Bisphosphonates May Reduce Breast Cancer Risk

BY BETSY BATES

SAN ANTONIO — Two differently designed studies found a nearly identical, roughly 30% reduction in the risk of breast cancer in postmenopausal women who took bisphosphonates to prevent or remediate bone loss.

The results of a retrospective analysis of data from the Women's Health Initiative (WHI) in the United States and a case-control study conducted in Israel were presented at the annual San Antonio Breast Cancer Symposium.

In both studies, cancer incidence was sharply lower among women prescribed bisphosphonates for low bone mineral density, suggesting that the impact of these agents may extend beyond bone. In the 151,592-patient database for the WHI, breast cancer development was exbone mineral density, since women at risk for osteoporosis are known to be at lower risk for breast cancer, likely due to a lower lifetime exposure to estrogen.

Following that statistical adjustment, researchers found that only 64 of 2,216 bisphosphonate users developed breast cancer after a mean 8 years of follow-up, and that 50 of the cancers were estrogen

This represents a 32% lower incidence

of breast cancer than was seen among non-bisphosphonate users, reported Dr. Rowan Chlebowski, a medical oncologist at the Harbor-University of California, Los Angeles Medical Center.

"This is a cohort study, not a definitive randomized, controlled trial, but I think it provides a strong signal," said Dr. Chlebowski during a press conference preceding his podium presentation. "Oral bisphosphonate use may directly inhibit breast cancer incidence.

No advantage was seen with respect to ductal carcinoma in situ (DCIS) in women taking bisphosphonates. Indeed, women taking bisphosphonates were slightly more likely to develop DCIS. This perhaps implies that the effects of bisphosphonates occur later in the development of breast cancer, Dr. Chlebowski said.

In Israel, women with breast cancer who reported taking bisphosphonates



"Oral bisphosphonate use may directly inhibit breast cancer incidence," said

for at least a year prior to their diagnosis were matched to demographically similar women who were not taking bisphosphonates and without cancer. (Controls were selected by age, neighborhood, and ethnicity.)

To ensure against recall bias, researchers used prescription records to confirm a prediagnosis history of bisphosphonate use, said Dr. Gad Rennert, chairman of community medicine and epidemiology at the Clalit National Cancer Control Center in Haifa, Israel.

Among the 4,575 subjects, those who took bisphosphonates for at least a year were 34% less likely to be diagnosed with breast cancer.

Risk reduction remained significant at 29% after controlling for other risk factors for breast cancer, including age, ethnicity, family history, fruit and vegetable intake, exercise, body mass index, pregnancy history, and use of calcium supplements and

"The tumors we saw were more commonly estrogen receptor positive, and more precisely, strongly estrogen receptor positive," Dr. Rennert said during his podium presentation. "They were more commonly well differentiated.3

Both estrogen receptor positivity and cell differentiation are associated with re-Continued on following page

Reference: 1. IMS Health Inc. National Sales Perspectives (12 months ending December 2008)

NovoLog[®] (insulin aspart [rDNA origin] injection)

Rx only

BRIEF SUMMARY. Please consult package insert for full prescribing information. INDICATIONS AND USAGE: NovoLog® is an insulin analog indicated to improve glycemic control in h diabetes mellitus.

CONTRAINDICATIONS: NovoLog[®] is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog[®] or one of its excipients.

