

Let Frequency, Pain Guide Restless Legs Treatment

BY JOHN R. BELL
Associate Editor

BALTIMORE — In the decision of which drug to prescribe a patient with restless legs syndrome, the frequency and painfulness of symptoms are crucial to making the correct choice, Dr. Christopher J. Earley said at a neurology meeting sponsored by Johns Hopkins University.

“For [75%]-80%, depending on the population that you deal with, pain is not what

they experience,” said Dr. Earley, a neurologist at Johns Hopkins. A far greater portion instead describe their RLS as uncomfortable, he said. But for those with painful RLS, that pain must be treated. “So I tend to use the antiseizure medications [e.g., gabapentin, lamotrigine, pregabalin] or the opiates as my first line of treatment, as opposed to the dopamine [DA] agents, when I’m dealing with painful symptoms,” he said. If it’s partially responsive... then I will consider the dopamine agonists. If I really

get desperate... I might consider sedation.”

For painless nightly RLS, he advises a DA agonist as first-line therapy, opiates as a second-line choice, and sedatives as third-line treatment. Frequent painless RLS (2-3 nights per week) warrants a sedative first, followed by opiates and, if those fail, levodopa. For occasional RLS (less than twice per week), he advises either a half or whole tablet of carbidopa 25 mg/levodopa 100 mg (available as Sinemet and Parcopa brands) as needed for first-line therapy.

“This is going to be effective in 99.9% of patients, barring side effects like nausea,” he said. He recommends a DA agonist and a sedative as second- and third-line treatment, respectively. Drugs that can aggravate RLS include neuroleptics and antiemetics, as well as SSRIs and tricyclic antidepressants (except for bupropion and trazodone) and antihistamines.

A disadvantage of the DA agonists is that they take 2 hours to reach peak dose effect (3 hours if taken with a meal or after symptom onset), compared with 30-60 minutes for opiates. Thus dopamine agonists are most useful for situations such as airplane flights, he said, but less practical for nighttime RLS. Dr. Earley favors levodopa for occasional nonpainful RLS. “If you have any doubts about whether this is RLS or not RLS, you can use the levodopa-carbidopa combination (carbidopa 25 mg/levodopa 100 mg) of half to 1½ tablets for 3 days. “If they get no real benefits from that, this is not RLS—at least not the RLS that I know.”

The DA agonists do have other disadvantages besides their delayed effect, Dr. Earley noted. They can cause compulsive behaviors—though this has been observed more in patients with Parkinson’s disease than with RLS. They also can cause hypersomnia. “It’s almost like narcolepsy,” he said. Moreover, DA agonists risk the phenomenon of augmentation, whereby an increase in dosage leads to an increase in symptoms, so that a patient is treated effectively for a time period in which RLS occurs (e.g., bedtime), but then the RLS begins to occur either before or after the treated period. “Augmentation is the single biggest reason why you have to stop this drug,” Dr. Earley warned. He consulted on the case of a woman whose RLS progressed over the course of 2 years from initially requiring one dose of Sinemet nightly “to taking Sinemet every hour on the hour, and she was only getting 2 or 3 hours of sleep.”

He advised that when patients taking a DA agonist for sleep complain of RLS symptoms before or after bedtime, the physician should not prescribe additional drug. As long as the patient can sleep without RLS awakening them or interfering with their falling asleep, RLS symptoms at other times of the day are not worth medicating. They are free to walk around in the evenings and the primary lifestyle problem of RLS interference with sleep is still under control, he said.

Notably, opiates do not pose augmentation risk, he said. With opiates, “you’re going to get about 85% of them up walking away relatively happy.” Options in this drug category are codeine, propoxyphene, controlled-release oxycodone, methadone, and the fentanyl patch. Dr. Earley observed that methadone is by far the least expensive, at approximately \$.05 per dose.

Iron deficiency has been implicated as a possible cause of RLS, he noted. “I check ferritins in everybody,” he said. Deficiency is defined as less than 18 ng/mL or iron saturation less than 16%. He recommends ferrous sulfate 325 mg plus 200 mg vitamin C or orange juice, to be given on an empty stomach in the absence of calcium or milk.

AMITIZA™

(lubiprostone) soft gelatin capsules

BRIEF SUMMARY OF PRESCRIBING INFORMATION—Please see package insert for complete prescribing information
720-03565

AMITIZA™

(lubiprostone)
Soft Gelatin Capsules

INDICATIONS AND USAGE

AMITIZA™ is indicated for the treatment of chronic idiopathic constipation in the adult population.

