these findings in man is unknown.

Pharmacodynamics
MYL-PREGABALIN binds with high affinity to the alpha$_2$-delta protein (a calcium channel subunit) of brain tissues and has analgesic, antiepileptic, and anxiolytic activity. Pregabalin is known chemically as (S)-3-(aminomethyl)-5-methylhexanoic acid.

Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally-related to pregabalin indicate that selective binding to the alpha$_2$-delta protein is required for analgesic, antiepileptic and anxiolytic action in animal models. In vitro, pregabalin reduces the release of several neurotransmitters, suggesting a modulatory action on calcium channel function.

Pregabalin does not mimic GABA at $GABA_A$ or $GABA_B$ receptors, nor does it augment $GABA_A$ responses like benzodiazepines or barbiturates. In contrast to vascular calcium channel blockers, pregabalin does not alter systemic blood pressure or cardiac function. Various in vitro and in vivo results differentiate pregabalin from GABA uptake inhibitors or GABA transaminase

inhibitors. In addition, pregabalin does not block sodium channels, it is not active at opiate receptors, it does not alter cyclooxygenase enzyme activity, it is not a serotonin agonist, it is not a dopamine antagonist, and it is not an inhibitor of dopamine, serotonin or noradrenaline reuptake.

Pregabalin treatment reduces pain-related behavior in neuropathic animal models of diabetes, peripheral nerve damage or chemotherapeutic insult and in a model of musculoskeletal-associated pain. Pregabalin given intrathecally prevents pain-related behaviors and reduces pain-related behavior caused by spinally administered agents, suggesting that it acts directly on tissues of the spinal cord or brain.

Pharmacokinetics

All pharmacological actions following pregabalin administration are due to the activity of the parent compound; pregabalin is not appreciably metabolized in humans. Mean steady-state plasma pregabalin concentration-time profiles following 75, 300, and 600 mg/day given in equally divided doses every 8 hours (TID) and 600 mg/day given in equally divided doses every 12 hours (BID) are shown in Table 14. Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (<20%).

Table 14. Pregabalin Mean (CV%[a]) Steady-State Pharmacokinetic Parameter Values in Healthy Volunteers

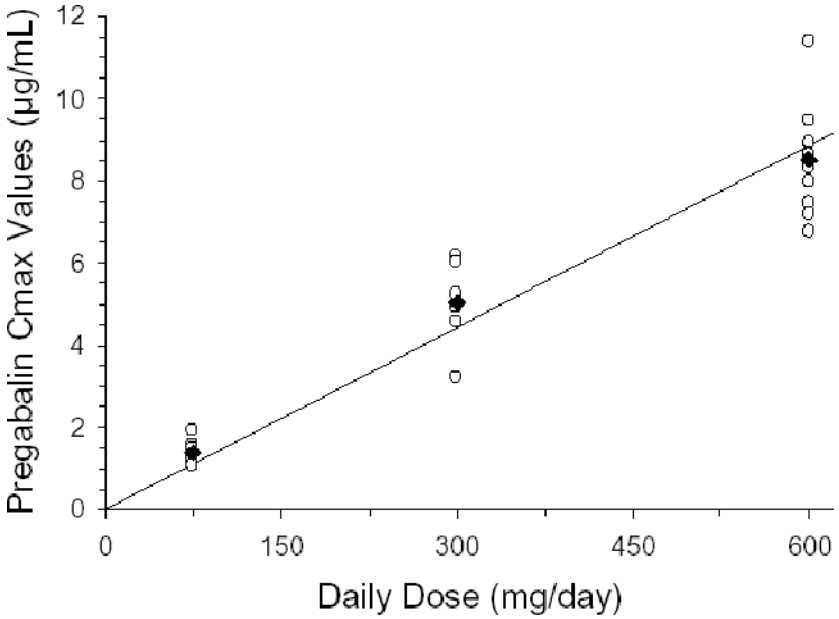
Dose (mg)	Regimen	Daily Dose (mg/day)	N	C_{maxss} (µg/mL)	t_{max} (hr)	C_{minss} (µg/mL)	$AUC_{(0-t)}$ (µg·hr/mL)	$t_{1/2}$ (hr)	$C_{L/F}$ (mL/min)
25	TID[b]	75	8	1.39	0.9	0.45	6.7	5.9	64.1
				-19.5	-34.2	-25	-18.3	-17.3	-16.1
100	TID	300	6	5.03	0.8	1.94	25.2	6.3	68.9
				-21.3	-31	-33.6	-23	-19.6	-20.9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

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

Absorption: Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1.5 hours following both single- and multiple-dose administration. Pregabalin oral bioavailability is ≥ 90% and is independent of dose. C_{max} (Figure 1) and AUC values increase proportionally following single- and multiple-dose administration.

Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple dose pharmacokinetics are predictable from single-dose data.

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



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

Distribution: In preclinical studies, pregabalin has been shown to readily cross the blood brain barrier in mice, rats, and monkeys. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood-brain barrier. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is not bound to plasma proteins. At clinically efficacious doses of 150 and 600 mg/day, the average steady-state plasma pregabalin concentrations were approximately 1.5 and 6.0 µg/mL, respectively.

Metabolism: Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Excretion: Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean $t_{1/2}$ is 6.3 hours. Pregabalin elimination is proportional to creatinine

clearance. Pregabalin clearance is reduced in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**).

Special Populations and Conditions

Pregabalin undergoes negligible metabolism, is not bound to plasma proteins, and is eliminated predominately as unchanged drug by renal excretion. Clinically important differences in pregabalin pharmacokinetics due to race and gender have not been observed and are not anticipated.

Pediatrics: Pharmacokinetics of pregabalin have not been studied in paediatric patients.

Geriatrics: Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Gender: A population pharmacokinetic analysis of the Phase 2/3 clinical program showed that the relationship between daily dose and pregabalin drug exposure is similar between genders when adjusted for gender-related differences in creatinine clearance.

Race: A population pharmacokinetic analysis of the Phase 2/3 clinical program showed that the relationship between daily dose and pregabalin drug exposure is similar among Caucasians, Blacks, and Hispanics.