WARNINGS AND PRECAUTIONS: Administration: NovoLog® has a more rapid onset of action and a shorter duration of activity than regular human insulin. An injection of NovoLog[®] should immediately be followed by a meal within 5-10 minutes. Because of NovoLog[®]'s short duration of action, a longer acting insulin should also be used in patients with type 1 diabetes and may also be needed in patients with type 2 diabetes. Glucose monitoring is recommended for all patients with diabetes and is particularly type 2 daddets, olicities motivationing is recommended for an patients with daddets and is particularly important for patients using external pump infusion therapy. Any change of insulin dose should be made cautiously and only under medical supervision. Changing from one insulin product to another or changing the insulin strength may result in the need for a change in dosage. As with all insulin preparations, the time course of NovoLog® action may vary in different individuals or at different times in the same individual and independent of the same individual and the same individual and the same individual and and the same individual and the same individuals or at different times in the same individual and independent of the same individual and independent of the same indit individual a Course of NovoLog* action may vary in omerent individuals of at omerent times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, temperature, and physical activity. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages. Insulin requirements may be altered during illness, emotional disturbances, or other stresses. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure. **Hypoglycemia:** Hypoglycemia is the most common adverse effect of all insulin therapies, including Nord art. Pypugycernia, hybogycernia is the most common averse effect of all insum elaples, including NovoLog[®]. Severe hypoglycernia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycernia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with NovoLog[®]. The timing of hypoglycernia usually reflects the time-action profile of the administered insulin formulations [see *Clinical Pharmacology*]. Other here a back are to be achieved by the ford in the ford of the insure of enderly bination of the administered insulin formulations. observed in clinical infaits with instrum, including traits with NovoLog². The timing of hypoglycernia usually reflects the time-action profile of the administered insulin formulations [*see Clinical Pharmacology*]. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycernia [*see Drug Interactions*]. As with all insulins, use caution in patients with hypoglycernia unawareness and in patients who may be predisposed to hypoglycernia (e.g., patients who are fasting or have erratic food intake). The patients ability to concentrate and react may be impaired as a result of hypoglycernia in persons with diabetes, regardless of the glucose levels may induce symptoms of hypoglycernia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycernia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic nerve disease, use of medications may result in severe hypoglycernia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycernia. Intravenously administered insulin has a more rapid onset of action than subcutaneously administered insulin, requiring more close monitoring for hypoglycernia. **Hypokalemia:** All insulin products, including NovoLog², cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications patients taking medications sensitive to serum potassium concentrations, and patients receiving intravenously administered insulin). **Renal Impairment:** As with other insulins, the dose requirements for NovoLog⁴ may be reduced in patients with renal impairment (*see Clinical Pharmacology*]. **Hepatie Mpairment:** As with other insulin therag

Impairment (see Clinical Pharmacology). Hypersensitivity and Allergic Reactions: Local Reactions - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of NovoLog[®] injection. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog[®]. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in NovoLog[®]. Systemic Reactions - Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin product, including NovoLog[®]. Anaphylactic reactions with NovoLog[®] have been reported post-approval. Generalized myalgias have been robust and so the several states and the several states and the several states and the several states and the several sever In an include in a display treatment groups observed at 3 and 6 months were no longer evident at 12 months. The clinical significance of these antibodies is not known. These antibodies do not appear to cause deterioration in glycemic control or necessitate increases in insulin dose. **Mixing of Insulins:** Mixing NovoLog[®], without significantly affecting the time to peak concentration of NovoLog[®], without significantly affecting the time to peak concentration or total bioavailability of NovoLog[®], without significantly affecting the time to peak concentration or total bioavailability of NovoLog[®], thouse of the maximum studie time to peak concentration or total bioavailability of NovoLog[®], the mixture should be injected immediately after mixing. The efficacy and safety of mixing NovoLog[®] with insulin preparations produced by other manufacturers have not been studied. Insulin mixtures should not be administered intravenously. **Subcutaneous continuous insulin infusion pump, NovoLog[®]** should not be mixed with any other insulin or diluent. When using NovoLog[®] in an external subcutaneous insulin infusion pump, NovoLog[®] should not be mixed with any other insulin or diluent. When using NovoLog[®] in an external insulin pump, the NovoLog[®] specific information should be followed (e.g., in-use time, frequency of changing infusion sets because of the small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required [*see Dosage and Administration, Warnings and Demonstrate*]

action, Fromp, test minimation and confection on the cause of hypergrytemia of Actions is factored with the terms of the action of the cause of hypergrytemia of Actions is traited and the actions, How Supplied/Storage and Handling, and Patient Counseling Information). NovoLog[®] is recommended for use in pump systems suitable for insulin infusion as listed below. **Pumps:** MiniMed 500 series and other equivalent pumps. **Reservoirs and infusion sets:** NovoLog[®] is recommended for use in reservoir and infusion sets that are compatible with insulin and the specific pump. In-vitro studies



Novo Log insulin aspart (rDNA origin) injection hormone replacement therapy.

Pages 24a—24dt>



receptor positive. plored only after controlling for baseline

> have shown that pump malfunction, loss of metacresol, and insulin degradation, may occur when NovoLog' is maintained in a pump system for longer than 48 hours. Reservoirs and infusion sets should be changer at least every 48 hours. NovoLog'' should not be exposed to temperatures greater than 37°C (98.6°F) NovoLog[®] that will be used in a pump should not be mixed with other insulin or or (source) NovoLog[®] that will be used in a pump should not be mixed with other insulin or with a diluent (see Dosage and Administration, Warnings and Precautions and How Supplied/Storage and Handling, Patient Counseling Information).