CONTRAINDICATIONS

AMITIZA™ is contraindicated in those patients with a known hypersensitivity to the drug or any of its excipients, and in patients with a history of mechanical gastrointestinal obstruction.

WARNINGS

Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be evaluated prior to initiating AMITIZA™ treatment.

The safety of AMITIZA™ in pregnancy has not been evaluated in humans. In guinea pigs, lubiprostone has been shown to have the potential to cause fetal loss. AMITIZA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who could become pregnant should have a negative pregnancy test prior to beginning therapy with AMITIZA™ and should be capable of complying with effective contraceptive measures (see **Teratogenic Effects: Pregnancy Category C**).

PRECAUTIONS

Patient Information:

AMITIZA™ may cause nausea. If this occurs, concomitant administration of food with AMITIZA™ may reduce symptoms of nausea. AMITIZA™ should not be administered to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment. If the diarrhea becomes severe consult your physician.

Drug Interactions:

Based upon the results of *in vitro* human microsomes studies, there is low likelihood of drug-drug interactions. *In vitro* studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. Further *in vitro* studies indicate microsomal carbonyl reductase may be involved in the extensive biotransformation of lubiprostone to M3. Additionally, *in vitro* studies in human liver microsomes demonstrate that lubiprostone does not inhibit cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitro* studies in primary cultures of human hepatocytes show no induction of the cytochrome P450 isoforms 1A2, 2B6, 2C9, and 3A4. No additional drug-drug interaction studies have been performed. Based on the available information, no protein binding-mediated drug interactions of clinical significance are anticipated.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two 2-year oral (gavage) carcinogenicity studies (one in Crl:B6C3F1 mice and one in Sprague-Dawley rats) were conducted with lubiprostone. In the 2-year carcinogenicity study in mice, lubiprostone doses of 25, 75, 200, and 500 mcg/kg/day (approximately 2, 6, 17, and 42 times the recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, lubiprostone doses of 20, 100, and 400 mcg/kg/day (approximately 3, 17, and 68 times the recommended human dose, respectively, based on body surface area) were used. In the mouse carcinogenicity study, there was no significant increase in any tumor incidences. There was a significant increase in the incidence of interstitial cell adenoma of the testes in male rats at the 400 mcg/kg/day dose. In female rats, treatment with lubiprostone produced hepatocellular adenoma at the 400 mcg/kg/day dose.

Lubiprostone was not genotoxic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma (L5178Y TK+/-) forward mutation assay, the *in vitro* Chinese hamster lung (CHL/IU) chromosomal aberration assay, and the *in vivo* mouse bone marrow micronucleus assay.

Lubiprostone, at oral doses of up to 1000 mcg/kg/day, had no effect on the fertility and reproductive function of male and female rats. The 1000 mcg/kg/day dose in rats is approximately 166 times the recommended human dose of 48 mcg/day, based on the body surface area.

Teratogenic Effects: Pregnancy Category C:

Teratology studies with lubiprostone have been con-

ducted in rats at oral doses up to 2000 mcg/kg/day (approximately 332 times the recommended human dose, based on body surface area), and in rabbits at oral doses of up to 100 mcg/kg/day (approximately 33 times the recommended human dose, based on body surface area). Lubiprostone was not teratogenic in rats and rabbits. In guinea pigs, lubiprostone caused fetal loss at repeated doses of 10 and 25 mcg/kg/day (approximately 2 and 6 times the human dose, respectively, based on body surface area) administered on days 40 to 53 of gestation.

There are no adequate and well-controlled studies in pregnant women. However, during clinical testing of AMITIZA™ at 24 mcg BID, four women became pregnant. Per protocol, AMITIZA™ was discontinued upon pregnancy detection. Three of the four women delivered healthy babies. The fourth woman was monitored for 1 month following discontinuation of study drug, at which time the pregnancy was progressing as expected; the patient was subsequently lost to follow-up.

AMITIZA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If a woman is or becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers:

It is not known whether lubiprostone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from lubiprostone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

AMITIZA™ has not been studied in pediatric patients.

ADVERSE REACTIONS

In clinical trials, 1429 patients received AMITIZA™ 24 mcg BID or placebo. Table 1 presents data for the adverse experiences that were reported in at least 1% of patients who received AMITIZA™ and that occurred more frequently on study drug than placebo. It should be noted that the placebo data presented are from short-term exposure (<4 weeks) whereas the AMITIZA™ data are cumulative data that were collected over 3- or 4-week, 6-month, and 12-month observational periods and that some conditions are common among otherwise healthy patients over a 6- and 12-month observational period.