Renal Insufficiency: Because renal elimination is the major elimination pathway, dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified (see **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Store at 15°C to 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

MYL-PREGABALIN (pregabalin) is supplied as a hard gelatin capsule for daily oral administration.

25 mg capsules: White hard gelatin capsule printed with black ink "PGN 25" on the cap, "PGN 25" on the body.

50 mg capsules: White hard gelatin capsule printed with black ink "PGN 50" on the cap, "PGN 50" on the body.

75 mg capsules: White/Orange hard gelatin capsule printed with black ink "PGN 75" on the cap, "PGN 75" on the body.

150 mg capsules: White hard gelatin capsule printed with black ink "PGN 150" on the cap, "PGN 150" on the body.

225 mg capsules: White/light orange hard gelatin capsule printed with black ink "PGN 225" on the cap, "PGN 225" on the body.

300 mg capsules: White/orange hard gelatin capsule printed with black ink "PGN 300" on the cap, "PGN 300" on the body.

Composition

Each capsule of MYL-PREGABALIN contains 25, 50, 75, 150, 225, or 300 mg pregabalin, lactose monohydrate, maize starch, and talc. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid, which may not be present. The markings on the capsules are in black ink, which contains shellac, black iron oxide, propylene glycol, potassium hydroxide and water.

Packaging

Capsules are packaged in HDPE bottles containing 60 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

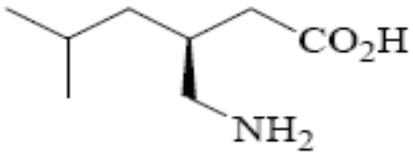
Proper name: Pregabalin

Chemical name: (S)-3 -(aminomethyl)-5-methylhexanoic acid

Molecular formula $C_8H_{17}NO_2$

Molecular mass: 159.23 g/mol

Structural formula:



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

CLINICAL TRIALS

Neuropathic Pain

Diabetic Peripheral Neuropathy Studies

The efficacy of pregabalin for the management of neuropathic pain associated with diabetic peripheral neuropathy was established in 4 double-blind, fixed-dose, placebo-controlled, multicenter studies with twice a day (BID) and 3 times a day (TID) dosing. Patients recorded their pain on a daily diary using an 11-point numerical pain rating scale ranging from 0 = "no pain" to 10 = "worst possible pain." To enter the study, patients had to have moderate to severe pain, ie, mean baseline score (mean of the last 7 daily diary pain score prior to study medication) of ≥ 4. The primary measure of efficacy was reduction in endpoint mean pain scores (mean of the last 7 daily pain scores while on study medication). Supplemental analyses included mean pain scores computed for each week during the study, and the proportion of responders (those patients reporting at least 50% reduction in endpoint mean pain score compared to baseline). Secondary outcome variables included daily sleep interference scores, and the Patient Global Impressions of Change (PGIC). Mean sleep scores were computed at endpoint and for each week during the study. The PGIC was completed at the end of the study and measured the patient's overall status compared to baseline using a 7-point categorical scale ranging from "very much improved" to "very much worse."

Studies DPN1, DPN2, DPN3 and DPN4 enrolled a total of 1124 patients with type 1 or 2 diabetes mellitus who had painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years. Across all 4 studies, the baseline mean pain scores ranged from 6.3 to 6.7. The analysis population for all primary and secondary analyses for each study was the intent-to-treat population. Among the pregabalin-treated patients enrolled in these studies, the completion rate was 86%.

Study DPN1: This 6-week study of 246 patients (161 received pregabalin and 85 received placebo) compared pregabalin 150 or 600 mg/day (TID regimen) with placebo. The treatment effect on endpoint mean pain scores was significantly better than placebo with pregabalin 600 mg/day ($p = 0.0002$), but not with pregabalin 150 mg/day. The proportion of responders at the 600 mg/day dose (39%) was significantly greater ($p = 0.002$) than placebo (15%). Secondary measures such as sleep disturbance ($p=0.0004$) and PGIC ($p = 0.002$) were also positive for 600 mg/day compared to placebo. The 600 mg/day arm was associated with higher reporting of adverse events and withdrawals due to adverse events.

Study DPN2: This 5-week study of 337 patients (240 received pregabalin and 97 received placebo) compared pregabalin 75, 300, or 600 mg/day (TID regimen) with placebo. Treatment effects on endpoint mean pain scores were similar for both pregabalin 300 and 600 mg/day and were significantly better than placebo ($p = 0.0001$). The proportion of responders at the 300 and 600 mg/day doses (46% and 48%, respectively) were significantly greater ($p = 0.001$ for each dose) than placebo (18%). Secondary efficacy measures such as sleep disturbance ($p \leq 0.0001$) and PGIC ($p \leq 0.00\ 1$) were also positive for both 300 and 600 mg/day doses compared to placebo. Compared to 300 mg/day treatment arm, patients treated with 600 mg/day experienced

more adverse reactions and discontinued the study more frequently (see Tables 1 and 2, **ADVERSE REACTIONS**).

Study DPN3: This 8-week study of 146 patients (76 received pregabalin and 70 received placebo) compared pregabalin 300 mg/day (100 mg TID) with placebo. The treatment effect on endpoint mean pain scores was significantly better than placebo with pregabalin 300 mg/day ($p = 0.0001$). The proportion of responders at the 300 mg/day dose (40%) was significantly greater ($p = 0.001$) than placebo (15%). Secondary efficacy measures such as sleep disturbance ($p = 0.0001$) and PGIC ($p = 0.001$) were also positive for pregabalin 300 mg/day group compared to placebo.

Study DPN4: This 12-week study of 384 patients (291 received pregabalin and 93 received placebo) compared pregabalin 150, 300, or 300/600 mg/day (BID regimen) with placebo. In the 300/600 mg/day pregabalin group, to achieve equivalent exposures, patients received either 300 or 600 mg/day, depending on their creatinine clearance rate. The treatment effect on endpoint mean pain scores was significantly better than placebo with pregabalin 300/600 mg/day ($p=0.0054$), but not with pregabalin 150 or 300 mg/day. The proportion of responders at the 300/600 mg/day dose (46%) was significantly greater ($p = 0.036$) than placebo (30%). Secondary measures such as sleep disturbance ($p=0.0030$) and PGIC ($p=0.021$) were also positive for 300/600 mg/day compared to placebo.

