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In This Issue:

- *Milnacipran*
- *Rufinamide*
- *Formulary Update*

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Formulary Information

Medication Inservices

A New Medication for Fibromyalgia: Milnacipran

by Katie Bartlett, Pharm.D.

Introduction: Milnacipran (Savella™; Forest Laboratories) was approved by the Food and Drug Administration (FDA) in January 2009 for the management of fibromyalgia (FM). Milnacipran is a selective serotonin and norepinephrine dual reuptake inhibitor. Besides milnacipran, the only other FDA-approved medications for FM are duloxetine (Cymbalta™) and pregabalin (Lyrica™). Milnacipran has also been approved for treatment of depression in parts of Europe and Asia since 1997.

Fibromyalgia is a chronic pain disorder characterized by widespread musculoskeletal pain, stiffness, paresthesias, disturbed sleep, fatigue, and tenderness at predefined anatomic sites. The etiology and pathophysiology of FM are unclear. Although FM was previously thought to be a muscle disease, it is now considered a disorder of central nervous system perception and regulation of pain. A variety of factors are suspected in contributing to the pathogenesis including sleep disturbances, growth hormone deficiencies, abnormal hypothalamic-pituitary-adrenal axis, and autonomic dysfunction.

Mechanism of Action: The mechanism by which milnacipran inhibits pain is unknown. However, low levels of serotonin metabolites were found in the cerebrospinal fluid of FM patients suggesting that serotonin deficiency may play a role in the pathophysiology.

Besides milnacipran, other serotonin and norepinephrine reuptake inhibitors (SNRIs) are venlafaxine (Effexor™) and duloxetine. All three of these SNRIs have demonstrated efficacy in various chronic pain syndromes, but have varying selectivity for serotonin (5-HT) and norepinephrine (NE) transporters. It has been suggested that norepinephrine may be more important than serotonin in the modulation of pain. *In vitro*, milnacipran demonstrates more selectivity for inhibiting norepinephrine reuptake compared to inhibiting serotonin reuptake. Venlafaxine and duloxetine are more selective for inhibiting serotonin reuptake.

Select Clinical Trials: In a 27-week multi-center study, Mease and colleagues evaluated the efficacy of milnacipran in 888 patients with FM (as defined by the American College of Rheumatology). The effects of two doses of milnacipran (100 mg per day and 200 mg per day, including a dose escalation phase and stable-dose phase) were compared to placebo. The primary endpoints were the rates of FM composite responders and FM pain composite responders. Fibromyalgia composite responders were patients who showed $\geq 30\%$ improvement in visual analog scale (VAS) pain scores for 24-hour morning recall, a Patient Global Impression of Change (PGIC) of *much improved*

Select Clinical Trials (continued):

or *very much improved*, and a ≥ 6 -point improvement in the Physical Component Summary of the 36-item Short-Form Health Survey (SF-36 PCS). Fibromyalgia pain composite responders were patients who met the response criteria for the VAS scores and PGIC ratings. Secondary endpoints included individual analyses of pain severity (using VAS), PGIC, and physical function (SF-36 PCS). There were no statistically significant differences in baseline characteristics. Compared with placebo, significantly greater proportions of milnacipran-treated patients met the criteria for FM composite responders (100 mg per day; $p=0.028$ and 200 mg per day; $p=0.017$). There were significantly greater proportions of patients in the milnacipran 200 mg per day group who met the criteria for FM pain composite responders compared to placebo (19.3% vs 26.8%; $p=0.032$), but only a trend towards a difference for the 100 mg per day group (27.2%; $p=0.056$). Milnacipran was shown to be safe and well tolerated with the most common adverse effects being nausea and headache. The authors concluded that milnacipran is safe and effective for the treatment of multiple symptoms of FM.