Table 1. Adverse Events Reported for Patients Treated with AMITIZA™

System/Adverse Experience	Placebo n=316		AMITIZA™ 24 mcg QD n=26		AMITIZA™ 24 mcg BID n=112		AMITIZA™ Any Active Dose* n=1175	
	n	%	n	%	n	%	n	%
Gastrointestinal disorders								
Nausea	5.1	1.7	3.1	12.2	3.1	13.2	30.9	2.6
Diarrhea	0.9	0.3	1.3	5.0	1.3	5.0	13.2	1.1
Abdominal distension	2.2	0.7	7.1	27.3	7.1	27.3	6.8	0.6
Abdominal pain	2.8	0.9	6.7	25.7	6.7	25.7	6.8	0.6
Flatulence	1.9	0.6	6.1	23.4	6.1	23.4	5.9	0.5
Vomiting	0.9	0.3	4.6	17.5	4.6	17.5	4.4	0.4
Loose stools	0.0	0.0	3.4	13.1	3.4	13.1	3.2	0.3
Dysphagia	1.3	0.4	2.9	11.3	2.9	11.3	2.7	0.2
Abdominal pain upper	1.9	0.6	2.2	8.6	2.2	8.6	2.1	0.2
Abdominal pain lower	0.6	0.2	1.9	7.4	1.9	7.4	1.8	0.2
Gastroesophageal reflux disease	0.6	0.2	1.8	7.0	1.8	7.0	1.7	0.1
Abdominal discomfort	0.0	0.0	1.5	5.8	1.5	5.8	1.5	0.1
Dry mouth	0.3	0.1	1.5	5.8	1.5	5.8	1.4	0.1
Constipation	0.9	0.3	1.1	4.3	1.1	4.3	1.0	0.1
Stomach discomfort	0.3	0.1	1.1	4.3	1.1	4.3	1.0	0.1
Infections and infestations								
Sinusitis	1.6	0.5	4.9	18.7	4.9	18.7	4.8	0.4
Upper respiratory tract infection	1.9	0.6	4.4	16.7	4.4	16.7	4.3	0.4
Lower respiratory tract infection	0.9	0.3	3.7	14.1	3.7	14.1	3.6	0.3
Nasopharyngitis	2.2	0.7	2.9	11.3	2.9	11.3	2.7	0.2
Influenza	0.6	0.2	2.0	7.8	2.0	7.8	1.9	0.2
Bronchitis	0.3	0.1	1.6	6.2	1.6	6.2	1.7	0.1
Gastroenteritis viral	0.0	0.0	1.0	3.9	1.0	3.9	1.0	0.1
Viral infection	0.3	0.1	0.5	1.9	0.5	1.9	0.6	0.0
Nervous system disorders								
Headache	6.6	2.1	13.2	50.0	13.2	50.0	13.0	1.1
Dizziness	1.3	0.4	4.1	15.6	4.1	15.6	4.0	0.3
Hyposthesia	0.0	0.0	0.5	1.9	0.5	1.9	0.6	0.0
General disorders and site administration conditions								
Edema peripheral	0.3	0.1	3.8	14.4	3.8	14.4	3.6	0.3
Fatigue	1.9	0.6	2.3	8.9	2.3	8.9	2.5	0.2
Chest discomfort	0.0	0.0	1.6	6.2	1.6	6.2	1.6	0.1
Chest pain	0.0	0.0	1.1	4.3	1.1	4.3	1.0	0.1
Pirrexia	0.3	0.1	1.1	4.3	1.1	4.3	1.0	0.1
Musculoskeletal and connective tissue disorders								
Arthralgia	0.3	0.1	3.1	12.1	3.1	12.1	3.0	0.3
Back pain	0.9	0.3	2.3	8.9	2.3	8.9	2.3	0.2
Pain in extremity	0.0	0.0	1.9	7.4	1.9	7.4	1.9	0.2
Muscle cramp	0.0	0.0	1.0	3.9	1.0	3.9	0.9	0.1
Respiratory, thoracic, and mediastinal disorders								
Dyspnea	0.0	0.0	2.4	9.3	2.4	9.3	2.5	0.2
Pharyngolaryngeal pain	2.2	0.7	1.7	6.6	1.7	6.6	1.6	0.1
Cough	0.6	0.2	1.6	6.2	1.6	6.2	1.5	0.1
Investigations								
Weight increased	0.0	0.0	1.0	3.9	1.0	3.9	0.9	0.1
Psychiatric disorders								
Depression	0.0	0.0	1.4	5.4	1.4	5.4	1.4	0.1
Insomnia	0.3	0.1	1.4	5.4	1.4	5.4	1.4	0.1
Vascular disorders								
Hypertension	0.0	0.0	1.0	3.9	1.0	3.9	0.9	0.1