Postherpetic Neuralgia Studies

The efficacy of pregabalin for the management of neuropathic pain associated with postherpetic neuralgia was established in 3 double-blind, fixed-dose, placebo-controlled, multicenter studies with twice a day (BID) and 3 times a day (TID) dosing. Patients recorded their pain on a daily diary using an 11-point numerical pain rating scale ranging from 0 = "no pain" to 10 = "worst possible pain." To enter the study, patients had to have moderate to severe pain, ie, mean baseline score (mean of the last 7 daily diary pain score prior to study medication) of ≥ 4. The primary measure of efficacy was reduction in endpoint mean pain scores (mean of the last 7 daily pain scores while on study medication). Supplemental analyses included mean pain scores computed for each week during the study, and the proportion of responders (those patients reporting at least 50% reduction in endpoint mean pain score compared to baseline). Secondary outcome variables included daily sleep interference scores, and the Patient Global Impressions of Change (PGIC). Mean sleep scores were computed at endpoint and for each week during the study. The PGIC was completed at the end of the study and measured the patient's overall status compared to baseline using a 7-point categorical scale ranging from "very much improved" to "very much worse."

Studies PHN1, PHN2 and PHN3 enrolled 779 patients with postherpetic neuralgia who continued to have pain for at least 6 months (Study PHN1) or 3 months (Study PHN2 and PHN3) after healing of the herpes zoster skin rash. Across all 3 studies, the baseline mean pain scores ranged from 6.4 to 6.8. The analysis population for all primary and secondary analyses for each

study was the intent-to-treat population. Among the pregabalin-treated patients enrolled in these studies, the completion rate was 71%.

In the trials described below, patients were randomly assigned to one of the treatment arms depending on their creatinine clearance rate. Compared to patients with creatinine clearance rate ≥ 60 mL/min, those with decreased creatinine clearance rate (≤ 60 mL/min) experienced markedly higher rates of adverse events and discontinued the trial more frequently.

Study PHN1: This 8-week study of 238 patients (157 received pregabalin and 81 received placebo) compared pregabalin 150 or 300 mg/day (50 mg or 100 mg TID) with placebo. This trial included patients with decreased creatinine clearance rate (30-60 mL/min) who were randomly assigned to one of the treatment arms. Similar efficacy results were observed for both pregabalin 150 and 300 mg/day groups. Treatment with both doses resulted in significant treatment effects on endpoint mean pain score (p=0.0002 for both comparisons). The proportion of responders at the 150 and 300 mg/day doses (26% and 28%, respectively) were significantly greater (p = 0.006, for each dose) than placebo (10%). Secondary efficacy measures such as sleep disturbance with both 150 and 300 mg/day (p = 0.0003 and p = 0.0002, respectively) and PGIC with 300 mg/day (p = 0.002) were also positive compared to placebo.

Study PHN 2: This 8-week study of 173 patients (89 received pregabalin and 84 received placebo) compared one pregabalin arm with placebo. To achieve equivalent exposures, patients in the pregabalin group received either 300 or 600 mg/day, depending on their creatinine clearance rate. Treatment with pregabalin 300/600 mg/day resulted in a significant treatment effect on endpoint mean pain score (p = 0.0001). The proportion of responders in the pregabalin arm (50%) was significantly greater (p≤0.001) than placebo (20%). Secondary efficacy measures such as sleep disturbance (p≤0.0001) and PGIC (p≤0.001) were also positive compared to placebo.

Study PHN3: This 13-week study of 368 patients (275 received pregabalin and 93 received placebo) compared pregabalin 150, 300, or 300/600 mg/day (75, 150, or 300 mg BID) with placebo. In the 300/600 mg/day pregabalin group, to achieve equivalent exposures, patients received either 300 or 600 mg/day, depending on their creatinine clearance rate. Treatment with pregabalin at 150, 300, and 300/600 mg/day resulted in significant treatment effects on endpoint mean pain score (150 mg/day, p = 0.0077; 300 mg/day, p = 0.0016; and 300/600 mg/day, p = 0.0003). The proportion of responders at the 150 mg/day (26%, p = 0.001), 300 mg/day (27%, p = 0.001) and 300/600 mg/day (38%, p = 0.001) doses were significantly greater than placebo (8%). For each dose (150 mg, 300 mg, and 300/600 mg), the secondary efficacy measure of sleep disturbance was positive compared to placebo (p = 0.0007, p = 0.0002, and p = 0.0002, respectively). PGIC was also positive at 150 and 300/600 mg/day compared to placebo (p≤0.020 and p = 0.003, respectively).

Overall Analysis of Diabetic Peripheral Neuropathy and Postherpetic Neuralgia Studies

When endpoint mean pain scores are combined across all controlled diabetic neuropathic pain and postherpetic neuralgia studies, no significant differences in efficacy based on gender, or race, were observed.

In controlled diabetic neuropathy and postherpetic neuralgia clinical trials, pregabalin, at doses of 150, 300, and 600 mg/day, was statistically significantly more effective than placebo in reducing sleep disturbance and improving PGIC.

Neuropathic Pain Associated with Spinal Cord Injury

A 12-week, randomized, double-blind, placebo-controlled, parallel group, multicenter study was conducted in 137 patients experiencing chronic neuropathic pain after traumatic spinal cord injury (paraplegia or tetraplegia of at least one year duration). Patients recorded their pain on a daily diary using an 11-point numerical scale ranging from 0 = "no pain" to 10 = "worst possible pain". To enter the study, patients had to have moderate to severe pain, i.e., mean baseline score (mean of the last 7 daily pain scores prior to study medication) of ≥ 4. Patients randomized to pregabalin received escalating doses of 150 mg/day, 300 mg/day and 600 mg/day administered BID with doses adjusted based on patient response and tolerability at weekly intervals up to the third week of treatment, after which patients were maintained on a fixed dose for the remainder of the study. In both the placebo and pregabalin groups, the majority of patients were taking concomitant analgesics, anti-inflammatories, and anti-depressants for pain during the study. The placebo group received a BID regimen, following the same blinded adjustment for the 12-week double-blind treatment as in the pregabalin group. 70% of patients in the pregabalin group completed the study as compared to the placebo group (55.2%).