In another multi-center, double-blind, placebo-controlled study by Clauw and colleagues, the effects of milnacipran were evaluated in 1196 patients with FM (as defined by the American College of Rheumatology) over 15 weeks. The effects of two doses of milnacipran (100 mg per day and 200 mg per day, including a dose escalation phase and stable-dose phase) were compared with placebo. Primary endpoints and definitions of FM composite responders and FM pain composite responders were the same as in the Mease study. Secondary endpoints were time-weighted averages of pain scores (VAS), PGIC scores, and SF-36 PCS scores. Compared to placebo, there was a higher percentage of FM composite responders in both the milnacipran 100 mg per day group ($p=0.01$) and the milnacipran 200 mg per day group ($p=0.02$). Compared to placebo, there was also a higher percentage of FM pain composite responders in the milnacipran 100 mg per day ($p=0.03$) and the milnacipran 200 mg per day ($p=0.004$) groups. The most common adverse events reported in the milnacipran-treated patients were nausea (~35%), headache (~18%), and constipation (~14 to 18%). Adverse events led to discontinuation of the study drug in 19.5% of the milnacipran 100 mg per day group, 23.7% of the 200 mg per day group, and 9.5% of the placebo group. The authors concluded that milnacipran 100- and 200-mg per day were significantly more effective than placebo in terms of improvements in pain, fatigue, and other FM symptoms.

Adverse Reactions and Drug-Drug Interactions: Milnacipran shares a black box warning for suicide risk with other SNRIs and selective serotonin reuptake inhibitors (SSRIs). Adverse reactions occurring in $\geq 5\%$ of patients taking milnacipran (and greater than placebo) were nausea, headache, constipation, dizziness, insomnia, hot flashes, hyperhidrosis, vomiting, palpitations, increased heart rate, dry mouth, and hypertension. As with other serotonergic drugs, co-administration of milnacipran and monoamine oxidase inhibitors (MAOIs) is contraindicated. Milnacipran should be used cautiously with other serotonergic drugs and lithium due to the risk of serotonin syndrome. Co-administration of milnacipran with epinephrine, norepinephrine, or digoxin may increase the risk of cardiovascular adverse events. Milnacipran is classified as a pregnancy-risk category C, and there are no adequate and well-controlled studies in nursing mothers.

Dose and Administration: The recommended dose titration schedule for milnacipran is 12.5 mg once on Day 1, then 12.5 mg twice a day on Days 2-3, and then 25 mg twice a day on Days 4-7, and then 50 mg twice a day after Day 7. In clinical trials, milnacipran was evaluated with a dose titration schedule. The daily dose may be increased to 200 mg (or 100 mg twice a day) based on individual response. Dosing should be adjusted in patients with severe renal impairment ($\text{CrCl} \leq 29$ ml/min) with a reduced maintenance dose to 25 mg twice a day. Following extended use, milnacipran should be tapered and not abruptly discontinued. Milnacipran may be taken with or without food, but taking it with food may improve tolerability.

Cost and Formulary Status: Milnacipran is available as 12.5-, 25-, 50-, and 100-mg tablets, as well as a 4-week titration pack that consists of three tablet strengths [12.5 mg (5 tablets); 25 mg (8 tablets); and 50 mg (42 tablets)] to help with the initial dose titration. The average wholesale price (AWP) for all strengths is \$1.24 per tablet (~\$74 per month). The AWP for the 4-week titration pack is \$114. Milnacipran is not on the Cleveland Clinic Formulary because it is mainly used in the outpatient setting.

Selected References:

1. Forest Laboratories, Inc., Cypress Bioscience, Inc. (January 14, 2009). Forest and Cypress announce FDA approval of Savella™ for the management of fibromyalgia. Press release. Retrieved on 2009-2-20 from <http://frx.com/news/PressRelease.aspx?ID=1244788>.
2. Savella [package insert]. New York, NY: Forest Pharmaceuticals, Inc.; July 2009.
3. Mease PJ, Clauw DJ, Gendreau RM, Rao SG, Kranzler J, Chen W et al. The efficacy and safety of milnacipran for treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2009;36:398-409.
4. Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multi-center, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. *Clin Ther* 2008;30:1988-2004.