ADVERSE REACTIONS: Clinical Trial Experience: Because clinical trials are conducted under ADVENSE NEAR THONS. CHINEM THIS EXperiments, because chinical trians are collidated under widely varying designs, the adverse reaction rates reported in one chinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice. <u>Hypoglycemia</u>; Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including NovoLog[®] (see Warnings and Precautions). <u>Insulin initiation and glucose control</u> <u>intensification</u>; Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful periphed expresents. transitiony, reversible ophinfamiliotigic relraction usorder, worsening of olabelic reinopativ, and acctle paintui peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic relinopathy and neuropathy. *Lipodystrophy*: Long-term use of insulin, including NovoLog[®], can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipodystrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. <u>Weight gain</u>: Weight gain can occur with some insulin therapies, including NovoLog[®], and has been attributed to the anabolic effects of insulin and the decrease in elucopautic.

Occur was some insum therapies, including NovoLog , and has been autobact to the attabulic effects of insulin and the decrease in glucosuria. <u>Peripheral Edema</u>; Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. <u>Frequencies</u> <u>of adverse drug reactions</u>; The frequencies of adverse drug reactions during NovoLog[®] clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (Adverse events with frequency ≥ 5% and occurring more frequently with NovoLog[®] compared to human regular insulin are listed)

	NovoLog N=)° + NPH 596	Human Regular Insulin + NPH N=286		
Preferred Term	N	(%)	N	(%)	
Hypoglycemia*	448	75%	205	72%	
Headache	70	12%	28	10%	
Injury accidental	65	11%	29	10%	
Nausea	43	7%	13	5%	
Diarrhea	28	5%	9	3%	

Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL with or without symptoms. See *Clinical Studies* for the incidence of serious hypoglycemia in the individual clinical trials Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus

(except for hypoglycemia, adverse events with frequency $\gtrsim 5\%$ and occurring more frequently with NovoLog* compared to human regular insulin are listed) NovoLog[®] + NPH Human Regular Insulin + NPH

	11=31		11=91		
	N	(%)	N	(%)	
-lypoglycemia*	25	27%	33	36%	
Hyporeflexia	10	11%	6	7%	
Onychomycosis	9	10%	5	5%	
Sensory disturbance	8	9%	6	7%	
Jrinary tract infection	7	8%	6	7%	
Chest pain	5	5%	3	3%	
Headache	5	5%	3	3%	
Skin disorder	5	5%	2	2%	
Abdominal pain	5	5%	1	1%	
Sinusitis	5	5%	1	1%	

⁴Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL, with or without symptoms. See *Clinical Studies* for the incidence of serious hypoglycemia in the individual clinical trials

Postmarketing Data: The following additional adverse reactions have been identified during postapproval use of NovoLog[®]. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. Medication errors in which other insulins have been accidentally substituted for NovoLog[®] have been identified during postapproval use for a direct domain a framework. use [see Patient Counseling Information].

OVERDOSAGE: Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate initia machine and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected

More detailed information is available on request

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Manufactured by Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark Manufactured for Novo Nordisk Inc., Princeton, New Jersey 08540 w.novonordisk-us.com

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NovoLog® is covered by US Patent Nos 5,618,913; 5,866,538; and other patents pending. © 2008 Novo Nordisk Inc. 134600 4/08

Continued from previous page

sponse to treatment and a better prognosis, he noted.

No effect on breast cancer risk was seen in women who took bisphosphonates for less than a year, but after 1 year, the risk was reduced at a fairly steady rate. "Five years of use was not dramatically better than 4 years of use," he said. This finding corresponds with the drugs' pharmacokinetic profile, characterized by a slow and steady cumulative effect on bone that stabilizes after a period of time.

"We are seeing an association here. It's

a very strong and robust association," Dr. Rennert said.

Initially, a hint of cancer protection arose in small studies comparing breast cancer patients receiving bisphosphonates for cancer- and treatment-related bone loss to those who did not receive the drugs. The evidence seemed to show that those receiving the bone-protecting drugs also developed fewer new cancers in their contralateral breasts.

Possible biologic explanations may lie in the ability of bisphosphonates to reduce angiogenesis and stimulate immune cells responsible for tumor cell detection, Dr. Chlebowski said in an interview. Dr. Theresa Guise, professor of med-

icine and oncology at Indiana University, Indianapolis, said the studies may hold "very important implications for a large population of patients."

The possibility that a "simple oral drug" could prevent both osteoporosis and breast cancer represents a "step forward in the prevention of ... common health problems of women today," Dr. Guise commented during a discussion of the papers at a press conference.

Bisphosphonates, which can be taken either orally or in an intravenous infusion, are prescribed to about 30 million patients each year.