The primary measure of efficacy was reduction in endpoint mean pain scores (mean of the last 7 daily pain scores while on study medication). Supplemental analyses included mean pain scores computed for each week during the study and the proportion of responders (those patients reporting at least a 30% or 50% reduction in endpoint mean pain score compared to baseline). Secondary measures included weekly pain-related sleep interference scores and Patient Global Impression of Change (PGIC).

At endpoint, the pregabalin group had a significantly larger reduction from baseline in mean pain score ($p<0.001$). Treatment differences were significant as early as the first week of treatment and were maintained for the duration of the study. The proportion of patients who had a ≥30% reduction from baseline to endpoint in mean pain score was significantly higher in the pregabalin group (42%) compared to the placebo group (16%). Similarly, the proportion of patients who had a ≥50% reduction from baseline to endpoint in mean pain score was significantly higher in the pregabalin group (22%) compared to the placebo group (8%). Secondary pain-related measures such as sleep disturbance and PGIC were also significantly better compared to placebo.

Following the 12-week double-blind placebo-controlled study, 103 patients were treated with pregabalin in an open-label extension study (see **ADVERSE REACTIONS**, Adverse Drug Reaction Overview). Mandatory drug holidays (from 3 to 28 days) occurred every 3 months for the duration of the open-label study. Subjects who relapsed during the drug holiday were allowed to restart pregabalin therapy for an additional 3-month period. The median duration of

open-label therapy was 545 days. The median duration of therapy across the double-blind and open-label studies for those subjects was 608 days.

During the drug holidays, most subjects indicated that their pain increased after temporarily stopping pregabalin.

Pain Associated with Fibromyalgia

Study Demographics and Trial Design

The efficacy of pregabalin for the management of pain associated with fibromyalgia was established in 4 double-blind, fixed-dose, placebo-controlled multicenter studies. Efficacy was also established in a 26-week long-term relapse observation study.

To enter the study, patients had to have moderate to severe pain, i.e., mean baseline score (mean of the last 7 daily diary pain scores prior to study medication) of ≥ 4, and a diagnosis of fibromyalgia based on the American College of Rheumatology criteria (history of widespread pain for 3 months, and pain present at 11 or more out of 18 specific tender points). During all studies described below, patients were allowed to take acetaminophen up to 4 g per day as needed for pain relief.

The primary efficacy endpoint in all 4 controlled studies was the reduction in endpoint mean pain scores (mean of the last 7 daily pain scores while on study medication). Patients recorded their pain on a daily diary using an 11-point numerical pain rating (Likert) scale ranging from 0="no pain" to 10="worst possible pain". Treatment differences, defined as the change in endpoint mean pain scores for pregabalin versus placebo (drug – placebo), were calculated.

Supplemental and secondary efficacy endpoints included Responder Rates (patients reporting at least 30% or 50% reduction in endpoint mean pain score compared to baseline), Patient Global Impression of Change (PGIC), Fibromyalgia Impact Questionnaire (FIQ), Medical Outcomes Study-Sleep Scale (MOS-SS) and daily sleep quality scores.

The primary efficacy endpoint in the 26-week long-term relapse observation study was the time to loss of therapeutic response as determined from the Pain Visual Analog Scale (VAS) or from worsening of fibromyalgia symptoms necessitating an alternative treatment per the clinical judgment of the principal investigator. Secondary endpoints included the time to worsening of PGIC, FIQ,and MOS-SS scores.

Table 15. Summary of Placebo-Controlled Trials Supporting the Efficacy of Pregabalin in the Management of Pain Associated with Fibromyalgia

Study #	Trial Design/ Duration	Study Subjects (N)	Mean Age (years) Age Range	Number of Completers (% Completed)	Mean Baseline Pain Score (SD) Baseline Pain Score Range	Primary Efficacy	Treatment Difference (Range)
F1	8-week, multicentre, parallel, double-blind, randomized, placebo-controlled study	N=529 Patients pregabalin 50mg **TID**: 132 pregabalin 100mg **TID**: 134 pregabalin 150mg **TID**: 132 placebo: 131	Mean: 48.6 Range: 20 to 78	pregabalin 50mg **TID**: 103 (78%) pregabalin 100mg **TID**: 111 (83) pregabalin 150mg **TID**: 99 (75%) placebo: 97 (74)	Mean: 7.0 (1.3) Range: 3.4 – 10. 0	*P*<0.005 only at pregabalin 150mg **TID** dose	-0.13 to -0.93
F2	13-week, multicentre, parallel, double-blind, randomized, placebo-controlled study	N=748 Patients pregabalin 150mg **BID**: 185 pregabalin 225mg **BID**: 183 pregabalin 300mg **BID**: 190 placebo: 190	Mean: 48.8 Range: 18 to 82	pregabalin 150mg **BID**: 123 (66%) pregabalin 225mg **BID**: 121 (66%) pregabalin 300mg **BID**: 111 (58%) placebo: 130 (68%)	Mean: 7.1 (1.3) Range: 3.6 – 10.0	*P*<0.05 at all doses studied	-0.43 to -0.66
F3	14-week, multicentre, parallel, double-blind, randomized, placebo-controlled study using enriched population, only	N=745 Patients pregabalin 150mg **BID**: 183 pregabalin 225mg **BID**: 190 pregabalin 300mg **BID**: 188 placebo: 184	Mean: 50.1 Range: 18 to 81	PGB 150 **BID**: 123 (67.2) PGB 225 **BID**: 125 (65.8) PGB 300 **BID**: 113 (60.1) PLC: 125 (67.9)	Mean: 6.7 (1.3) Range: 1.0 – 10.0	*P*<0.0005 at all doses studied	-0.71 to -1.00
F4	14-week, multicentre, parallel, double-blind, randomized, placebo-controlled study using enriched population, only	N=735 Patients pregabalin 150mg **BID**: 183 pregabalin 225mg **BID**: 182 pregabalin 300mg **BID**: 186 placebo: 184	Mean age: 48.5 Range: 20 to 81	pregabalin 150mg **BID**: 123 (67%) pregabalin 225mg **BID**: 133 (73%) pregabalin 300mg **BID**: 121 (65%) placebo: 141 (76%)	Mean: 6.7 (1.4) Range: 1.0 – 10.0	*P*<0.05 at pregabalin 225mg BID dose, only	-0.23 to -0.54