Note: At the time of writing this article, Katie Bartlett was a Pharm.D. Candidate from the University of Toledo.

Did You Know. . .

Rufinamide (Banzel™) *by Christopher Tuttle, Pharm.D. Candidate*

Rufinamide (Banzel™) is a new oral medication FDA-approved as an adjunctive agent in patients 4 years and older with Lennox-Gestaut syndrome. Rufinamide is structurally unrelated to other antiepileptic medications currently available. The precise mechanism of action is not completely understood, but *in vitro* studies suggest that rufinamide stabilizes hyperexcitable neurons and reduces seizure propagation through modulation and prolongation of the inactive phase of voltage-gated sodium channels.

Rufinamide is well absorbed after oral administration with bioavailability being 85%. Food has been shown to further increase the drug's absorption, therefore product labeling recommends taking the medication with food. Metabolism occurs in the liver via carboxylesterase-mediated hydrolysis without cytochrome (CYP) P450 involvement; however, rufinamide is a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 enzymes. Rufinamide is excreted renally, and it is removed with hemodialysis.

The common adverse effects reported in clinical trials were headache (16%-21%), somnolence (11%-24.3%), fatigue (9%-16%), nausea (7%-12%), vomiting (5%-17%) and dizziness (2.7%-19%). Most adverse effects were reported as mild-to-moderate and transient. Rare serious adverse effects included hypersensitivity syndrome and status epilepticus. Status epilepticus occurred in 0.9% of patients treated with rufinamide, but did not occur in patients receiving placebo. A standard definition for status epilepticus was not used, therefore actual incidence is unknown. Antiepileptic drugs, including rufinamide, have been labeled with an increased risk of suicidal ideation and behavior. Patients, families, and caregivers should monitor for changes in behavior and immediately contact healthcare providers with concerns. During clinical trials, 46%-65% of patients receiving rufinamide compared to 5%-10% receiving placebo experienced QT shortening (greater than 20 msec); therefore, rufinamide is contraindicated in patients with Familial Short QT syndrome. Rufinamide is classified as a pregnancy-risk category C, and it is contraindicated in nursing mothers as the drug is likely excreted into breast milk.

The recommended dose for children 4 years old through adolescence is to start with 10 mg/kg/day and then increase by 10 mg/kg increments every other day until the target dose of 45 mg/kg/day or 3200 mg per day, whichever is less, is reached. Adult treatment should begin with 400 to 800 mg per day and titrated by 400 to 800 mg per day increments every 2 days to reach a target dose of 3200 mg per day. Antiepileptic efficacy at doses below the target amount is unknown. The total daily dose in adults and children should be taken in two equally divided doses. Rufinamide tablets are commercially available in 200- and 400-mg tablets that may be split in half for ease in dose titration. Rufinamide is not recommended for patients with severe liver impairment and caution is advised in patients with mild-to-moderate liver disease. Patients with renal impairment (CrCl < 30 mL/min) do not require dosage adjustments. When therapy is not tolerated, or no longer required, gradual tapering of the drug is recommended (decrease the dose by 25% every 2 days) to avoid seizures. Rufinamide is on the Cleveland Clinic Formulary for both adult and pediatric patients (initiation of rufinamide in pediatric patients is restricted to Pediatric Neurology). The average wholesale price (AWP) is \$1.50 and \$3.00 for the 200- and 400-mg strength tablets, respectively.

