**Dizziness and Somnolence**

LYRIC A may cause dizziness and somnolence. Patients should be informed that LYRIC A may cause dizziness, which may lead to the risk of falling, injury, or other accidents. Patients should be advised to discontinue LYRIC A if dizziness becomes severe or is accompanied by other symptoms. Dizziness and somnolence generally began shortly after the initiation of LYRIC A therapy and occurred more frequently at the start of treatment.

**Peripheral Edema**

LYRIC A treatment may cause peripheral edema. In short-term trials of patients without peripheral edema at baseline, a higher proportion of patients treated with LYRIC A compared to the placebo group developed peripheral edema (12% vs 7%). In clinical trials of patients reporting peripheral edema at baseline, LYRIC A group compared with 5% in the placebo group. In controlled clinical trials, 0.3% of LYRIC A patients and 0.2% placebo patients withdrew due to peripheral edema. Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRIC A and a thiazolidinedione antihyperglycemic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antihyperglycemic agents in the overall safety database were patients in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 2% of LYRIC A-treated patients compared to 7% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of LYRIC A therapy and occurred more frequently at the start of treatment.

**Weight Gain**

LYRIC A treatment may cause weight gain. In controlled clinical trials of up to 14 weeks, a gain of 7% or more over baseline was observed in 0.4% of patients taking LYRIC A and 0.2% of placebo patients. LYRIC A-treated patients gained an average of 1.6 kg (range: 1.6-10 kg) compared to 1.0 kg (range: 1.0-10 kg) weight gain in placebo patients. In a cohort of 353 diabetic patients with peripheral neuropathy, weight gain was 5.2 kg. While the effects of LYRIC A on glycemic control have not been systematically assessed, in controlled and longer-term open-label clinical trials, weight gain, defined as a percentage increase in weight from baseline, did not appear to be associated with loss of glycemic control (as measured by HbA1c).

**Abrupt or Rapid Discontinuation**

Following abrupt or rapid discontinuation of LYRIC A, some patients reported adverse reactions, including nausea, headache, blurred vision, vertigo, dizziness, and somnolence. Patients should be advised to taper the dose over a minimum of 1 week rather than discontinue abruptly. Tapering should be gradual to avoid the risk of discontinuation reaction. For patients at high risk of treatment withdrawal, continued treatment may cause weight gain. In LYRIC A-controlled clinical trials of up to 14 weeks, a gain of 7% or more over baseline was observed in 0.4% of patients taking LYRIC A and 0.2% of placebo patients. LYRIC A-treated patients gained an average of 1.6 kg (range: 1.6-10 kg) compared to 1.0 kg (range: 1.0-10 kg) weight gain in placebo patients. In a cohort of 353 diabetic patients with peripheral neuropathy, weight gain was 5.2 kg. While the effects of LYRIC A on glycemic control have not been systematically assessed, in controlled and longer-term open-label clinical trials, weight gain, defined as a percentage increase in weight from baseline, did not appear to be associated with loss of glycemic control (as measured by HbA1c).

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### Table 3: Treatment-emergent adverse event incidence in controlled trials in neuropathic pain associated with postherpetic neuralgia (Events ≥ 2% in LYRICA-treated patients and greater than those in placebo in the Table)

<table>
<thead>
<tr>
<th>Event Category</th>
<th>LYRICA 75 mg</th>
<th>LYRICA 150 mg</th>
<th>LYRICA 300 mg</th>
<th>LYRICA 600 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a whole</td>
<td>4%</td>
<td>5%</td>
<td>5%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>6%</td>
<td>7%</td>
<td>8%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>8%</td>
<td>10%</td>
<td>12%</td>
<td>15%</td>
<td>7%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>4%</td>
<td>6%</td>
<td>7%</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Visual</td>
<td>5%</td>
<td>7%</td>
<td>9%</td>
<td>12%</td>
<td>5%</td>
</tr>
<tr>
<td>Auditory</td>
<td>4%</td>
<td>6%</td>
<td>8%</td>
<td>12%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Other adverse reactions observed during the clinical studies of LYRICA were dizziness, tremor, headache, upper respiratory tract infection, infection and infestation, and myalgia.

### Other Adverse Reactions Observed During the Clinical Studies of LYRICA

In a study of female rats dosed with LYRICA (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of cranial sutures) were increased at 1250 mg/kg. In a study of rabbits dosed with LYRICA (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of cranial sutures) were increased at 1250 mg/kg.

### Overdose

Overdose, Seizure, and Laboratory Findings of Acute Overdose in Humans

LYRICA has limited exposure to overdose of LYRICA. The highest reported accidental overdose of LYRICA during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg. The types of adverse events reported included seizures, convulsions, dizziness, agitation, tremors, and ataxia. Ingestion of a single dose of 60 mg/kg in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low dose effect for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. In a no-effect dose was not established. Geriatric Use (in controlled clinical studies of LYRICA in neuropathic pain associated with diabetic peripheral neuropathy, 78% of patients were 65 years of age or older, 27% were 75 years of age or older, 73% patients were 75 years of age or older, in controlled clinical studies of LYRICA in neuropathic pain associated with postherpetic neuralgia, 55% of patients were 75 years of age or older, 20% were 85 years of age or older). In elderly patients, the risk of adverse reactions is greater than in younger patients. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment.

### Reproduction

Pregnancy

In a double-blind, placebo-controlled 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 sperm percent with normal motility was -4%, and neither group had mean change from baseline of more than 2%. Other effects on male reproductive parameters in humans have not been adequately studied.

### Nonclinical Toxicology

### Dermatologic

### Animal Toxicology and/or Pharmacology

### Dermatotoxicity

Skin lesions ranging from erythema to necrosis were seen in repeated dose toxicity studies in both rats and monkeys. The etiology of these skin lesions is unknown. All the maximum recommended human dose (MRD) of 600 mg/day, there are a 2-fold safety margin for the dermatological lesions. The most severe dermatologic reactions noted in rats were associated with pregabalin exposures (as expressed by plasma AUC) of 1000 mg·h/ml or greater. Significant skin lesions were noted for repeated dose toxicity studies in rats at doses of 50, 100, and 250 mg/kg and for repeated dose Toxicology studies in rats, rabbits, and dogs at doses of 50, 100, and 250 mg/kg. Significant skin lesions were noted for repeated dose Toxicology studies in rats at doses of 50, 100, and 250 mg/kg.