Study F1: This 8-week study treated patients with pregabalin 150, 300, or 450 mg/day (total of 398 patients; 79% completed) or placebo (131 patients; 74% completed). The treatment effect on

endpoint mean pain scores was significantly better than placebo with pregabalin 450 mg/day (p=0.0009), but not with pregabalin 150 or 300 mg/day. Treatment differences ranged between -0.13 to -0.93. Most supplemental and secondary endpoints were supportive of the primary efficacy measure; the FIQ was not measured in Study F1. A dose-related increase in adverse events and withdrawals due to adverse events was observed.

Study F2: This 13-week study treated patients with pregabalin 300, 450, or 600 mg/day (total of 558 patients; 64% completed) or placebo (190 patients; 68% completed). Baseline mean pain score ranged between 3.6 to 10.0 for pregabalin arms and 4.3 to 10.0 for placebo. The treatment effect on endpoint mean pain was significantly better than placebo for all pregabalin doses (p=0.0449 for 300 and 450 mg/day, p=0.0070 for 600 mg/day). Treatment differences ranged between -0.43 to -0.66. Most supplemental and secondary endpoints were supportive of the primary efficacy measure. A dose-related increase in adverse events and withdrawals due to adverse events was observed.

Study F3: This 14-week study treated patients with pregabalin 300, 450, or 600 mg/day (total of 561 patients; 64% completed) or placebo (184 patients; 68% completed). This study used an enriched population as placebo-responders (≥30% reduction in mean pain scores) during the one-week run-in phase were discontinued and did not participate in the double-blind phase. The treatment effect on endpoint mean pain score was significantly better than placebo for all pregabalin doses (p=0.0009 for 300 mg/day and p<0.0001 for 450 and 600 mg/day). Treatment differences ranged between -0.71 to -1.00. Most supplemental and secondary endpoints were supportive of the primary efficacy measure. A dose-related increase in adverse events and withdrawals due to adverse events was observed.

Study F4: This 14-week study treated patients with pregabalin 300, 450, or 600 mg/day (total of 551 patients; 68% completed) or placebo (184 patients; 76% completed). This study used an enriched population as placebo-responders (≥30% reduction in mean pain scores) during the one-week run-in phase were discontinued and did not participate in the double-blind phase. The treatment effect on endpoint mean pain scores was significantly better than placebo with pregabalin 450 mg/day (p=0.0164), but not with pregabalin 300 or 600 mg/day. Treatment differences ranged between -0.13 to -0.54. Most supplemental and secondary endpoints were supportive of the primary efficacy measure. A dose-related increase in adverse events and withdrawals due to adverse events was observed.

Study F5: This 26-week long-term relapse observation study compared pregabalin with placebo. Patients who met the American College of Rheumatology criteria for fibromyalgia (history of widespread pain for 3 months, and pain present at 11 or more out of 18 specific tender points) and with a score of ≥ 40 mm 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. Patients were considered to be pregabalin responders if they had both at least a 50% reduction in pain on the VAS and rated their overall improvement on the PGIC as “much improved” or “very much improved.” A total of 566 pregabalin responders were then randomized in the double-blind phase to either their optimized pregabalin dose (279 patients) achieved in the open-label phase (therapy continued) or to placebo (287 patients;

therapy discontinued). Patients were treated for up to 26 weeks in the double-blind phase. Treatment with pregabalin resulted in a significantly longer time to loss of therapeutic response than treatment with placebo ($p<0.0001$), with fewer relapses on pregabalin (32%) compared to placebo (61%). Of the pregabalin responders entering the double-blind phase assigned to remain on pregabalin, 38% completed 26 weeks of treatment, versus 19% of those assigned to receive placebo. All supplemental and secondary endpoints were supportive of the primary efficacy measure.

DETAILED PHARMACOLOGY

Preclinical Pharmacology

Pregabalin has analgesic, antiepileptic and anxiolytic activity in animal models. In rat models, pregabalin does not prevent behaviors in response to acute nociceptive pain, but it reduces behaviors caused in animals sensitized by inflammation or damage to sensory nerves (neuropathic pain). The analgesic-like actions of pregabalin are seen against both somatic and lower gastrointestinal (visceral) pain responses. Pregabalin reduces nociceptive spinal reflex activity in anesthetized rats particularly after inflammation or neuropathic damage. Pregabalin prevents pain-related behaviors when administered in low doses to the intrathecal space, suggesting it acts directly on tissues of the spinal cord. In rodent seizure models, pregabalin prevents partial and generalized tonic-clonic seizures, but not absence seizures. The (R)- enantiomer of pregabalin was generally inactive in these models.

Pregabalin produces anxiolytic-like responses in the mouse tail-suspension test, the rat Vogel and Geller conflict tests, the rat elevated X-maze and rhesus monkey Geller conflict test. In addition, pregabalin administration increases spontaneous slow-wave sleep in rats and causes subtle ataxia, but does not prevent locomotion or consciousness in rats or mice.