WOMEN'S HEALTH

Disclosures: Dr. Chlebowski disclosed that he has been a consultant for, or served on speakers bureaus for AstraZeneca, Novartis, Pfizer, Amgen, and Eli Lilly. Dr. Rennert disclosed no relevant financial relationships. Dr. Guise said she has been a consultant for or served on speakers bureaus

for Amgen, Novartis, Eli Lilly, and Roche Pharmaceuticals.

A related video is at www.youtube.com/ InternalMedicineNews (search for 71010).

LYRICA® (pregabalin) CAPSULES © BRIEF SUMMARY: For full prescribing information, see package insert. INDICATIONS AND USAGE LYRICA is indicated for: • Management of fibromyalgia

DOSAGE AND ADMINISTRATION

LYRICA is given orally with or without food. When discontinuing LYRICA, taper gradually over a minimum of 1 week

Fibromyalgia:

Administer in 2 divided doses per day
Begin dosing at 150 mg/day

Begin dosing at 150 mg/day
Begin dosing at 150 mg/day
May be increased to 300 mg/day within 1 week
Maximum dose of 450 mg/day
Dose should be adjusted for patients with reduced renal function

CONTRAINDICATIONS

d in patients with known hypersensitivity to pregabalin or any of its other com WARNINGS AND PRECAUTIONS

LYNICA is contraindicated in patients with known hypersensitivity to pregabalin or any of its other components. WARNINGS AND PRECAUTIONS Angioedema There have been postmarketing reports of angioedema in patients during initial and chronic treatment with LYRICA. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and lanyx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. LYRICA should be discontinued immediately in patients with these symptoms. Caution should be exercised when prescribing LYNICA to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema (e.g., angiotensin converting enzyme inhibitors [ACE-inhibitors] may be at increased risk of developing angioedema. **Hypersensitivity** There have been postmarketing reports of hypersensitivity in patients shortly after initiation of treatment with LYRICA. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. LYRICA should be discontinued immediately in patients with these symptoms. Withdrawal of Antiepileptic Drugs (AEDs) As with all AEDs, LYRICA should be withdrawn gradually to minimize the potential of neraesed seizure frequency in patients with seizure disorders. If LYRICA is blould be discontinued this should be done gradually over a minimum of 1 week. Suicidal Behavior and Ideation Antiepileptic drugs (AEDs), including LYRICA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Pooled analyses of 199 placebo-controlled clinical trials (mono-and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative R but the number is too small to allow any conclusion about drug effect on suicide. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.



 Energy
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 The relative risk for suicidal thoughts or behavior was higher in clinical trials for englesy that in clinical trials for support of the conditions. We the about or differences were similar for the englesy and psychiatric indications. Aryone considering prescripting Criter Order conditions. We the about or differences were similar for the englesy and psychiatric indications. Aryone considering prescripting Criter Order Crit

(primarily blurred vision). 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 platebt treated with LYRICA, and 5% of placebt-reated patients. Visual field changes were detected in 13% of LYRICA-treated, and 12% of placebt-treated patients. Funduscopic changes were observed in 7% of tVRICA-treated, and 12% of placebt-treated patients. Houscopic changes were observed in 7% of VRICA-treated and 2% of placebt-treated patients. Although the 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 should be considered. More frequent assessment should be considered for patients and your placebt preated placebt. **Created placebt** preated placebt preated placebt preated placebt preated placebt preated placebt preated placebt. The placebt placeb The transfer are caused or controlated to trace events. Trescrines and/or instruct patients to priority report instruction to the events. The second patients and interval patients to priority report instruction to the event of the event o

ADVERSE REACTIONS

ADVERSE REACTIONS Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In all controlled and uncontrolled trials across various patient populations during the premarketing development of LYRICA, more than 10,000 patients have received LYRICA. Approximately 5000 patients were treated for 6 months or more, over 3100 patients have received LYRICA. Approximately 5000 patients were treated for a least 2 years. Adverse Reactions Most Commonly Leading to Discontinuation in All Premarketing Controlled Clinical Studies In premarketing controlled trials of all populations combined, 14% of patients treated with LYRICA and 7% of patients treated with placebo discontinued prematurely due to adverse reactions. In the LYRICA treatment group, the adverse reactions most frequently leading to discontinuation were dizziness (4%) and somnolence (3%). In the placebo group, 1% of patients withdrew due to dizziness and -1% withdrew due to somnolence. Other adverse reactions that led to discontinuation from controlled trials more frequently in the LYRICA group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred Vision, incoordination, and peripheral edema (1% each). Most Common Adverse Reactions in All Premarketing Controlled Clinical Studies In premarketing controlled trials of all patient populations combined, dizziness, somnolence, dry mouth, edema, blured vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention) were more commonly reported by subjects treated with LYRICA thas by subjects treated with placebo (>5% and twice the rate of the states and in placebo). n placebol