Selected References:

1. Banzel™ (rufinamide) Tablets [prescribing information]. Woodcliff Lake, NJ: Eisai Co., Ltd; 2008.
2. Lexi-Drugs Online® [database on the Internet]. Hudson (OH): Lexi-Comp, Inc. [updated periodically; cited 2009 1 July]. Available from URL: <http://online.lexi.com>
3. Micromedex® [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc. [updated 2009 Jan 23; cited 2009 1 July]. Available from URL: <http://www.thomsonhc.com>
4. Clinical Pharmacology® [database on the Internet]. Tampa (FL): Gold Standard, Inc. [updated 2009 Jan 6; cited 2009 1 July]. Available from URL: <http://www.clinicalpharmacology.com>

Formulary Update

The Pharmacy and Therapeutics (P&T) Committee met on Tuesday, July 7, 2009, and the following decisions were made:

Additions:

- 1) **Rufinamide tablets (Banzel[®]):** It is FDA-approved for adjunctive therapy in the treatment of generalized seizures of Lennox-Gastaut syndrome. For pediatric patients with Lennox-Gastaut (adjunctive), the dosing recommendations are for children ≥ 4 years, the initial dose is 10 mg/kg/day in two equally divided doses and increase dose by ~ 10 mg/kg/day every other day to a target dose of 45 mg/kg/day or 3200 mg/day (whichever is lower) in two equally divided doses. Rufinamide use in pediatrics was approved at the April P&T Meeting, and now it is approved for use in adult patients. For adult dosing, see rufinamide article on previous page.
- 2) **C1 inhibitor, human (Cinryze[®]):** It is FDA-approved for the routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE). Other existing therapies for HAE include fresh frozen plasma (FFP), androgens, and antifibrinolytic agents. Cinryze[®] is an intravenous medication that is potentially administered every 3 to 4 days. Each course of therapy is \sim \$4000. For adult and pediatric patients, it is *restricted* to the Department of Allergy and Immunology for prophylaxis of HAE in the outpatient setting only (any inpatient orders **MUST BE APPROVED BY THE DRUG INFORMATION CENTER**). Additionally, specific usage guidelines for pediatric patients will be developed by Pediatric Allergy and Immunology.
- 3) **Generic mycophenolate mofetil:** The P&T Committee (along with all of the Transplant Programs) approved using only generic mycophenolate mofetil (i.e., we will no longer carry Cellcept[®] brand product for inpatients). The CC Department of Pharmacy will only carry one generic manufacturer of mycophenolate. The mycophenolate mofetil suspension and intravenous formulation are still only available as brand (Cellcept[®]).
- 4) **Palifermin (Kepivance[®]):** It is a keratinocyte growth factor FDA-approved to decrease the incidence and duration of mucositis during hematopoietic stem cell transplant. It is given as a 60 mcg/kg dose daily for 3 days prior to the chemotherapy/total body irradiation (TBI) conditioning regimen for transplant and then another three doses after the chemotherapy/TBI is finished. The CC Bone Marrow Transplant (BMT) program is changing the protocol for methotrexate which will use higher doses, increasing the risk of oral mucositis. The course of therapy is six doses (three doses will be administered in the outpatient setting and then three doses will be administered in the inpatient setting). It is *restricted* to the Department of Hematologic Oncology and Blood Disorders for the adult BMT program.
- 5) **Febuxostat (Uloric[®]):** It is FDA-approved for chronic management of hyperuricemia in patients with gout. Febuxostat is a non-purine selective inhibitor of xanthine oxidase. A 40 mg dose of febuxostat is comparable to a 300 mg dose of allopurinol in terms of a patient being able to achieve uric acid < 6 mg/dL. Unlike allopurinol, there is no dose adjustment needed in patients with renal dysfunction. Because febuxostat can increase concentrations of substrates of xanthine oxidase (e.g., theophylline, aminophylline 6-mercaptopurine), concurrent use should be avoided. The recommended starting dose of febuxostat is 40 mg once daily. For patients that do not achieve a serum uric acid level < 6 mg/dL after 2 weeks, the dose may be increased to 80 mg once daily. Febuxostat is considerably more expensive than allopurinol (\$4.36/day versus \$0.05/day). It is *restricted* to adult patients for 1) continuation of therapy from home (since febuxostat and allopurinol are not interchangeable; no data available at this time), or 2) for initiation of therapy in patients with gout who are allergic to or intolerant of allopurinol, or have significant renal dysfunction.
- 6) **Abobotulinumtoxin type A (Dysport[®]):** It is FDA-approved for the temporary improvement in the appearance of moderate-to-severe glabellar lines (cosmetic indication). Abobotulinumtoxin type A is an acetylcholine release inhibitor and a neurotransmitter blocking agent and botulinum toxin A is the active ingredient; however, it is different from botulinum toxin A (Botox[®]) and is not interchangeable. Dysport[®] should be administered no more frequently than every 3 months, and the clinical effect may last up to 4 months. Dysport[®] is *restricted* to the Department of Dermatology for treatment of glabellar lines in adult patients in the outpatient setting.
- 7) **Certolizumab (Cimzia[®]):** It was added for use in pediatric patients (it is already on the Formulary and restricted for use in adults); however, its use in pediatric patients is *restricted* to Pediatric Gastroenterologists and usage guidelines will be developed.