Pregabalin is structurally related to both the naturally occurring inhibitory neurotransmitter, GABA, and to the endogenous amino acid L-leucine. However, it is not active at $GABA_A$, $GABA_B$, or benzodiazepine receptors, and it does not alter GABA degradation nor acutely change GABA uptake in brain tissue. Pregabalin and L-leucine bind with high affinity to an auxiliary protein associated with voltage-gated calcium channels ($alpha_2$-delta protein) and the pharmacological activity of pregabalin and structural derivatives in animal models is related to binding affinity at this site. Furthermore, analgesic and anticonvulsant actions of pregabalin are reduced in mutant mice with defective drug binding to $alpha_2$-delta Type 1 protein. These findings indicate binding of pregabalin to $alpha_2$-delta protein is required for pharmacological activity in vivo. The (R)-enantiomer of pregabalin was 10-fold less potent than pregabalin in binding at these sites, consistent with the general lack of effect in efficacy models. In vitro, pregabalin reduces the release of glutamate, norepinephrine, Substance P, and calcitonin gene-related peptide from certain brain tissues and also reduces calcium influx in isolated presynaptic terminals (synaptosomes). Effects of pregabalin on neurotransmitter release and calcium influx result from subtle modulation of voltage-gated calcium channels, but pregabalin does not block

calcium channel conductance or completely inhibit neurotransmitter release, even at high concentrations.

Pregabalin also is a substrate for the System L amino acid transporter of cell membranes that contribute to the permeation of pregabalin across membrane barriers. Prolonged exposure of cultured neurons to low concentrations of pregabalin causes the redistribution of GAT1 GABA transporters from the cytosol to the cell membrane, but pregabalin does not change the content of GABA in neuronal tissues in vitro. Pregabalin has no effect on the electrophysiology of GABA receptors nor on glutamate or GABA synaptic transmission, and it does not alter long term synaptic potentiation in vitro. Pregabalin, at high concentrations, reduces activation of certain kinases in cultured mammalian cell systems and increases the activity of the GABA synthetic enzyme, glutamic acid decarboxylase. Pregabalin is inactive at 38 commonly studied drug and neurotransmitter radioligand binding sites, and it does not alter monoamine neurotransmitter uptake in isolated brain tissues.

Pregabalin demonstrates low potential for abuse. Decreased spontaneous locomotor activity and/or ataxia in animals are common findings with CNS active drugs. No significant cardiovascular, renal, gastrointestinal, or pulmonary liabilities were identified.

Pharmacokinetics

Pregabalin is well absorbed after oral administration. Absolute bioavailability is high in rodents and monkeys, and exposure is dose-proportional at doses up to 2500 mg/kg in rats and up to 50 mg/kg in monkeys. Bioavailability decreases at higher doses, possibly due to saturated absorption. Pregabalin is widely distributed in most tissues and readily crosses the blood-brain barrier in mice, rats, and monkeys. Pregabalin radioequivalents concentrate in mouse and rat but not monkey pancreas. Pregabalin does not bind to mouse, rat, monkey, or human plasma proteins; therefore, potential drug-drug interactions through displacement of protein-bound drugs are not expected at clinically relevant doses.

Pregabalin undergoes minimal metabolism in mouse, rat, and monkey with unchanged parent representing ≥ 90% of drug-derived material in urine. A minor metabolite representing 2% to 3% of the urinary radioactivity in mouse and rat was identified as the N-methyl metabolite. In monkey, only 1 minor (<1%) unidentified component is detected in the urine. In contrast to other animal species and humans, approximately 45% of the pregabalin dose is excreted in urine as N-methyl metabolite in dogs. These data also confirm selection of the rat and monkey as appropriate species for toxicology studies. No significant inhibition of major cytochrome CYP450 isoforms was observed at pregabalin concentrations up to 1 mM, therefore metabolism-related drug-drug interactions are not expected at therapeutic concentrations of pregabalin.

Urinary elimination is the principal route of excretion following pregabalin administration in experimental animals, similar to elimination in humans (see **ACTION AND CLINICAL PHARMACOLOGY**). In mouse, rat, and dog, ≥ 80% of an oral dose was excreted in 24 hours, while at least 71% was excreted by the monkey during the same interval.

TOXICOLOGY

Acute and Repeated-Dose Toxicity

The acute toxicity of pregabalin is low. Animals given oral doses of pregabalin in acute and repeated-dose studies were hypoactive, hyperactive, and/or ataxic, signs commonly observed with CNS-active drugs. No significant target organ toxicity was observed in rats treated for up to 52 weeks or in monkeys treated for up to 69 weeks at exposures at least 8 times the mean human exposure at the maximum recommended dose of 600 mg/day. Effects of pregabalin in juvenile animals were similar to those in adults.

Acute Toxicity

Acute oral and IV studies were conducted in mice and rats. Hypoactivity in mice and rats, and diarrhea and urine staining in rats, but no deaths or changes in clinical biochemical parameters, occurred following administration of single oral doses of 5000 mg/kg or single IV doses of 300 mg/kg, the highest IV dose achievable based on solubility and dose volume limitations. No drug-related gross or histopathologic changes were observed in rodents given single oral or IV doses.

Repeated-Dose Toxicity

Repeated-dose studies in definitive toxicology species are listed in Table 16 and results are discussed in the sections below.

Table 16. Repeated-Dose Oral Studies with Pregabalin

Species	Duration (Weeks)	Dose Range (mg/kg)
Rat	2	500 – 2500
	4	500 – 5000
	4	50 – 250
	13	50 – 1250
	26/52	50 – 500
Monkey	Escalating-Dose	50 – 2000
	2	100 – 2000
	4	100 – 2000
	4-day (toxicokinetic)	500 – 1000
	4	25 - 500 BID
	13	10 – 500
	65-69	10 -500

Rat: Ataxia and hypoactivity were seen in rats given repeated oral doses >500 mg/kg with associated $AUC_{(0-24)}$ >1280 µg·hr/mL; tail dermatopathy and urine staining were seen at >250 mg/kg with associated $AUC_{(0-24)}$ >802 µg·hr/mL. Body weight gain decreased 18% to 70% in rats given pregabalin at 500 to 5000 mg/kg for 4, 13, or 52 weeks. No effects on body weight gain occurred at 50 or 250 mg/kg for 52 weeks with associated exposures <1210 µg·hr/mL. Urinary bladder