*Includes patients dosed at 24 mcg QD, 24 mcg BID, and 24 mcg TID



AMITIZA™-induced Nausea:

Among constipated patients, 31.1% of those receiving AMITIZA™ 24 mcg BID reported nausea. Of those patients, 3.4% reported severe nausea and 8.7% discontinued treatment due to nausea. It should be noted that the incidence of nausea increased in a dose-dependent manner with the lowest overall incidence for nausea seen at the 24 mcg QD dose (17.2%). Further analysis of nausea has shown that long-term exposure to AMITIZA™ does not appear to place patients at elevated risk for experiencing nausea. In the open-label, long-term studies, patients were allowed to titrate the dose of AMITIZA™ down to 24 mcg QD from 24 mcg BID if experiencing nausea. It should also be noted that nausea decreased when AMITIZA™ was administered with food and that, across all dose groups, the rate of nausea was substantially lower among constipated men (13.2%) and constipated elderly patients (18.6%) when compared to the overall rate (30.9%). No patients in the trials were hospitalized due to nausea.

AMITIZA™-induced Diarrhea:

Among constipated patients, 13.2% of those receiving AMITIZA™ 24 mcg BID reported diarrhea. Of those patients, 3.4% reported severe diarrhea and 2.2% discontinued treatment due to diarrhea. The incidence of diarrhea did not appear to be dose-dependent. No serious adverse events were reported for electrolyte imbalance in the six clinical trials and no clinically significant changes were seen in serum electrolyte levels while patients were receiving AMITIZA™.

Other Adverse Events:

The following list of adverse events include those that were considered by the investigator to be possibly related to AMITIZA™ and reported more frequently (>0.2%) on AMITIZA™ than placebo and those that lead to discontinuation more frequently (>0.2%) on AMITIZA™ than placebo. Although the events reported occurred during treatment with AMITIZA™, they were not necessarily attributed to dosing of AMITIZA™.

- Gastrointestinal disorders:** watery stools, fecal incontinence, abnormal bowel sounds, frequent bowel movements, retching
- Nervous system disorders:** syncope, tremor, dysgeusia, paraesthesia
- General disorders and administration site conditions:** rigors, pain, asthenia, malaise, edema
- Respiratory, thoracic, and mediastinal disorders:** asthma, painful respiration, throat tightness
- Skin and subcutaneous tissue disorders:** hyperhidrosis, urticaria, rash
- Psychiatric disorders:** nervousness
- Vascular disorders:** flushing, palpitations
- Metabolism and nutrition disorders:** decreased appetite
- Ear and labyrinth disorders:** vertigo

Overdosage:

There have been two confirmed reports of overdosage with AMITIZA™. The first report involved a 3-year-old child who accidentally ingested 7 to 8 capsules of 24 mcg of AMITIZA™ and fully recovered. The second report was a study subject who self-administered a total of 96 mcg AMITIZA™ per day for 8 days. The subject experienced no adverse events during this time. Additionally, in a definitive Phase 1 cardiac repolarization study, 51 patients administered a single oral dose of 144 mcg of AMITIZA™, which is 6 times the normal single administration dose. Thirty-nine (39) of the 51 patients experienced an adverse event. The adverse events reported in >1% of this group included the following: nausea (45.1%), vomiting (27.5%), diarrhea (25.5%), dizziness (17.6%), loose or watery stools (13.7%), headache (11.8%), retching (7.8%), abdominal pain (5.9%), flushing or hot flush (5.9%), dyspnea (3.9%), pallor (3.9%), stomach discomfort (3.9%), syncope (3.9%), upper abdominal pain (2.0%), anorexia (2.0%), asthenia (2.0%), chest discomfort (2.0%), dry mouth (2.0%), hyperhidrosis (2.0%), skin irritation (2.0%), and vasovagal episode (2.0%).

DOSAGE AND ADMINISTRATION

The recommended dosage for AMITIZA™ is 24 mcg taken twice daily (BID) orally with food. Physicians and patients should periodically assess the need for continued therapy.

MARKETED BY:

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