- 8) **Advate®**: This is a recombinant factor VIII product and will be the recombinant factor VIII product used in pediatric patients. The majority of pediatric patients who are receiving a recombinant factor VIII product are on Advate®. The recombinant factor VIII product for adult patients is Recombinate®.

New Formulary Restriction:

IV Chlorothiazide (Diuril®): The cost of IV chlorothiazide has substantially increased to ~\$280 per 500 mg vial from ~\$22 per 500 mg vial. Due to the cost increase, the P&T Committee approved the following formulary restriction:

For adult patients, chlorothiazide intravenous (Diuril®) is **restricted** to:

- A. Department of Nephrology, **or**
- B. Inadequate response to at least 12 hours of IV furosemide (> 200 mg/12 hrs) and:
 - 1. The patient is NPO, **or**
 - 2. The patient is taking medications orally or via corpak and failed a trial of oral thiazide or thiazide-like diuretic (*See Online Formulary for initial dosing recommendations for oral thiazides and for initial dosing recommendations for IV chlorothiazide*)

Change to Formulary Restriction:

Dexmedetomidine (Precedex®): The restriction now includes use in the adult NeuroICU, but with a 24-hour stop on the infusion. The physician will need to evaluate continued use after 24 hours.

Change in Therapeutics Interchange:

Rapid Acting Insulin Therapeutic Interchange: All adult inpatient orders for insulin aspart (Novolog®) or insulin lispro (Humalog®) are automatically converted to insulin glulisine (Apidra®) as part of a therapeutic interchange program. The **exceptions to the interchange** include:

- a. Pediatric patients: Can receive Apidra®, Humalog®, or Novolog®
- b. **Patients with insulin pumps (new exception):** May receive Apidra®, Humalog®, or Novolog® (the rationale is for refill purposes if the pump runs out of insulin while the patient is admitted). There are about 8 patients per week in the hospital with insulin pumps. Humalog® and Novolog® will be re-packaged in 3 ml vials by the Department of Pharmacy.

New Therapeutic Interchange:

Sevelamer hydrochloride (Renagel®) to sevelamer carbonate (Renvela®): In the near future, Renagel® will no longer be commercially available [the manufacturer (Genzyme) is discontinuing the product]. The CC Department of Nephrology requested an automatic interchange from Renagel® to Renvela®.

Dose Conversion of Renagel® to Renvela®

Sevelamer Hydrochloride (Renagel®) Dose	Sevelamer Carbonate (Renvela®) Dose
400 mg	800 mg
800 mg	800 mg
1200 mg	1600 mg
1600 mg	1600 mg
2000 mg	2400 mg
2400 mg	2400 mg
2800 mg	3200 mg
3200 mg	3200 mg

(e.g., Renagel® 1200 mg PO TID would be automatically converted by the pharmacist to Renvela® 1600 mg PO TID)