changes (dilatation, edema, and hemorrhage) and sporadic mortality associated with pyelonephritis and/or cystitis occurred in rats at >250 mg/kg; associated $AUC_{(0-24)}$ was >802 µg·hr/mL. Red blood cell (RBC) parameters increased 6% to 16% in rats given pregabalin at 500 to 5000 mg/kg for 4 weeks, and were reversible. RBC count only increased 5% to 11% at 50 to 1250 mg/kg in Weeks 13, 26, and 52 with associated exposures >228 µg·hr/mL. Platelet count decreased 14% to 36% in male rats given >50 mg/kg and in female rats given >100 mg/kg for up to 52 weeks with associated $AUC_{(0-24)}$ >228 µg·hr/mL. Changes in platelet count were reversed during a 4-week withdrawal period after 4 weeks of dosing. Total nucleated cells in the bone marrow decreased 18% to 44% in rats given pregabalin at 250 to 1250 mg/kg for 13, 26, or 52 weeks. No drug-related effects on bone marrow occurred at 50 mg/kg for up to 52 weeks with associated exposures <228 µg·hr/mL. In rats given pregabalin for 4 weeks, epididymal hypospermia occurred at >500 mg/kg and spermatogenic epithelial degeneration occurred at 1250 mg/kg with associated $AUC_{(0-24)}$ >1690 µg·hr/mL. Similar changes were not seen in the 52-week study at doses up to 500 mg/kg. No adverse effects were observed in rats given 50 mg/kg for 13 weeks, with associated combined-sex $AUC_{(0-24)}$ of 188 µg·hr/mL; effects at this dose in the 52-week study were minimal.

Monkeys: Nasal discharge and soft feces/diarrhea occurred in monkeys given repeated oral doses >100 mg/kg for up to 13 weeks, with associated $AUC_{(0-24)}$ >398 µg·hr/mL. Hypoactivity occurred at >500 mg/kg; $AUC_{(0-24)}$ was at least 974 µg·hr/mL. Deaths occurred within 3 days after treatment initiation in monkeys given 500 mg/kg BID or 1000 or 2000 mg/kg. Although toxicokinetic data were not available for all these monkeys, the lowest $AUC_{(0-24)}$ in an animal that died was 1640 µg·hr/mL. Myocardial effects seen in monkeys at >50 mg/kg in 4-week studies were not seen in subchronic and chronic studies and, therefore, not considered drug- related. There were no effects on body weight gain, hematology, or bone marrow parameters in monkeys given pregabalin at 10 to 500 mg/kg for up to 69 weeks. Sperm count, motility, and morphology were not affected in monkeys given up to 500 mg/kg for 69 weeks. Tail dermatopathy was observed in monkeys at >25 mg/kg. With the exception of tail dermatopathy, no significant effects were observed in monkeys given up to 500 mg/kg up to 69 weeks with associated plasma concentrations up to 76.2 µg·/mL. Based on the 4-week toxicokinetic profiles and single time point samples in Week 52, combined-sex $AUC_{(0-24)}$ was estimated to be 1040 µg·hr/mL.

Genetic Toxicity

The genotoxic potential of pregabalin was evaluated in an extensive battery of tests. Pregabalin was not mutagenic in bacteria up to 5000 µg/plate with or without metabolic activation provided by postmitochondrial supernatant fractions from livers of B6C3F1 or CD-1 mice or Wistar rats treated with Arochlor 1254. In mammalian cells in vitro, no evidence of mutagenicity or structural chromosome aberrations was observed up to 1600 µg/mL with or without metabolic activation. Pregabalin did not induce unscheduled DNA synthesis in hepatocytes of B6C3F1 or CD-1 mice or Wistar rats given single oral doses up to 2000 mg/kg. Micronucleus frequency was not increased in bone marrow from B6C3F1 or CD-1 mice or Wistar rats given single oral doses of pregabalin up to 2000 mg/kg.

These results demonstrate pregabalin is not genotoxic in vitro or in vivo.

Reproduction and Teratology

In female rats, although estrus and diestrus stages were prolonged at 1250 and 2500 mg/kg, no effects on fertility were observed in females given 500 to 2500 mg/kg prior to mating with untreated males. In male rats, pregabalin administration resulted in decreased sperm motility and decreased fertility at exposures ≥27 times the mean human exposure at the maximum recommended clinical dose and were reversible. There were no drug-related effects on sperm parameters in monkeys treated for 69 weeks with exposures up to 8 times the maximum human exposure.

In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo- and pregabalin-treated subjects in mean percent sperm with normal motility was <4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied (see **WARNINGS AND PRECAUTIONS**).

Pregabalin induced maternal toxicity in embryo-fetal development studies in rats at ≥500 mg/kg and rabbits at ≥250 mg/kg, and fetal toxicity in rats at 2500 mg/kg and in rabbits at 1250 mg/kg. Pregabalin was not teratogenic in mice, rats, or rabbits at exposures 31 to 77 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In the prenatal-postnatal toxicity study in rats, pregabalin induced offspring developmental toxicity at exposures ≥5 times the mean human exposure. No effects occurred at exposures twice the mean human exposure at the maximum recommended clinical dose (see **WARNINGS AND PRECAUTIONS**).

Pregabalin is excreted in milk of lactating rats. It is not known if pregabalin is excreted in breast milk of humans. Because of the potential exposure in breast-feeding infants, breast feeding is not recommended (see **WARNINGS AND PRECAUTIONS**).

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20. LYRICA® Product Monograph dated October 23, 2014. Pfizer Canada Inc. Submission Control No. 176683.

PART III: CONSUMER INFORMATION

Pr MYL-PREGABALIN
Pregabalin Capsules

This leaflet is part III of a three-part "Product Monograph" published when MYL-PREGABALIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MYL-PREGABALIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What is the most important information I should know about MYL-PREGABALIN?

1. MYL-PREGABALIN may cause serious allergic reactions. Call your doctor right away if you think you have any of the following symptoms of a serious allergic reaction:
- swelling of the face, mouth, lips, gums, tongue or neck
- have any trouble breathing
- other allergic reactions may include rash, hives and blisters.

2. MYL-PREGABALIN may cause dizziness and sleepiness.
- Do not drive a car, work with machines, or do other dangerous activities until you know how MYL-PREGABALIN affects how alert you are. Ask your doctor when it is okay to do these activities.

3. MYL-PREGABALIN may cause problems with your eyesight, including blurry vision. Call your doctor if you have any changes in your eyesight.