In placebo. <u>Controlled</u> Studies with <u>Fibromyalgia</u> Adverse Reactions Leading to Discontinuation In Clinical trials of patients with fibromyalgia, 19% of patients treated with pregabalin (150–600 mg/dav) and 10% of patients treated with placebo discontinued prematurely due to adverse reactions. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse reactions were dizziness (6%) and somolence (3%). In comparison, <1% of placebo-treated patients withdrew due to dizziness and somolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin treatment group than in the placebo treatment group, were fatigue, headache, balance disorder, and weight increased. Each of these adverse reactions led to withdrawal in approximately 1% of patients. *Most Common Adverse Reactions* Table 2 lists all adverse reactions, regardless of causality, occurring in 2% of patients with fibromyalgia in the 'all pregabalin-treatment group for which the incidence was greater than in the placebo treatment group. A majority of pregabalin-treated patients in clinical studies experienced adverse reactions with a maximum intensity of 'mild' or 'moderate''. **Table 2 Treatment-emergent adverse reaction incidence in controlled trials in Fibromyalgia (Events in at least 2% of all LYRICA-**

rgent adverse reaction incidence in controlled trials in Fibromyalgia (Events in at least 2% of all LYRICA

treated patients and occurring more frequently in the all pregabalin-group than in the placebo treatment group)							
System Organ Class	150 mg/d [N=132]	300 mg/d [N=502]	450 mg/d [N=505]	600 mg/d [N=378]	All PGB* [N=1517]	Placebo [N=505]	
- Preterred term	70	70	70	70	70	70	
Ear and Labyrinth Disc	orders						
Vertigo	2	2	2	1	2	U	
Vision blurred	0	7	7	12	0	1	
Contraintenting Diser	0 dara	/	/	12	0		
Dry mouth	7	6	q	q	8	2	
Constination	1	4	7	10	7	2	
Vomiting	2	3	3	2	3	2	
Flatulence	1	1	2	2	2	1	
Abdominal distension	2	2	2	2	2	i	
General Disorders and	Administrativ	e Site Conditions	-	-	-		
Fatique	5	7	6	8	7	4	
Edema peripheral	5	5	6	9	6	2	
Chest nain	2	1	1	2	2	1	
Feeling abnormal	ī	3	2	2	2	Ó	
Edema	1	2	1	2	2	1	
Feeling drunk	1	2	1	2	2	0	
Infections and Infestat	tions						
Sinusitis	4	5	7	5	5	4	
Investigations							
Weight increased	8	10	10	14	11	2	
Metabolism and Nutri	tion Disorders						
Increased appetite	4	3	5	7	5	1	
Fluid retention	2	3	3	2	2	1	
Musculoskeletal and	Connective Tis	sue Disorders					
Arthralgia	4	3	3	6	4	2	
Muscle spasms	2	4	4	4	4	2	
Back pain	2	3	4	3	3	3	
Nervous System Disor	ders						
Dizziness	23	31	43	45	38	9	
Somnolence	13	18	22	22	20	4	
Headache	1	12	14	10	12	12	
Disturbance in	4	4	b	b	5	1	
attention Deleges diseader	2	2	c	0	-	0	
Balance disorder	2 1	3	0	9	2	U	
Coordination obnormal	2	3	4	4	3	1	
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Lothorau	2	2	J 1	2	2	0	
Tromor	2	2	2	2	2	0	
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Euphoric mood	2	5	6	7	6	1	
Confusional state	ĥ	2	3	Á	3	'n	
Anxiety	2	2	2	2	2	1	
Disorientation	1	ñ	2	1	2	ń	
Depression	2	2	2	2	2	2	
Respiratory Thoracic	and Mediastin	al Disorders	2	2	2	-	
Pharyngolaryngeal pain	2	1	3	3	2	2	
*PGB: pregabalin							

Other Adverse Reactions Observed During the Clinical Studies of LYRICA Following is a list of treatment-emergent adverse reactions reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. Events are categorized by body system and listed in order of decreasing frequenty according to the following definitions: frequent adverse reactions are those occurring in patients, infrequent adverse reactions are those occurring in 1/000 patients; rare reactions are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the Warnings and Precautions section. Body as a Whole – frequent: Abdominal pain, Allergic reaction, Fever, Infrequent: Abscess, Cellulitis, Chilis, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction; Rare: Anaphylactoid reaction, Ascites, Granuloma, Hangover