What the medication is used for:
MYL-PREGABALIN is a prescription medicine used for the symptomatic relief of neuropathic pain associated with:
- Diabetic peripheral neuropathy (Pain from damaged nerves due to diabetes)
- Postherpetic neuralgia (Persisting pain following rash due to shingles)
- Pain from damaged nerves in the spinal cord
- MYL-PREGABALIN is also used for the symptomatic relief of pain associated with fibromyalgia (a condition which includes widespread pain).

What it does:
MYL-PREGABALIN can relieve pain. Some patients taking pregabalin showed improvement as early as the first week of treatment.

When it should not be used:
You should not take MYL-PREGABALIN if you are allergic to pregabalin, the main ingredient in MYL-PREGABALIN, or any other ingredient in MYL-PREGABALIN (see "What the non-medicinal ingredients are"). Children under the age of 18 years.

What the medicinal ingredient is:
Pregabalin

What the non-medicinal ingredients are:

The non-medicinal ingredients that make up the capsule core are corn starch, lactose monohydrate, and talc.

The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain colloidal silicon dioxide and sodium lauryl sulphate.

The markings on the capsules are in black ink, which contains black iron oxide, propylene glycol, potassium hydroxide, shellac and water.

What dosage forms it comes in:
Capsules containing 25 mg, 50 mg, 75 mg, 150 mg, 225 mg, or 300 mg of pregabalin.

WARNINGS AND PRECAUTIONS

BEFORE you use MYL-PREGABALIN tell your doctor or pharmacist if:

- you are taking any other prescription or nonprescription medicines, or natural/herbal remedies.
- you have any kidney problems.
- you are pregnant, plan to become pregnant, or think you might be pregnant.
- you are breastfeeding. Pregabalin passes into breast milk and it is not known if it can harm your baby. You and your healthcare provider should discuss whether you should take MYL-PREGABALIN or breast-feed, but you should not do both.
- you have ever had an allergic reaction (itching, wheezing, hives, or swelling of the throat or face) to pregabalin or any of the nonmedicinal ingredients listed in "What the nonmedicinal ingredients are":
- you have a history of heart disease called congestive heart failure.
- you have a history of lower gastrointestinal problems (eg., constipation, blocked or paralysed bowel), or you are taking medication(s) that may cause constipation.

Pregnancy Registry: If you become pregnant while taking MYL-PREGABALIN, talk to your doctor about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of anticonvulsant medicines during pregnancy. Any woman who is currently pregnant and is taking antiepileptic drugs for any reason, can enroll in the registry. Information on the registry can also be found at the website http://www.massgeneral.org/aed/.

INTERACTIONS WITH THIS MEDICATION

While you are taking MYL-PREGABALIN, don't start any new medicines, including natural or herbal medicines, without talking to your doctor first. Your doctor or pharmacist will know which medicines are safe for you to take together. MYL-PREGABALIN does not interfere with birth control pills.

You may have a higher chance for dizziness and sleepiness if the following drugs are taken with MYL-PREGABALIN:

- Alcohol
- Medicines for anxiety (such as lorazepam)
- Narcotic pain medicine (such as oxycodone)
- Any medicines that make you sleepy

You may have a higher chance of weight gain or swelling if the antidiabetic pills, Avandia (rosiglitazone) or Actos (pioglitazone) are taken with MYL-PREGABALIN.

PROPER USE OF THIS MEDICATION

You can take MYL-PREGABALIN with or without food. Avoid alcoholic drinks while taking MYL-PREGABALIN.

Usual adult dose:
Your doctor will tell you how much to take and when to take it.

Overdose:

In case of a drug overdose, immediately go to the nearest emergency room even if you do not feel sick. Make sure you take your medicine bottle with you to show the doctor.

Missed Dose:
If you miss a dose by a few hours, take it as soon as you remember. If it is close to your next dose, do NOT take the missed capsules. Simply wait and restart MYL-PREGABALIN with your next scheduled dose.

Do not suddenly stop taking MYL-PREGABALIN. Talk to your doctor first. Plan ahead to have a refill so you don't run out.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some patients may have side effects while taking MYL-PREGABALIN. Side effects are usually mild. In studies, few patients stopped taking pregabalin due to side effects.

The most common side effects were: dizziness, sleepiness, blurred vision, dry mouth, swelling of the extremities, weight gain, trouble concentrating, lack of energy, muscle weakness, constipation, and forgetfulness.

A small number of patients taking a drug of this type may experience thoughts of suicide. Your doctor should be informed immediately if this occurs.

When you start MYL-PREGABALIN, you may get sleepy or experience dizziness. Avoid potentially hazardous tasks: do not drive a car or operate machinery until you are sure that this medication does not affect your ability to drive or operate machinery or until you get used to MYL-PREGABALIN.

When MYL-PREGABALIN is taken with other medications that may cause constipation (such as opioid pain medications), it is possible that gastrointestinal problems may occur (eg., constipation, blocked or paralysed bowel).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical assistance
		Only if severe	In all cases	
Common	Dizziness	√		
	Sleepiness	√		
	Blurred vision		√	
Uncommon	Weight gain	√		
	Swelling of hands and feet (edema)		√	
	Swelling of the face, mouth, lips, gums, neck or throat,			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek emergency medical assistance**
		Only if severe	**In all cases**	
	trouble breathing			
	Extreme fatigue		√	
	Increased cough		√	
	Allergic reactions (skin rash, hives, blisters)			√
	Decrease in the amount of urine		√	
	Thoughts of suicide		√	
Very rare	Seizures			√

This is not a complete list of side effects. If you have any unexpected effects while taking MYL-PREGABALIN, contact your doctor or pharmacist.

HOW TO STORE IT

Keep MYL-PREGABALIN out of reach of children. Store it at controlled room temperature (15°C to 30°C) in the package it came in.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: **Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.**

MORE INFORMATION

This document can be found at: www.mylan.ca

The full product monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC at: 1-800-575-1379

This leaflet was prepared by Mylan Pharmaceuticals ULC
Etobicoke, Ontario M8Z 2S6

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